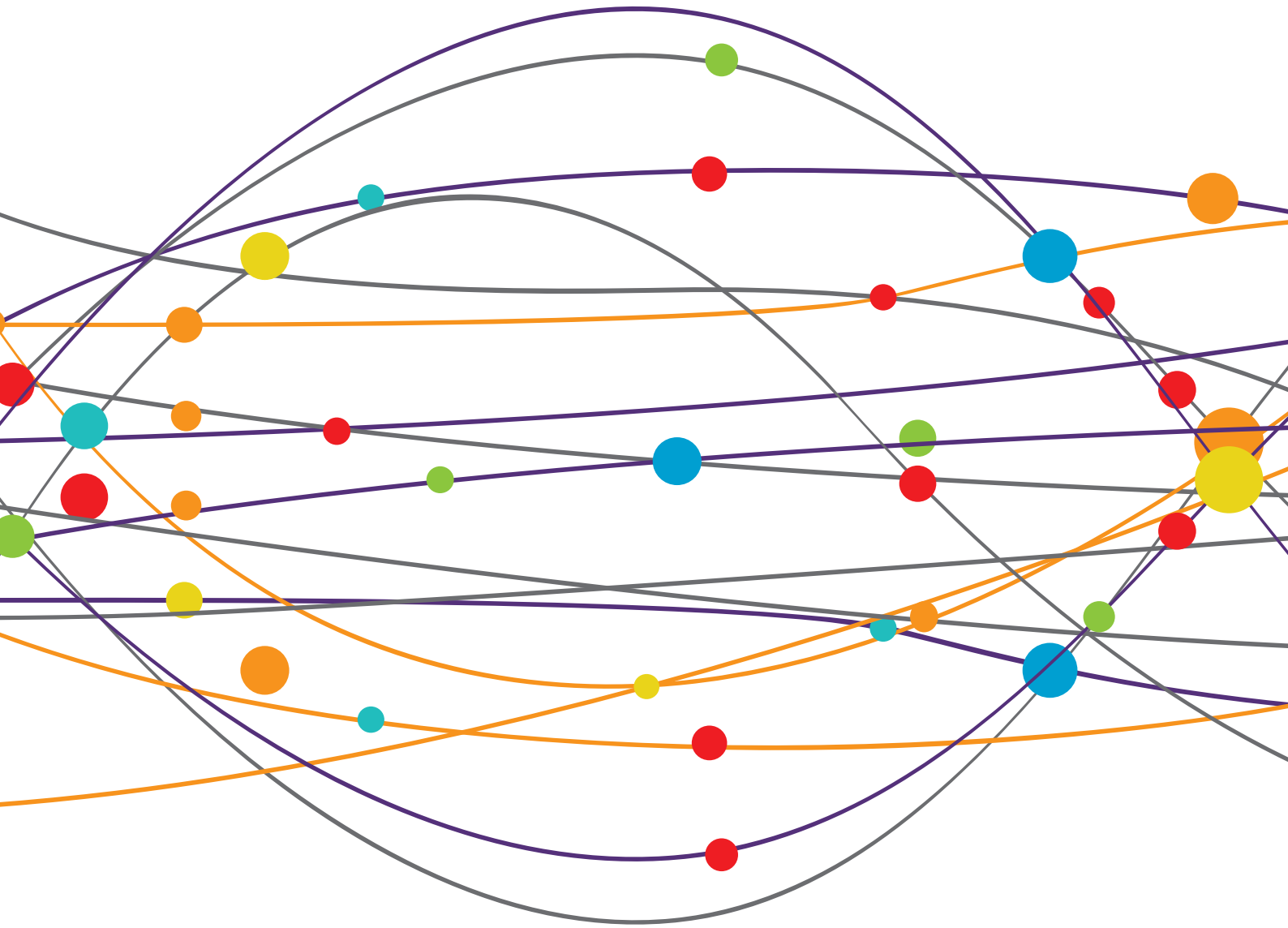
NEUROIMAGING FOR THE MEASUREMENT AND MANAGEMENT OF PAIN

EDITED BY: Flavia Di Pietro, Susanne Becker, Marie-Eve Hoeppli and Marina Lopez-Sola

PUBLISHED IN: Frontiers in Neurology



frontiers Research Topics

Frontiers eBook Copyright Statement

The copyright in the text of individual articles in this eBook is the property of their respective authors or their respective institutions or funders. The copyright in graphics and images within each article may be subject to copyright of other parties. In both cases this is subject to a license granted to Frontiers.

The compilation of articles constituting this eBook is the property of Frontiers.

Each article within this eBook, and the eBook itself, are published under the most recent version of the Creative Commons CC-BY licence. The version current at the date of publication of this eBook is CC-BY 4.0. If the CC-BY licence is updated, the licence granted by Frontiers is automatically updated to the new version.

When exercising any right under the CC-BY licence, Frontiers must be attributed as the original publisher of the article or eBook, as applicable.

Authors have the responsibility of ensuring that any graphics or other materials which are the property of others may be included in the CC-BY licence, but this should be checked before relying on the CC-BY licence to reproduce those materials. Any copyright notices relating to those materials must be complied with.

Copyright and source acknowledgement notices may not be removed and must be displayed in any copy, derivative work or partial copy which includes the elements in question.

All copyright, and all rights therein, are protected by national and international copyright laws. The above represents a summary only. For further information please read Frontiers' Conditions for Website Use and Copyright Statement, and the applicable CC-BY licence.

ISSN 1664-8714
ISBN 978-2-83250-485-7
DOI 10.3389/978-2-83250-485-7

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: frontiersin.org/about/contact

NEUROIMAGING FOR THE MEASUREMENT AND MANAGEMENT OF PAIN

Topic Editors:
Flavia Di Pietro, Curtin University, Australia
Susanne Becker, Heinrich Heine University of Düsseldorf, Germany
Marie-Eve Hoeppli, Cincinnati Children's Hospital Medical Center, United States
Marina Lopez-Sola, University of Barcelona, Spain

Citation: Di Pietro, F., Becker, S., Hoeppli, M.-E., Lopez-Sola, M., eds. (2022). Neuroimaging for the Measurement and Management of Pain. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-83250-485-7

Table of Contents

05 ***Editorial: Neuroimaging for the Measurement and Management of Pain***
Marie-Eve Hoeppli, Susanne Becker, Marina López-Solà and Flavia Di Pietro

08 ***Functional Disruptions of the Brain in Low Back Pain: A Potential Imaging Biomarker of Functional Disability***
Bidhan Lamichhane, Dinal Jayasekera, Rachel Jakes, Wilson Z. Ray, Eric C. Leuthardt and Ammar H. Hawasli

19 ***Modulation of the Somatosensory Evoked Potential by Attention and Spinal Cord Stimulation***
Guiomar Niso, Marleen C. Tjepkema-Cloostermans, Mathieu W. P. M. Lenders and Cecile C. de Vos

30 ***Spinal Cord Resting State Activity in Individuals With Fibromyalgia Who Take Opioids***
Katherine T. Martucci, Kenneth A. Weber II and Sean C. Mackey

43 ***Brain Circuits Involved in the Development of Chronic Musculoskeletal Pain: Evidence From Non-invasive Brain Stimulation***
Mina Kandić, Vera Moliadze, Jamila Andoh, Herta Flor and Frauke Nees

58 ***Recommendations for the Development of Socioeconomically-Situated and Clinically-Relevant Neuroimaging Models of Pain***
Marianne C. Reddan

68 ***Complex Regional Pain Syndrome: Thalamic GMV Atrophy and Associations of Lower GMV With Clinical and Sensorimotor Performance Data***
Martin Domin, Sebastian Strauss, James H. McAuley and Martin Lotze

77 ***Pre-operative Limbic System Functional Connectivity Distinguishes Responders From Non-responders to Surgical Treatment for Trigeminal Neuralgia***
Hayden Danyluk, Stefan Lang, Oury Monchi and Tejas Sankar

87 ***Identification and Therapeutic Outcome Prediction of Cervical Spondylotic Myelopathy Based on the Functional Connectivity From Resting-State Functional MRI Data: A Preliminary Machine Learning Study***
Qian Su, Rui Zhao, ShuoWen Wang, HaoYang Tu, Xing Guo and Fan Yang

101 ***Altered Brain Structure in Chronic Visceral Pain: Specific Differences in Gray Matter Volume and Associations With Visceral Symptoms and Chronic Stress***
Hanna Öhlmann, Laura Ricarda Koenen, Franziska Labrenz, Harald Engler, Nina Theysohn, Jost Langhorst and Sigrid Elsenbruch

114 ***Brain Imaging Biomarkers for Chronic Pain***
Zhengwu Zhang, Jennifer S. Gewandter and Paul Geha

129 ***Gamma Band Oscillations Reflect Sensory and Affective Dimensions of Pain***
Yuanyuan Lyu, Francesca Zidda, Stefan T. Radev, Hongcai Liu, Xiaoli Guo, Shanbao Tong, Herta Flor and Jamila Andoh

140 ***Structural and Functional Asymmetry in Precentral and Postcentral Gyrus in Patients With Unilateral Chronic Shoulder Pain***
Xiaoya Wei, Guangxia Shi, Jianfeng Tu, Hang Zhou, Yanshan Duan, Chin Kai Lee, Xu Wang and Cunzhi Liu

151 ***The Influence of Social Signals on the Self-Experience of Pain: A Neuroimaging Review***
Gil Sharvit and Petra Schweinhardt

frontiers | Frontiers in Neurology

TYPE Editorial
PUBLISHED 28 September 2022
DOI 10.3389/fneur.2022.1029238

Check for updates

OPEN ACCESS

EDITED AND REVIEWED BY
Patrick Stroman,
Queen's University, Canada

*CORRESPONDENCE
Flavia Di Pietro
flavia.dipietro@curtin.edu.au

SPECIALTY SECTION
This article was submitted to Applied Neuroimaging, a section of the journal Frontiers in Neurology

RECEIVED 27 August 2022
ACCEPTED 05 September 2022
PUBLISHED 28 September 2022

CITATION
Hoeppli M-E, Becker S, López-Solà M and Di Pietro F (2022) Editorial: Neuroimaging for the measurement and management of pain. *Front. Neurol.* 13:1029238. doi: 10.3389/fneur.2022.1029238

COPYRIGHT
© 2022 Hoeppli, Becker, López-Solà and Di Pietro. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Editorial: Neuroimaging for the measurement and management of pain

Marie-Eve Hoeppli[1,2], Susanne Becker[3,4], Marina López-Solà[5] and Flavia Di Pietro[6,7]*

[1]Pediatric Pain Research Center (PPRC), Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States, [2]Division of Behavioral Medicine and Clinical Psychology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States, [3]Department of Chiropractic Medicine, Balgrist University Hospital, University of Zurich, Zurich, Switzerland, [4]Clinical Psychology, Department of Experimental Psychology, Heinrich Heine University, Düsseldorf, Germany, [5]Department of Medicine, School of Medicine and Health Sciences, University of Barcelona, Barcelona, Spain, [6]Curtin Medical School, Curtin University, Bentley, WA, Australia, [7]Curtin Health Innovation Research Institute, Curtin University, Bentley, WA, Australia

KEYWORDS

pain, brain imaging, chronic pain, biomarkers, resting state functional magnetic resonance imaging (fMRI), voxel-based morphometry (VBM)

Editorial on the Research Topic
Neuroimaging for the measurement and management of pain

The article collection titled *Neuroimaging for the Measurement and Management of Pain*, a Research Topic within Frontiers in Neurology: Applied Neuroimaging, sought to bring together quality neuroimaging studies of the role of the central nervous system in pain. Pain is enormously complex. While there has been great progress in neuroimaging technology and methodology there is still much we do not understand about the nervous system in pain disorders, particularly the role of the spinal cord, and there is ongoing debate around optimal practices for data analysis and interpretation.

The Research Topic includes work from 59 authors across 7 countries, and a range of issues is addressed. New and exciting directions in data analysis and machine learning are presented, as well as neuroimaging investigation of the spinal cord. An important inclusion is the exploration of the fundamental social and emotional influences of pain, and structural neuroimaging work on specific pain disorders—both somatic and visceral. Overall the collection of rigorous work showcases the progress made in this field and the bright future ahead.

Exciting directions in machine learning and the development of biomarkers

Lamichhane et al. used graph theory measures derived from resting state functional connectivity (FC) scans to achieve high classification accuracy of low back pain patients from healthy controls. They raise the question of whether graph matrices from resting state functional magnetic resonance imaging (rsfMRI) might be useful as brain biomarkers of low back pain, particularly when supplemented by a hybrid feature selection method to remove redundant variables thus improving machine learning classification accuracy.

In their review, Zhang et al. discuss the costs and benefits of brain biomarkers for chronic pain. Even with the advent of advanced analysis such as machine learning, there remains a significant knowledge gap—how does nociception result in pain? Thus the authors focus on the concept of learning in the emergence of pain and the limbic brain circuitry and dopaminergic signaling. Together with the use of big data, machine learning and the use of hybrid feature selection models, they propose that biomarker learning is possible and has potential for clinical translation.

Finally, in a perspective piece that calls to incorporate the biopsychosocial approach to neuroimaging biomarker development, Reddan argues that three levels of inquiry should be addressed to increase the clinical relevance of pain neuroimaging models. Needed first is more diverse sampling for the development of diagnostic biomarkers (population-based, nomothetic approach); second is the development of treatment-relevant models tailored at the individual level (person-based, idiographic approach); and third is prevention-relevant models that combine neuroimaging data and one's own socioeconomic conditions (social epidemiologic approach). The author recommends ways that pain's complexity can be leveraged in service of the individual and society.

Personalizing treatment and predicting the transition to chronicity

Although not directly measuring pain as an outcome, Su et al. explored the potential of preoperative brain biomarkers for prediction of recovery from cervical spondylotic myelopathy (CSM). Using rsfMRI and machine learning, the authors were able to classify CSM patients from healthy controls with high classification accuracy, and furthermore predict neurological recovery in CSM patients. Cross-site validation analyses demonstrated good reproducibility and generalization, and thus the study provides a step toward novel strategies of predicting neurological recovery—with clear implications for the use of such techniques and analyses in chronic pain.

Also using rsfMRI to determine the predictive value of brain networks, Danyluk et al. recruited a sample of trigeminal neuralgia patients. They compared FC between limbic and accessory sensory networks in patients and healthy controls, as well as determining whether pre-operative variability in such networks might distinguish responders from non-responders to surgery. Their results suggest not only FC differences in the TN patients, but differences in FC in the limbic system between those patients who did and did not respond to surgery. They also present interesting correlations between brain FC and illness duration.

In their review, Kandic et al. sought to elucidate the brain circuits implicated in pain chronicity. They review the evidence from non-invasive brain stimulation studies, focussing on the motor cortex and the dorsolateral prefrontal cortex, to explore the transition from acute to chronic pain. The evidence presented also provides exciting potential targets for non-invasive stimulation as therapy, in the transition to the chronic phase.

Investigation and stimulation of the spinal cord

Owing to exciting developments in technology and methodology, MRI of the spinal cord is now possible and increasingly available. Martucci et al. conducted an rsfMRI investigation of the spinal cord in fibromyalgia patients both taking and not taking opioid medications, as well as pain-free controls. Interestingly, regional spinal cord activity in the opioid group was more similar to controls, whereas the non-opioid group displayed differences in both ventral and dorsal spinal cord activity (low frequency fluctuations). In further exploration, fatigue was found to be correlated with regional spinal cord activity differences.

In an aim to explore the efficacy of different settings (tonic and burst) of implanted spinal-cord stimulation in chronic pain, Niso et al. assessed the influence of attention on the somatosensory-evoked brain responses (SEPs) read with electroencephalography (EEG). Late SEP responses were reduced in both the attended and unattended (mind-wandering) conditions in the burst stimulation group, but only in the unattended condition in the more traditional tonic stimulation group. They propose that neuroimaging could potentially be used to personalize spinal-cord stimulation treatment in chronic pain.

Emotional and social influences on pain

Lyu et al. explored the modulation of pain by emotion. By recording the EEG response to an electrical painful stimulation primed by visual images of different emotional valence (negative, positive and neutral), the authors were able to demonstrate that pain unpleasantness, but not pain intensity, was modulated by emotion. Further, they report two gamma band oscillations (GBO), one early and one late, differentially related to pain intensity and unpleasantness. They conclude that the early GBO might reflect the sensory dimension of pain, while the affective dimension might be related to the late GBO component.

Sharvit and Schweinhardt review the effects of social manipulation on pain, highlighting that the social influences of pain have been under-studied in neuroimaging, in contrast to the psychological. Indeed the authors remind us of the inclusion of the social dimension in a recently updated definition of

pain from the International Association for the Study of Pain. Discussing social manipulations such as verbal and non-verbal signals and social support, the authors present a schematic summary graphic of different social modulatory themes on pain intensity ratings.

Structural brain alterations in specific chronic pain states

Domin et al. investigated gray matter volume alterations in the brains of upper limb complex regional pain syndrome (CRPS) sufferers, as well as their association to clinical characteristics and sensorimotor performance. CRPS patients showed lower GMV in the bilateral thalamus; there were associations with pain intensity and duration in the ACC, and associations between the posterior insula and sensorimotor performance. Also investigating limb pain using MRI, Wei et al. studied the structural asymmetry of the pre and post central gyrus in chronic shoulder pain. They report precentral gyrus surface area asymmetry, between pain (according to pain side) and pain-free controls. Further, fMRI and seed-based FC analysis showed significant group differences in the postcentral gyrus and other areas. Notably, both structural and functional imaging asymmetry was correlated with pain and functional impairments.

By no means as widely studied as chronic musculoskeletal pain, Ohlmann et al. report on two cohorts of chronic visceral pain: ulcerative colitis and irritable bowel syndrome (IBS), as well as a comparative healthy control group. GMV was reduced in the frontal cortex and the anterior insula in ulcerative colitis. In IBS there were more widespread differences comprising both increases and decreases in GMV in several brain areas and networks. Interestingly, there was an association between visceral symptoms and GMV in frontal brain regions in both groups. Future work will hopefully elucidate the partly distinct alterations in brain morphology in patients with chronic inflammatory vs. functional bowel disorders.

Together, the studies in the Research Topic, *Neuroimaging for the Measurement and Management of Pain,* address fundamental aspects of pain and its complexity, and will contribute to push the field forward with explorations of the spinal cord and with work on the potential for brain biomarkers of pain, its prognosis and its response to therapy.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Funding

ML-S is supported by the Serra Hunter Programme of the Generalitat de Catalonia, Spain.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Neurology

ORIGINAL RESEARCH
published: 14 July 2021
doi: 10.3389/fneur.2021.669076

Functional Disruptions of the Brain in Low Back Pain: A Potential Imaging Biomarker of Functional Disability

Bidhan Lamichhane[1†], Dinal Jayasekera[2†], Rachel Jakes[2], Wilson Z. Ray[1,2], Eric C. Leuthardt[1,2] and Ammar H. Hawasli[1,3]*

[1] Department of Neurosurgery, Washington University School of Medicine, St. Louis, MO, United States, [2] Department of Biomedical Engineering, Washington University in St. Louis McKelvey School of Engineering, St. Louis, MO, United States, [3] Meritas Health Neurosurgery, North Kansas City, MO, United States

Chronic low back pain (LBP) is one of the leading causes of disability worldwide. While LBP research has largely focused on the spine, many studies have demonstrated a restructuring of human brain architecture accompanying LBP and other chronic pain states. Brain imaging presents a promising source for discovering noninvasive biomarkers that can improve diagnostic and prognostication outcomes for chronic LBP. This study evaluated graph theory measures derived from brain resting-state functional connectivity (rsFC) as prospective noninvasive biomarkers of LBP. We also proposed and tested a hybrid feature selection method (Enet-subset) that combines Elastic Net and an optimal subset selection method. We collected resting-state functional MRI scans from 24 LBP patients and 27 age-matched healthy controls (HC). We then derived graph-theoretical features and trained a support vector machine (SVM) to classify patient group. The degree centrality (DC), clustering coefficient (CC), and betweenness centrality (BC) were found to be significant predictors of patient group. We achieved an average classification accuracy of 83.1% ($p < 0.004$) and AUC of 0.937 ($p < 0.002$), respectively. Similarly, we achieved a sensitivity and specificity of 87.0 and 79.7%. The classification results from this study suggest that graph matrices derived from rsFC can be used as biomarkers of LBP. In addition, our findings suggest that the proposed feature selection method, Enet-subset, might act as a better technique to remove redundant variables and improve the performance of the machine learning classifier.

Keywords: chronic low back pain, graph theory, support vector machine, feature selection, elastic net

OPEN ACCESS

Edited by:
Flavia Di Pietro,
Curtin University, Australia

Reviewed by:
Dahua Yu,
Inner Mongolia University of Science and Technology, China
Carl Saab,
Case Western Reserve University, United States

***Correspondence:**
Dinal Jayasekera
dinal.jayasekera@wustl.edu

† These authors have contributed equally to this work

Specialty section:
This article was submitted to Applied Neuroimaging, a section of the journal Frontiers in Neurology

Received: *17 February 2021*
Accepted: *17 June 2021*
Published: *14 July 2021*

Citation:
Lamichhane B, Jayasekera D, Jakes R, Ray WZ, Leuthardt EC and Hawasli AH (2021) Functional Disruptions of the Brain in Low Back Pain: A Potential Imaging Biomarker of Functional Disability. Front. Neurol. 12:669076. doi: 10.3389/fneur.2021.669076

INTRODUCTION

Chronic low back pain (LBP) is a leading contributor to disability globally. In the United States, LBP is linked to higher healthcare and socioeconomic costs, including reduced employee productivity (1) and lost wages estimated at $100 billion in 2006 (2). Despite advancements in diagnostic and therapeutic technology, researchers and clinicians have found the clinical management of LBP challenging due to its complex pathophysiology (3). This could be attributed to the absence of significant abnormalities in modern spinal imaging of LBP patients (4). These findings have given impetus to the identification of noninvasive biomarkers that have the potential to facilitate early diagnoses, guide treatment plans, and improve our understanding of LBP progression and severity.

In the past, several putative non-imaging biomarkers have been investigated in LBP (5–7). However, these biomarkers are often invasive and do not assess the impact of LBP on the brain. Contrastingly, a neuroimaging biomarker for pain uses different imaging modalities to reveal underlying information about the anatomical circuity and functional pathways that form a signature for chronic pain (8). Functional magnetic resonance imaging (fMRI) is a popular imaging modality used to study functional interactions between brain regions based on the performance of a task (task-fMRI) (9, 10) or while at rest (11, 12). However, task-fMRI can present physical challenges for some LBP patients who are unable to perform the required tasks. Resting-state fMRI (rs-fMRI) is a suitable alternative modality in which spontaneous changes in the blood-oxygen level dependent (BOLD) signal are recorded to identify patterns of functional connectivity while the patient is at rest (13). In fact, rs-fMRI can be used to gain a better understanding of the organization of the brain's cognitive function (14) and overcome some of the limitations of task-fMRI (15).

Resting-state functional connectivity (rsFC) is commonly used as a noninvasive biomarker for various neurological conditions (16). Functional connectivity refers to the temporal dependence of patterns of neural activity in spatially distant regions of the brain (17–20). Past studies have shown that aberrant functional processing within certain brain regions can cause sustained, and sometimes amplified perception of pain (21). This is supported by a growing body of evidence across many chronic pain disorders (22–24) including LBP (25–28). Using novel methods when analyzing brain activity can reveal unique insights (for example, reorganization of hub activity) into chronic pain conditions (29–32). Graph theory measures can be used to model patterns of rsFC as nodes (cortical regions) and edges (functional connections between cortical regions), which can help outline the organization of brain networks. This approach enables us to analyze the topology of networks, revealing underlying information about the higher-order organization of brain networks (33). Many studies have investigated graph measures across chronic pain conditions such as knee pain (34), fibromyalgia (35), and neck pain (24). However, this approach has only rarely been used in practice for LBP (36).

It can be difficult to identify disruptions in functional connectivity, especially in chronic pain, as rsFC matrices tend to be multivariate in nature (37, 38). This problem can be addressed by using a machine learning classifier (39, 40). Classification learning algorithms can accurately predict an unseen test dataset by using a set of essential training features. However, redundant features need to be removed from the dataset by using an appropriate feature selection method to improve classification accuracy (41). Elastic Net (Enet) is a widely used feature selection method that eliminates redundant variables that affect prediction accuracy (42). Enet is especially favorable when the number of predictors is higher than the sample size or when there are many correlated predictor variables. However, certain feature sets selected by Enet may not always constitute a best performing subset of features, as removing additional redundant variables could increase the classifier's performance. Thus, there is an unmet need for an optimal feature selection method. To address this need, we proposed and tested a new hybrid feature selection approach which sorted features according to the magnitude of their Enet coefficients. The best subset of predictors to be retained in the final model was then determined by the maximum cross validated AUC of the feature set. This feature selection approach is the combination of Enet with an optimal subset selection extension which we refer to as Elastic Net-subset (or Enet-subset).

TABLE 1 | Participants' demographic information.

Variable	Healthy controls	LBP
Participants (*n*)	27	24
Sex (M/F)	15/12	9/15
Age (in years)	46.9 ± 17.3 (25–75)	53.5 ± 10.2 (29–67)

In summary, our group (36) and other researchers have shown that LBP patients present with disruptions in cortical functional connectivity. We have also shown that an SVM is capable of using variations in cortical thickness to classify LBP from HC (36). To further expand on our previous work, we (1) extracted local graph measures from functional connectomes and determined their ability to predict LBP by (2) testing a new hybrid feature selection technique (Enet-subset). We hypothesized that LBP patients would show differences in functional connectivity in previously implicated pain processing regions, which a machine learning classifier could use to predict patient group. We also examined if an Enet-subset feature selection approach could improve classifier performance by removing additional redundant variables. We collected high-resolution resting-state scans and parcellated the processed data using a multi-modal parcellation (MMP) developed by the Human Connectome Project (HCP) (43). We also collected self-reported clinical data for the Oswestry Disability Index (ODI) outcome measure.

METHODS AND MATERIALS

Participants

The subjects who participated in this study included 27 healthy controls (HC) and 24 LBP subjects (age matched; $p = 0.21$). This study received approval from the Washington University in Saint Louis Institutional Review Board. All LBP subjects recruited for this study had been diagnosed with chronic LBP due to lumbar spondyloarthropathy with a history of 6 months without lower extremity symptoms. All LBP patients had not received lumbar spine surgery at the time of scanning. All HCs had no history of neurological injury or disease prior to their scan. **Table 1** summarizes the participant information (refer **Supplementary Material** for inclusion and exclusion criteria).

All participants were recruited through the Washington University School of Medicine Research Participant Registry (Volunteer for Health) and direct patient contact during clinical visits at the Barnes Jewish Hospital, Washington University School of Medicine, and Barnes Jewish West County Hospital. All participants were screened by a physician prior to enrollment

in the study, and written informed consent was obtained prior to scanning.

Clinical Data Acquisition

Data for the Oswestry Disability Index (ODI) questionnaire (44, 45) was collected from each participant. The ODI is considered the clinical "gold standard" for assessing functional disability in individuals with LBP (46). The ODI is a self-administered, 10-item questionnaire related to impairments like pain, and abilities such as standing, walking, traveling, lifting, socializing, sitting, personal care, sleeping, and sex life (45). Each item is scored from 0 to 5, and the total of the ten items is expressed as a percentage of the maximum score ranging from 0 (no disability) to 100 (maximum disability).

fMRI Data Acquisition and Pre-processing

A 3T Siemens Prisma with a 32-channel head coil was used to collect 0.8 mm isotropic T1-weighted and T2-weighted scans from all participants. Resting state fMRI images were acquired on the same day using multi-band gradient echo EPI (multi-band accel. factor = 6). The scans had high spatial (2.4 mm × 2.4 mm × 2.4 mm) and temporal (TR = 800ms) resolution [repetition time (TR) = 800 ms, echo time (TE) = 33 ms and flip angle = 52°]. A 2.4 mm isotropic spin echo field map was also collected during fMRI acquisition to correct for any distortion in the fMRI data.

We collected six resting-state fMRI scans that were 5 min long, with AP/PA phase encoding directions (60 axial slices each). Volumetric navigator sequences were used to collect T1- and T2-weighted sequences that were corrected for motion by repeating scans (47). During the resting scans, subjects focused their attention on a visual crosshair.

The imaging data was preprocessed using the HCP's preprocessing pipelines (v4.0.0) (43, 48–51). The structural preprocessing pipelines were used to generate subcortical segmentations and cortical surfaces. Following structural pre-processing, the functional pre-processing pipelines corrected for EPI distortion, registered the fMRI data to structural MRI, and then brought the cortical time series from the volume dimension to the surface. The denoising pipelines then registered the fMRI data to the structural MRI data and corrected for motion and distortions within fMRI data by mapping it onto a CIFTI grayordinate space and removing spatially specific noise. The MSMAll areal-feature-based cross-subject surface registration pipeline was then applied to align the individual subject's cortical regions to the HCP's multi-modal parcellation. This process is more accurate than using cortical folding alone. Finally, temporal ICA (50, 52) was used to clean global noise from the MSMAll aligned rs-fMRI data. For this process, weighted regression (43) of group spatial ICA components from a much larger HCP-Young Adult 1,071-subject dataset with an existing temporal ICA decomposition was applied and the resulting concatenated individual subject time series were unmixed using the previously computed temporal ICA unmixing matrix. The noise temporal ICA individual subject component timeseries from this larger dataset were then non-aggressively regressed out from the subject's timeseries (see **Supplementary Methods** for more information on pre-processing methods). DVARS excursions were used to quantify patient movement (53) and revealed no statistically significant difference between the two patient groups.

Graph Theory Analyses

Nodes of the functional network were defined as one of 360 non-overlapping parcels from the HCP's MMP. We constructed functional connectivity matrices for each subject by taking the average timeseries of each of the 360 cortical regions from the pre-processed fMRI data. We then computed the Pearson's correlation coefficient for each pair of cortical regions before applying a Fisher-z transformation (**Figure 1A**). We then thresholded all graphs at the same network densities and binarized them to avoid biased graph metric comparisons between patient populations (54–56). Binarization is a very effective method of preserving the most probable functional connections (57, 58). Since there is no universally accepted threshold for functional connectivity strength, we decided to threshold connections within the top 15% by network density for each individual, in steps of 2.5% up to 30% density, to create binary undirected graphs for each density. The graph theory metrics were then averaged across these thresholds for each node (35, 36, 59).

We used the Brain Connectivity Toolbox (60) to calculate the following local graph measures for each patient: clustering coefficient, local efficiency, degree centrality, and betweenness centrality (**Figure 1B**). The *clustering coefficient* (the fraction of connected triangles in a network) measures the degree to which a node's neighbors are connected to each other (60). The *degree centrality* (the number of edges for a specific node) assumes that the importance of a node is related to the number of nodes that it is directly connected to Barabási and Albert (61). The *betweenness centrality* (a centrality measure based on shortest paths) is a measure of how influential a node is as information passes through it to other nodes (62). The *local efficiency* measures the efficiency of information transfer within the local neighborhood of a node (63). These metrics investigate network properties within the local neighborhood of a node and have been the subject of many studies across various chronic pain conditions (25, 34, 59).

Machine Learning Classification

We used a support vector machine (SVM) with a linear kernel as a classifier in this study. The pool of subject data was randomly separated into training and testing sets in a 70/30 ratio, keeping the ratio of patients in each group constant (i.e., the ratio of HC to LBP). The training dataset was used for the feature selection (**Figure 1C**) and model training (**Figure 1D**) phases. The model's performance was tested using the testing dataset (**Figure 1E**). We used the caret and glmnet packages available in RStudio (64, 65) for our machine learning analysis.

Feature Selection

Each cortical parcel was modeled as a node such that 360 features were extracted for each graph theory measure. These features were then used in two different feature selection approaches

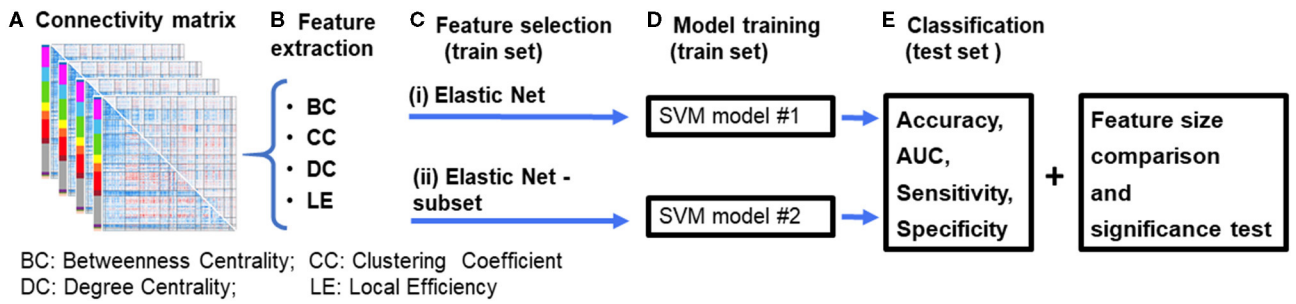


FIGURE 1 | Diagrammatic representation of the data processing pipeline. **(A)** First, resting-state functional connectivity (rsFC) matrices are computed for each subject. **(B)** Graph theory features are then extracted from the connectivity matrices. **(C)** Features were selected using an (i) Elastic Net feature selection method, and (ii) proposed Elastic Net-subset (Elastic Net + optimal subset selection) approach to identify predictive features while reducing feature redundancy. **(D)** Two SVM models were constructed for each of the feature selection approaches. **(E)** Each model's performance (accuracy, AUC, sensitivity, specificity, and the total number of features used in the final model) were computed and then compared between both models. A significance test was performed using a permutation test approach. The whole process was repeated for each feature set and their combinations (for example, BC+CC+DC). BC, Betweenness Centrality; CC, Clustering Coefficient; DC, Degree Centrality; LE, Local Efficiency.

that aimed to remove any redundant features to increase the classifier's performance and lead to better generalization of independent datasets. The first feature selection approach, Elastic Net (Enet), shrinks the coefficients of the input features to zero if they are not positively contributing. Parameter optimization was done by using a grid approach on the predefined penalty parameter $\lambda = \text{seq}\ (0.1, 0.9, \text{by} = 0.1]$ and $\alpha = \text{seq}\ ([0.0001, 0.005, \text{by} = 0.001)$. We were constrained to a small alpha value due to the small number of features that survived (non-zero coefficients). In addition, we chose a small alpha value as increasing it would have led to underfitting the SVM classifier with this dataset. Following this, all the features with non-zero coefficients that form the Enet were used as the input to the SVM classifier (SVM model #1 in **Figure 1D**).

The second feature selection approach**,** Enet-subset, uses the coefficients estimated by Enet. The features were sorted in descending order based on the absolute values of the coefficients (Step #1). The sorted features were then used to build an SVM classifier (model #2, **Figure 1D**). We trained the classifier using a subset starting with the top 25 features, ranked by feature coefficient, with a step size of 25 (Step #2). The best subset of predictors retained in the final model was then determined by the maximum cross-validated AUC. The procedure for the Enet-subset method is summarized below:

Step #1: Sort the absolute value of Enet coefficients in descending order.

Step #2: In a loop,

for, each subset = range [25: the total number of features, step size = 25].

AUC was computed for each subset using an SVM linear classifier and nested 4-fold cross-validation approach.

end

Step #3 The AUC was determined for all subsets, and the best performing subset (out of the subsets tested) was used in the final SVM (model #2, **Figure 1D**).

Model Training and Classification

In the model training phase, features selected using the Enet and Enet-subset methods were used to train two separate SVM models (SVM model #1 and SVM model #2, **Figure 1D**). As before, the features were normalized, and optimal model parameters were fed into each final SVM model. We used a grid-search algorithm to optimize the cost (C) of each SVM classifier. The search scale was set to C = 1:10, and the cost with the highest performance was used in each final model. To generalize the training process and obtain a more accurate model, we used a K-fold ($K = 4$) cross-validation, which was repeated five times. This technique divides data into equal disjointed subsets of size four. The model was then trained on all folds except one. The remaining subset was reserved for testing purposes. This process was then repeated three ($K-1$) times, selecting each fold to be used for testing once. We repeated this process five times to ensure that our trained model acquired most of the patterns from the training dataset.

We evaluated the performance of each SVM model using the test dataset where HCs were classified as positive and LBP as negative for the true positive (TP), false positive (FP), true negative (TN), and false negative (FN) calculations. We determined the corresponding accuracy, sensitivity, and specificity of each model. The accuracy (%) is defined as the fraction of correctly classified subjects {(TP+TN)/(TP+TN+FP+FN)}. Sensitivity is defined as the fraction of correctly classified positive samples from all positive samples {TP/(TP+FN)}. Specificity is defined as the fraction of correctly classified negative samples from all negative samples {TN/(TN+FP)}. We then determined the area under the receiver operating characteristics curve (AUC) to evaluate each model's overall performance.

Statistical Tests

We used an unpaired two-sample Wilcoxon rank-sum test to determine any statistically significant ($p < 0.05$) relationships in graph measures between both patient groups. We corrected for multiple comparisons by using False Discovery Rate Correction with $q < 0.05$.

During the model training phase, the data was randomly divided into testing and training datasets which may produce slightly different models depending on the division. To address

TABLE 2 | ODI scores for each patient group.

Patient group	Mean	Median	Standard deviation
Low back pain	33.3	34.0	15.3
Healthy controls	5.63	6.00	5.60

this, the SVM was run 100 times (**Figures 1C–E**) and the results were averaged to calculate final performance measures. The arithmetic mean of the accuracy, sensitivity, specificity, and AUC of the 100 repetitions was computed for the final analysis.

Statistical significance of the classification accuracy and AUC were tested using permutation testing with 1,000 permutations. For this step, the subject's class (group) was randomly assigned. The resulting accuracy produced a null-hypothesis distribution that was then used to calculate the p-value of the corresponding accuracy (i.e., the fraction of permutations that produced a greater accuracy than the accuracy found for the classification models) (66).

RESULTS

Clinical Survey Data

We used a Wilcoxon rank-sum test to compare the total ODI outcome scores from LBP patients to those from HC (**Table 2**). There was a significant difference ($p = 7.21e\text{-}9$; $z = 5.79$) in the total ODI scores of LBP and HCs. Patients with chronic LBP had a higher total ODI score which was indicative of higher functional disability.

Differences in Graph Metrics Between LBP and HC

Our analysis showed no significant differences in the local efficiency (LE), clustering coefficient (CC), degree centrality (DC), and betweenness centrality (BC) of individual nodes from the reconstructed brain networks between LBP patients and HCs after FDR correction (all $p > 0.05$, see **Supplementary Table 1**). While this may be unexpected, some studies have shown that chronic pain states show no univariate associations with local graph measures (67). A non-significant group difference in a univariate analysis does not necessarily imply a weak feature in a multivariate machine learning analysis approach (68). In fact, a univariate analysis is often less comprehensive than a multivariate model and is unable to show relationships between multiple variables (or parcels) (69, 70). We demonstrate (**Supplementary Figures 1, 2**) that, while not significant, multiple parcels show differences in graph metrics between LBP and HCs. A multivariate approach can use these differences to chart meaningful relationships. In addition, we use feature selection to discard noisy features and reduce the number of features. For these reasons, we used a multivariate approach with an SVM to overcome the shortcomings of univariate analyses.

Machine Learning to Predict LBP

We used the BC, CC, DC, and LE of all 360 parcels to train an SVM to correctly predict each subject's patient group (see section Graph Theory Analyses) and determine the matrix of best performing features for each graph measure. Of the four graph theory matrices used, BC, CC, and DC had very high classification accuracies when used on their own with both feature selection approaches. However, LE proved to have a low classification accuracy with both feature selection approaches. We repeated our analyses to determine if a combination of graph measures led to a higher classification accuracy than a single measure. We then combined the BC, CC, and DC datasets, and compared their predictive power between the two feature selection methods. In all iterations, the performance of the classifier increased when using Enet-subset features (except for LE). We achieved a maximum (mean of 100 iterations) classification accuracy of 83.1% ($p < 0.004$), AUC of 0.94 ($p < 0.002$), sensitivity of 87 % ($p < 0.076$), and a specificity of 79.7% ($p < 0.054$) when using BC, CC, and DC with an Enet-subset feature selection approach. **Table 3** summarizes the overall classification results (see **Supplementary Table 2** for the sensitivity and specificity of each model using each feature selection method).

We saw that the Enet-subset feature selection method was successful in reducing the total number of selected features used in the final models. As a result, the prediction accuracy of the proposed Enet-subset feature selection approach is higher in all instances when compared to using Enet as a baseline (except for LE). This supports our hypothesis that the Enet-subset method performs better at removing redundant features (i.e., fewer noisy features results in a higher model accuracy). This effect is most noticeable when the total number of features used is relatively large (for example, using 360 features from BC vs. using 1,080 features by combining features from BC+CC+DC) while also having the best classifier performance of all the models tested.

Frequently Selected Features

In order to further understand the role of individual parcels in the classification, we identified the top 60 cortical regions (ranked by frequency) of the best performing SVM classifier in which BC, CC, and DC were used as features and Enet-subset was used for feature selection during each iteration. We then sorted the cortical regions according to their frequency of repetition. The top 60 frequently selected cortical regions that contributed to the classification were plotted on a brain mesh surface based on a scale corresponding to their frequency values (**Figure 2**, see **Supplementary Table 3** details on individual areas). In addition, we plotted the top 60 frequently selected cortical regions that contributed to the classification of each individual graph measure (see **Supplementary Figures 3–5** and **Supplementary Tables 4–6** for more details on individual parcels).

We also conducted a Pearson's correlation to determine any correlations between the graph measures of the top 60 frequently selected cortical parcels (**Figure 2** and **Supplementary Table 3**) and the patient's corresponding total

TABLE 3 | A summary (mean of 100 iterations) of the classification accuracy and AUC using the Enet and proposed Enet-subset feature selection methods.

Biomarker(s)	Using all Enet selected features		Using Enet-subset selected features	
	ACC (%), AUC (mean)	Features (mean/total #)	ACC (%), AUC (mean)	Features (mean/total #)
BC	81.7, 0.919	349/360	82.6, 0.920	326/360
CC	81.0, 0.92	349/360	82.3, 0.925	328/360
DC	80.9, 0.898	348/360	81.2, 0.895	324/360
LE	50.8, 0.598	348/360	50.4, 0.590	155/360
BC+CC	81.0, 0.923	679/720	82.5, 0.92	634/720
BC+DC	81.2, 0.907	680/720	83.2, 0.924	636/720
CC+DC	80.8, 0.913	680/720	81.8, 0.921	640/720
BC+CC+DC	80.9, 0.916	1,006/1,080	83.1, 0.937	945/1,080

ACC, Accuracy; AUC, Area under curve; BC, Betweenness centrality; CC, Clustering coefficient; DC, Degree centrality; LE, Local efficiency.

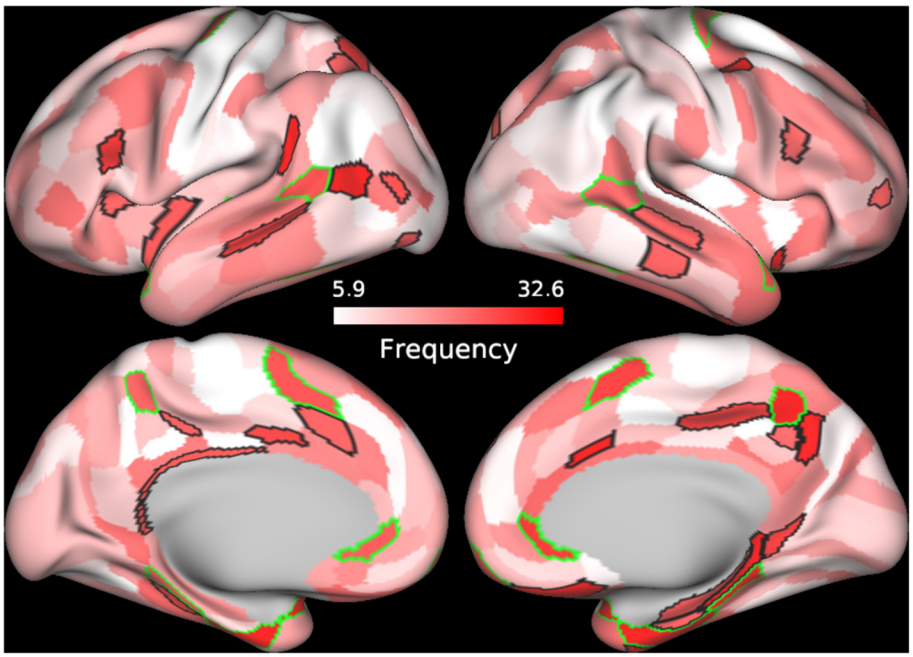


FIGURE 2 | Frequently selected features. The frequency of selection for each cortical feature used to train the SVM model using BC+CC+DC and proposed Enet-subset feature selection method was plotted onto a cortical mesh surface. The top 60 features were selected in all 100 iterations and sorted according to the frequency of its selection during the 100 iterations. Cortical regions outlined in green are bilateral while those outlined in black are unilateral.

ODI scores. However, we did not find any significant correlations between these graph measures and the calculated total ODI scores.

DISCUSSION

The literature has shown that a high level of functional interaction between cortical regions is necessary to cope with the demand of cognitive activities (71–73). We used noninvasive imaging in this study to model these functional interactions and measure network properties. This study builds on our previous work (36) by using graph theory metrics in the classification process to understand a complementary component of cortical changes in the LBP syndrome. The results from this study (1) validate our hypothesis that the use of certain graph measures as a biomarker may lead to the integration of more effective information on pain states like LBP and (2) support the Enet-subset method as a more effective feature selection algorithm for removing redundant variables and improving the classifier's performance. In addition, we found graph measures to be very accurate predictors of patient group irrespective of the feature selection technique used. The success we have seen with the machine learning models supports the notion that groups of cortical regions are more predictive of the patient group than individual cortical regions.

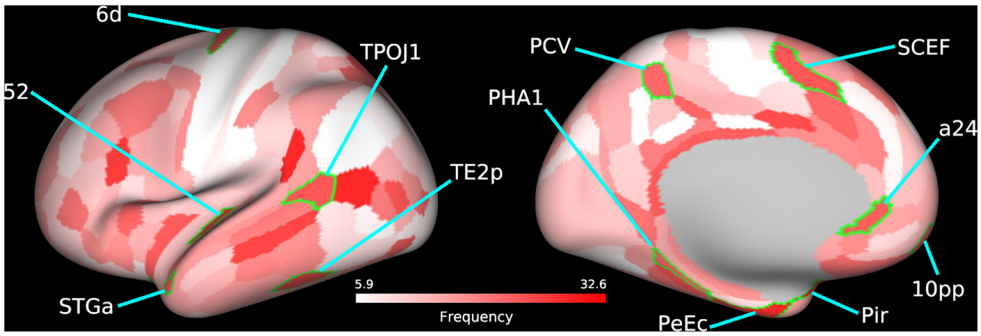


FIGURE 3 | Bilateral frequently selected features. Bilateral cortical regions from the 60 most frequently selected parcels used to train the SVM model using BC+CC+DC and an Enet-subset feature selection method are highlighted on a cortical mesh surface of the left hemisphere. Right hemisphere is not shown. Cortical regions are outlined in green and labeled according to the abbreviations in **Table 4**. Frequency of selection is indicated in red.

TABLE 4 | A summary of the bilateral regions from the top 60 cortical regions, selected for by frequency, that contributed to the classification accuracy of the Enet-subset model when trained using the betweenness centrality, degree centrality, and clustering coefficient graph measures.

Area name	Area description
PCV	Precuneus visual area
SCEF	Supplementary and cingulate eye field
6d	Dorsal area 6
a24	Area a24
10pp	Polar 10p (Orbitofrontal cortex)
52	Area 52 (Parainsular area)
Pir	Pirform cortex (Olfactory)
PeEc	Perirhinal ectorhinal cortex
STGa	Area STGa (auditory)
PHA1	Parahippocampal area 1
TE2p	Area TE2 posterior
TPOJ1	Area TemporoParietoOccipital Junction 1

Predictive Cortical Regions Are Involved in Spatio-Temporal Processing and Its Associated Visual and Motor Coordination

The temporal-parietal-occipital junction (TPOJ), precuneus visual area, supplementary and cingulate eye field (SCEF), parahippocampal area (PHA), and perirhinal cortex are some key bilateral cortical regions (**Figure 3**; **Table 4**; **Supplementary Figure 6**) that were frequently selected as predictive features and are involved in spatial navigation. Spatial navigation is a resource-demanding process that involves determining and maintaining an optimal trajectory to a target based on incoming sensory stimuli from surrounding spatial references (74).

The TPOJ has been implicated in numerous functions (75, 76) such as attentional reorienting between spatial locations (77), timing of visual events (78), visual awareness (79), and the integration of these different sensory inputs (80, 81). The precuneus visual area plays an important role in spatial navigation (82) and spatial processing (83). Previous studies have shown that damage to this part of the parietal cortex leads to deficits in spatial representational (84), simultagnosia (85), and oculomotor apraxia (86), all of which are related to visuospatial processing. These findings suggest that the precuneus may likely be involved with how we interpret external events as painful but not directly involved in the cortical representation of pain (87).

The SCEF is a part of the supplementary motor complex that is associated with the regulation of eye movement (88). The SCEF has anatomical connections to the frontal eye field, superior colliculus, and lateral intraparietal cortex, which puts it in a unique position to regulate goal-directed behavior (89, 90). Dorsal area 6 is a part of the dorsal premotor cortex (DPC), which is also implicated in goal-directed actions involving target object, hand, and eye positioning (91). Inhibiting activity of the DPC using transcranial magnetic stimulation in human patients increases reaction times which supports its role in motor planning (92). These findings are bolstered by the significant increase in functional disability in LBP patients as shown by the differences in ODI scores between both patient groups.

The PHA is a subregion of the ParaHippocampal cortex (PHC) reported to be involved in visuospatial processing (93), including place perception (94), and spatial representation (95, 96). Individuals with lesions to the PHC show impaired visuospatial processing and difficulties with spatial orientation, navigation, and landmark identification (97, 98). Area a24, a part of the anterior cingulate cortex (ACC), has been reported to show vestibular activations (99, 100). In addition, there is growing evidence that spatial memories may become supported by certain extrahippocampal structures over time. The ACC is believed to be one of these structures that stores past spatial memories (101).

The perirhinal cortex adds semantic knowledge to aid in item identification (102). In addition, the perirhinal cortex integrates item information with spatio-temporal information and transmits this data to the hippocampus *via* the entorhinal cortex (103). The temporal area 2 posterior (TE2p) is a newly identified cortical area that lies on the inferior temporal gyrus (43) and may play a role in visual pathways, specifically object recognition.

These bilaterally affected regions are engaged in the coordination of motor control and other sensory processes that facilitate spatial navigation. Studies have shown that physical

self-awareness and perception of one's relative position is impaired in patients with severe chronic LBP (104, 105). Our previous work on this LBP population also found several cortical regions involved in spatial navigation to be predictive of patient group when trained using variations in cortical thickness (36). This evidence compounded by the downstream hand and shoulder motor deficits, as shown by differences in patient ODI scores, further supports the predictive features selected by our model. The identified regions could therefore serve as putative therapeutic biomarkers of functional motor disability.

Feature Selection Using Enet-Subset

Embedded feature selection is a popular feature selection technique, as it incorporates feature selection into the machine learning algorithm (106). The Least Absolute Shrinkage and Selection Operator (LASSO) (107) is a common embedded method used to identify a small number of informative features (108). This is because of its ability to zero the coefficients of non-informative features and assign positive or negative coefficients to more informative features. However, the maximum number of features that LASSO can select is less than the total sample size. As a result, LASSO is an ineffective option when many features are required to train the classifier. We encountered this problem with our dataset when applying LASSO. In many of its iterations (out of 100), LASSO selected very few features even after optimizing the penalty parameter (λ). This led to the underfitting of our models resulting in a poor model performance. For this reason, we did not use LASSO in our final analysis.

We then applied Enet (42), an embedded feature selection method based on a relatively sparse model, to select for significant variables within each graph measure. However, it was apparent that Enet still selected redundant variables. Therefore, the performance of the model could be further improved by removing such variables. This was clearly seen when models trained using features selected by the Enet-subset feature selection method performed better with fewer features than when using Enet. These redundant variables need to be removed to increase the accuracy of the classifier. Redundant variables also lead to overfitting and an increase in calculation load which is computationally expensive. The proposed Enet-subset method further selects for significant variables using the optimal subset selection extension based on the feature's coefficient following Enet. As a result, the Enet-subset method is capable of reducing additional non-informative features. Therefore, the Enet-subset method is effective in reducing model complexity and calculation load with complex neuroimaging data. By using fewer features with the Enet-subset method, we improved the accuracy, AUC, sensitivity, and specificity of all models (see **Table 3** and **Supplementary Table 2**). This would be another useful feature for large neuroimaging datasets.

LIMITATIONS

There are several limitations in this study. We did not explore the cerebellum or subcortical regions, as the HCP's MMP does not parcellate these regions. The subcortical regions of the brain and cerebellum have been shown to play an important role in the coordination and control of movement and balance. Future studies should include these regions of the brain in their analysis for a more comprehensive outlook. In addition, these studies should also investigate the classification accuracy of lesser researched graph metrics such as K-coreness, flow coefficient, and participation coefficient.

Although our study shows that graph measures are of promising clinical value in predicting pain, there are some limitations mainly due to sample size. Therefore, our results should be considered with due caution. A suitable next step would include testing these models with a large sample and using regression models instead of classification models (for example—prediction of clinical pain and emotional measures which would help understand the progression and severity of the pain). It is also important to note that the validation of a biomarker would require testing its efficacy in identifying a disease state in the presence of other disease states. Therefore, future studies should replicate this approach with a sample population that includes other chronic pain states in addition to LBP. It is also important to note that pain is a multidimensional process which involves multiple brain networks interacting with each other. This can present challenges when interpreting the functional role of cortical regions and should be considered with care.

Chronic LBP is a syndrome that presents with numerous etiologies and varying symptomatology. Therefore, our attempts to recruit a homogenous population of subjects without a history of spine surgery were met with difficulty. Finally, some potential pitfalls that could arise from the machine learning methods include incomplete, biased data or noisy datasets and overfitting. These drawbacks could be addressed by recruiting larger matched samples and testing the models on more unseen data.

CONCLUSION

In conclusion, the highly predictive graph theory network approach used to train the classifiers support the notion of brain function alteration in LBP. Our results demonstrate that machine-assisted classification algorithms can accurately classify patients into their respective cohort using graph theory metrics. This supports our hypothesis that these graph measures can be used as a biomarker of LBP. Our results also show that an Enet-subset feature selection method is more effective when improving a model's performance.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because, per the guidelines of the Institutional Review Board, they cannot be shared with individuals not included as research members on the project. Requests to access the datasets should be directed to Dinal Jayasekera, dinal.jayasekera@wustl.edu.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Washington University in St. Louis Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

BL and DJ: conceptualization, data collection, methodology, investigation, data analysis, visualization, and writing original draft. AH: conceptualization, data curation, funding acquisition, supervision, resources, and software. RJ: data analysis and writing original draft. WR and EL: supervision. All authors provided validation and helped with reviewing and editing the manuscript.

FUNDING

This work was supported by the Cervical Spine Research Society, Neurosurgery Research and Education Foundation and the Barnes-Jewish Hospital Foundation.

ACKNOWLEDGMENTS

The authors would like to thank Timothy Coalson, Dr. Matthew Glasser, and Dr. David Van Essen for their support with setting up and troubleshooting the HCP's pre-processing pipeline and Connectome Workbench. The authors are also very appreciative of Derayvia Grimes, Tyler Frank, Linda Hood, and Glenn Foster, for their help with collecting the MRI and fMRI data.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.669076/full#supplementary-material

REFERENCES

1. Andersson GBJ. Epidemiological features of chronic low-back pain. *Lancet.* (1999) 354:581–5. doi: 10.1016/S0140-6736(99)01312-4
2. Katz JN. Lumbar disc disorders and low-back pain: socioeconomic factors and consequences. *JBJS.* (2006) 88:21–4. doi: 10.2106/00004623-200604002-00005
3. Last AR, Hulbert K. Chronic low back pain: evaluation and management. *Am Fam Physician.* (2009) 79:1067–74. doi: 10.1080/20786204.2010.10873969
4. Rubinstein SM, van Tulder M. A best-evidence review of diagnostic procedures for neck and low-back pain. *Best Pract Res Clin Rheumatol.* (2008) 22:471–82. doi: 10.1016/j.berh.2007.12.003
5. Boisson M, Borderie D, Henrotin Y, Teboul-Coré S, Lefèvre-Colau M-M, Rannou F, et al. Serum biomarkers in people with chronic low back pain and Modic 1 changes: a case-control study. *Sci Rep.* (2019) 9:1–5. doi: 10.1038/s41598-019-46508-x
6. Allegri M, De Gregori M, Minella CE, Klersy C, Wang W, Sim M, et al. 'Omics' biomarkers associated with chronic low back pain: protocol of a retrospective longitudinal study. *BMJ Open.* (2016) 6:e012070. doi: 10.1136/bmjopen-2016-012070
7. Morris P, Ali K, Merritt M, Pelletier J, Macedo LG. A systematic review of the role of inflammatory biomarkers in acute, subacute and chronic non-specific low back pain. *BMC Musculoskelet Disord.* (2020) 21:1–12. doi: 10.1186/s12891-020-3154-3
8. Davis KD, Aghaeepour N, Ahn AH, Angst MS, Borsook D, Brenton A, et al. Discovery and validation of biomarkers to aid the development of safe and effective pain therapeutics: challenges and opportunities. *Nat Rev Neurol.* (2020) 16:381–400. doi: 10.1038/s41582-020-0362-2
9. Worsley KJ, Friston KJ. Analysis of fMRI time-series revisited–again. *Neuroimage.* (1995) 2:173–81. doi: 10.1006/nimg.1995.1023
10. Heeger DJ, Ress D. What does fMRI tell us about neuronal activity? *Nat Rev Neurosci.* (2002) 3:142–51. doi: 10.1038/nrn730
11. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. *Proc Natl Acad Sci U S A.* (2001) 98:676–82. doi: 10.1073/pnas.98.2.676
12. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat Rev Neurosci.* (2007) 8:700–11. doi: 10.1038/nrn2201
13. Shen HH. Core concept: Resting-state connectivity. *Proc Natl Acad Sci U S A.* (2015) 112:14115–6. doi: 10.1073/pnas.1518785112
14. Logothetis NK. What we can do and what we cannot do with fMRI. *Nature.* (2008) 453:869–78. doi: 10.1038/nature06976
15. Lee MH, Smyser CD, Shimony JS. Resting-state fMRI: a review of methods and clinical applications. *Am J Neuroradiol.* (2013) 34:1866–72. doi: 10.3174/ajnr.A3263
16. Hohenfeld C, Werner CJ, Reetz K. Resting-state connectivity in neurodegenerative disorders: is there potential for an imaging biomarker? *NeuroImage Clin.* (2018) 18:849–70. doi: 10.1016/j.nicl.2018.03.013
17. Aertsen AM, Gerstein GL, Habib MK, Palm G. Dynamics of neuronal firing correlation: modulation of "effective connectivity". *J Neurophysiol.* (1989) 61:900–17. doi: 10.1152/jn.1989.61.5.900
18. Friston KJ, Frith CD, Liddle PF, Frackowiak RSJ. Functional connectivity: the principal-component analysis of large (PET) data sets. *J Cereb Blood Flow Metab.* (1993) 13:5–14. doi: 10.1038/jcbfm.1993.4
19. Ji JL, Spronk M, Kulkarni K, Repovš G, Anticevic A, Cole MW. Mapping the human brain's cortical-subcortical functional network organization. *Neuroimage.* (2019) 185:35–57. doi: 10.1016/j.neuroimage.2018.10.006
20. Van Den Heuvel MP, Pol HEH. Exploring the brain network: a review on resting-state fMRI functional connectivity. *Eur Neuropsychopharmacol.* (2010) 20:519–34. doi: 10.1016/j.euroneuro.2010.03.008
21. Sluka KA, Clauw DJ. Neurobiology of fibromyalgia and chronic widespread pain. *Neuroscience.* (2016) 338:114–29. doi: 10.1016/j.neuroscience.2016.06.006
22. Balenzuela P, Chernomoretz A, Fraiman D, Cifre I, Sitges C, Montoya P, et al. Modular organization of brain resting state networks in chronic back pain patients. *Front Neuroinform.* (2010) 4:116. doi: 10.3389/fninf.2010.00116
23. Liu J, Zhao L, Li G, Xiong S, Nan J, Li J, et al. Hierarchical alteration of brain structural and functional networks in female migraine sufferers. *PLoS One.* (2012) 7:e051250. doi: 10.1371/journal.pone.0051250
24. De Pauw R, Aerts H, Siugzdaite R, Meeus M, Coppieters I, Caeyenberghs K, et al. Hub disruption in patients with chronic neck pain: a graph analytical approach. *Pain.* (2020) 161:729–41. doi: 10.1097/j.pain.0000000000001762
25. Mansour A, Baria AT, Tetreault P, Vachon-Presseau E, Chang P-CC, Huang L, et al. Global disruption of degree rank order: a hallmark of chronic pain. *Sci Rep.* (2016) 6:34853. doi: 10.1038/srep34853
26. Shen W, Tu Y, Gollub RL, Ortiz A, Napadow V, Yu S, et al. Visual network alterations in brain functional connectivity in chronic low back pain: A resting state functional connectivity and machine learning study. *Neuroimage Clin.* (2019) 22:101775. doi: 10.1016/j.nicl.2019.101775
27. Yu R, Gollub RL, Spaeth R, Napadow V, Wasan A, Kong J. Disrupted functional connectivity of the periaqueductal gray in chronic low back pain. *Neuroimage Clin.* (2014) 6:100–8. doi: 10.1016/j.nicl.2014.08.019
28. Tu Y, Jung M, Gollub RL, Napadow V, Gerber J, Ortiz A, et al. Abnormal medial prefrontal cortex functional connectivity and its association with clinical symptoms in chronic low back pain. *Pain.* (2019) 160:1308–18. doi: 10.1097/j.pain.0000000000001507
29. Farmer MA, Baliki MN, Apkarian AV. A dynamic network perspective of chronic pain. *Neurosci Lett.* (2012) 520:197–203. doi: 10.1016/j.neulet.2012.05.001
30. Kucyi A, Davis KD. The dynamic pain connectome. *Trends Neurosci.* (2015) 38:86–95. doi: 10.1016/j.tins.2014.11.006

31. Wager TD, Atlas LY, Lindquist MA, Roy M, Woo C-W, Kross E. An fMRI-based neurologic signature of physical pain. *N Engl J Med.* (2013) 368:1388–97. doi: 10.1056/NEJMoa1204471
32. Apkarian AV. The brain in chronic pain: clinical implications. *Pain Manag.* (2011) 1:577–86. doi: 10.2217/pmt.11.53
33. Wang Y, Nelissen N, Adamczuk K, De Weer A-S, Vandenbulcke M, Sunaert S, et al. Reproducibility and robustness of graph measures of the associative-semantic network. *PLoS One.* (2014) 9:e115215. doi: 10.1371/journal.pone.0115215
34. Hashmi JA, Kong J, Spaeth R, Khan S, Kaptchuk TJ, Gollub RL. Functional network architecture predicts psychologically mediated analgesia related to treatment in chronic knee pain patients. *J Neurosci.* (2014) 34:3924–36. doi: 10.1523/JNEUROSCI.3155-13.2014
35. Kaplan CM, Schrepf A, Vatansever D, Larkin TE, Mawla I, Ichesco E, et al. Functional and neurochemical disruptions of brain hub topology in chronic pain. *Pain.* (2019) 160:973. doi: 10.1097/j.pain.0000000000001480
36. Lamichhane B, Jayasekera D, Jakes R, Glasser MF, Zhang J, Yang C, et al. Multi-modal biomarkers of low back pain: a machine learning approach. *NeuroImage Clin.* (2021) 29:102530. doi: 10.1016/j.nicl.2020.102530
37. Tu Y, Ortiz A, Gollub RL, Cao J, Gerber J, Lang C, et al. Multivariate resting-state functional connectivity predicts responses to real and sham acupuncture treatment in chronic low back pain. *Neuroimage Clin.* (2019) 23:101885. doi: 10.1016/j.nicl.2019.101885
38. Zeng L-L, Shen H, Liu L, Wang L, Li B, Fang P, et al. Identifying major depression using whole-brain functional connectivity: a multivariate pattern analysis. *Brain.* (2012) 135:1498–507. doi: 10.1093/brain/aws059
39. Vergun S, Deshpande A, Meier TB, Song J, Tudorascu DL, Nair VA, et al. Characterizing functional connectivity differences in aging adults using machine learning on resting state fMRI data. *Front Comput Neurosci.* (2013) 7:38. doi: 10.3389/fncom.2013.00038
40. Fair D, Nigg JT, Iyer S, Bathula D, Mills KL, Dosenbach NUF, et al. Distinct neural signatures detected for ADHD subtypes after controlling for micro-movements in resting state functional connectivity MRI data. *Front Syst Neurosci.* (2013) 6:80. doi: 10.3389/fnsys.2012.00080
41. Dash M, Liu H. Feature selection for classification. *Intell Data Anal.* (1997) 1:131–56. doi: 10.3233/IDA-1997-1302
42. Zou H, Hastie T. Regularization and variable selection *via* the elastic net. *J R Stat Soc Ser B.* (2005) 67:301–20. doi: 10.1111/j.1467-9868.2005.00503.x
43. Glasser MF, Coalson TS, Robinson EC, Hacker CD, Harwell J, Yacoub E, et al. A multi-modal parcellation of human cerebral cortex. *Nature.* (2016) 536:171–8. doi: 10.1038/nature18933
44. Fairbank JCT, Pynsent PB. The Oswestry disability index. *Spine.* (2000) 25:2940–53. doi: 10.1097/00007632-200011150-00017
45. Fairbank JC, Couper J, Davies JB, O'Brien JP. The Oswestry low back pain disability questionnaire. *Physiotherapy.* (1980) 66:271–3. doi: 10.1037/t04205-000
46. Yates M, Shastri-Hurst N. The oswestry disability index. *Occup Med.* (2017) 67:241–2. doi: 10.1093/occmed/kqw051
47. Tisdall MD, Hess AT, Reuter M, Meintjes EM, Fischl B, van der Kouwe AJW. Volumetric navigators for prospective motion correction and selective reacquisition in neuroanatomical MRI. *Magn Reson Med.* (2012) 68:389–99. doi: 10.1002/mrm.23228
48. Glasser MF, Smith SM, Marcus DS, Andersson JLR, Auerbach EJ, Behrens TEJ, et al. The human connectome project's neuroimaging approach. *Nat Neurosci.* (2016) 19:1175. doi: 10.1038/nn.4361
49. Glasser MF, Sotiropoulos SN, Wilson JA, Coalson TS, Fischl B, Andersson JL, et al. The minimal preprocessing pipelines for the Human Connectome Project. *Neuroimage.* (2013) 80:105–24. doi: 10.1016/j.neuroimage.2013.04.127
50. Glasser MF, Coalson TS, Bijsterbosch JD, Harrison SJ, Harms MP, Anticevic A, et al. Using temporal ICA to selectively remove global noise while preserving global signal in functional MRI data. *Neuroimage.* (2018) 181:692–717. doi: 10.1016/j.neuroimage.2018.04.076
51. Robinson EC, Garcia K, Glasser MF, Chen Z, Coalson TS, Makropoulos A, et al. Multimodal surface matching with higher-order smoothness constraints. *Neuroimage.* (2018) 167:453–65. doi: 10.1016/j.neuroimage.2017.10.037
52. Glasser MF, Coalson TS, Bijsterbosch JD, Harrison SJ, Harms MP, Anticevic A, et al. Classification of temporal ICA components for separating global noise from fMRI data: reply to Power. *Neuroimage.* (2019) 197:435–8. doi: 10.1016/j.neuroimage.2019.04.046
53. Afyouni S, Nichols TE. Insight and inference for DVARS. *Neuroimage.* (2018) 172:291–312. doi: 10.1016/j.neuroimage.2017.12.098
54. Ginestet CE, Nichols TE, Bullmore T, Simmons A. Brain network analysis: separating cost from topology using cost-integration. *PLoS One.* (2011) 6:e021570. doi: 10.1371/journal.pone.0021570
55. Schwarz AJ, McGonigle J. Negative edges and soft thresholding in complex network analysis of resting state functional connectivity data. *Neuroimage.* (2011) 55:1132–46. doi: 10.1016/j.neuroimage.2010.12.047
56. Bassett DS, Nelson BG, Mueller BA, Camchong J, Lim KO. Altered resting state complexity in schizophrenia. *Neuroimage.* (2012) 59:2196–207. doi: 10.1016/j.neuroimage.2011.10.002
57. Achard S, Bullmore E. Efficiency and cost of economical brain functional networks. *PLoS Comput Biol.* (2007) 3:e17. doi: 10.1371/journal.pcbi.0030017
58. Supekar K, Menon V, Rubin D, Musen M, Greicius MD. Network analysis of intrinsic functional brain connectivity in Alzheimer's disease. *PLoS Comput Biol.* (2008) 4:e1000100. doi: 10.1371/journal.pcbi.1000100
59. Achard S, Delon-Martin C, Vértes PE, Renard F, Schenck M, Schneider F, et al. Hubs of brain functional networks are radically reorganized in comatose patients. *Proc Natl Acad Sci U S A.* (2012) 109:20608–13. doi: 10.1073/pnas.1208933109
60. Rubinov M, Sporns O. Complex network measures of brain connectivity: uses and interpretations. *Neuroimage.* (2010) 52:1059–69. doi: 10.1016/j.neuroimage.2009.10.003
61. Barabási A-L, Albert R. Emergence of scaling in random networks. *Science.* (1999) 286:509–12. doi: 10.1126/science.286.5439.509
62. Barthelemy M. Betweenness centrality in large complex networks. *Eur Phys J B.* (2004) 38:163–8. doi: 10.1140/epjb/e2004-00111-4
63. Latora V, Marchiori M. Economic small-world behavior in weighted networks. *Eur Phys J B.* (2003) 32:249–63. doi: 10.1140/epjb/e2003-00095-5
64. Kuhn M. Building predictive models in R using the caret package. *J Stat Softw.* (2008) 28:1–26. doi: 10.18637/jss.v028.i05
65. Friedman J, Hastie T, Tibshirani R. Regularization paths for generalized linear models *via* coordinate descent. *J Stat Softw.* (2010) 33:1. doi: 10.18637/jss.v033.i01
66. Frick A, Gingnell M, Marquand AF, Howner K, Fischer H, Kristiansson M, et al. Classifying social anxiety disorder using multivoxel pattern analyses of brain function and structure. *Behav Brain Res.* (2014) 259:330–5. doi: 10.1016/j.bbr.2013.11.003
67. Kano M, Grinsvall C, Ran Q, Dupont P, Morishita J, Muratsubaki T, et al. Resting state functional connectivity of the pain matrix and default mode network in irritable bowel syndrome: a graph theoretical analysis. *Sci Rep.* (2020) 10:11015. doi: 10.1038/s41598-020-67048-9
68. Arbabshirani MR, Plis S, Sui J, Calhoun VD. Single subject prediction of brain disorders in neuroimaging: promises and pitfalls. *Neuroimage.* (2017) 145:137–65. doi: 10.1016/j.neuroimage.2016.02.079
69. Mahajan BK, Lal S. Methods in biostatistics for medical students and research workers. *Indian J Community Med.* (1999) 24:140.
70. Dawson-Saunders B. Basic & clinical biostatistics. *ALANGE Med B. 2nd edn*, (1994) 42–161.
71. Hertzog C, Kramer AF, Wilson RS, Lindenberger U. Enrichment effects on adult cognitive development: can the functional capacity of older adults be preserved and enhanced? *Psychol Sci Public Interest.* (2008) 9:1–65. doi: 10.1111/j.1539-6053.2009.01034.x
72. Egner T, Hirsch J. The neural correlates and functional integration of cognitive control in a Stroop task. *Neuroimage.* (2005) 24:539–47. doi: 10.1016/j.neuroimage.2004.09.007
73. Horwitz B, Tagamets MA, McIntosh AR. Neural modeling, functional brain imaging, and cognition. *Trends Cogn Sci.* (1999) 3:91–8. doi: 10.1016/S1364-6613(99)01282-6
74. Coughlan G, Laczó J, Hort J, Minihane A-M, Hornberger M. Spatial navigation deficits-overlooked cognitive marker for preclinical Alzheimer disease? *Nat Rev Neurol.* (2018) 14:496–506. doi: 10.1038/s41582-018-0031-x

75. Bzdok D, Langner R, Schilbach L, Jakobs O, Roski C, Caspers S, et al. Characterization of the temporo-parietal junction by combining data-driven parcellation, complementary connectivity analyses, and functional decoding. *Neuroimage.* (2013) 81:381–92. doi: 10.1016/j.neuroimage.2013.05.046
76. Carter RM, Huettel SA. A nexus model of the temporal-parietal junction. *Trends Cogn Sci.* (2013) 17:328–36. doi: 10.1016/j.tics.2013.05.007
77. Corbetta M, Patel G, Shulman GL. The reorienting system of the human brain: from environment to theory of mind. *Neuron.* (2008) 58:306–24. doi: 10.1016/j.neuron.2008.04.017
78. Battelli L, Pascual-Leone A, Cavanagh P. The 'when'pathway of the right parietal lobe. *Trends Cogn Sci.* (2007) 11:204–10. doi: 10.1016/j.tics.2007.03.001
79. Webb TW, Igelström KM, Schurger A, Graziano MSA. Cortical networks involved in visual awareness independent of visual attention. *Proc Natl Acad Sci U S A.* (2016) 113:13923–28. doi: 10.1073/pnas.1611505113
80. Mars RB, Sallet J, Schüffelgen U, Jbabdi S, Toni I, Rushworth MFS. Connectivity-based subdivisions of the human right "temporoparietal junction area": evidence for different areas participating in different cortical networks. *Cereb Cortex.* (2012) 22:1894–903. doi: 10.1093/cercor/bhr268
81. Nieuwenhuys R, Voogd J, Van Huijzen C. *The Human Central Nervous System: A Synopsis and Atlas*. Berlin: Springer Science & Business Media (2007).
82. Marchette SA, Vass LK, Ryan J, Epstein RA. Anchoring the neural compass: coding of local spatial reference frames in human medial parietal lobe. *Nat Neurosci.* (2014) 17:1598. doi: 10.1038/nn.3834
83. Burgess NE, Jeffery KJ, O'Keefe JE. *The Hippocampal and Parietal Foundations of Spatial Cognition*. Oxford: Oxford University Press (1999).
84. Frings L, Wagner K, Quiske A, Schwarzwald R, Spreer J, Halsband U, et al. Precuneus is involved in allocentric spatial location encoding and recognition. *Exp Brain Res.* (2006) 173:661–72. doi: 10.1007/s00221-006-0408-8
85. Coslett HB, Saffran E. Simultanagnosia. To see but not two see. *Brain.* (1991) 114(Pt 4:1523–45. doi: 10.1093/brain/114.4.1523
86. Cavanna AE, Trimble MR. The precuneus: a review of its functional anatomy and behavioural correlates. *Brain.* (2006) 129:564–83. doi: 10.1093/brain/awl004
87. Goffaux P, Girard-Tremblay L, Marchand S, Daigle K, Whittingstall K. Individual differences in pain sensitivity vary as a function of precuneus reactivity. *Brain Topogr.* (2014) 27:366–74. doi: 10.1007/s10548-013-0291-0
88. Nachev P, Kennard C, Husain M. Functional role of the supplementary and pre-supplementary motor areas. *Nat Rev Neurosci.* (2008) 9:856–69. doi: 10.1038/nrn2478
89. Stuphorn V. The role of supplementary eye field in goal-directed behavior. *J Physiol.* (2015) 109:118–28. doi: 10.1016/j.jphysparis.2015.02.002
90. Stuphorn V, Schall JD. Executive control of countermanding saccades by the supplementary eye field. *Nat Neurosci.* (2006) 9:925–31. doi: 10.1038/nn1714
91. Pesaran B, Nelson MJ, Andersen RA. Dorsal premotor neurons encode the relative position of the hand, eye, and goal during reach planning. *Neuron.* (2006) 51:125–34. doi: 10.1016/j.neuron.2006.05.025
92. Schluter ND, Rushworth MF, Passingham RE, Mills KR. Temporary interference in human lateral premotor cortex suggests dominance for the selection of movements. A study using transcranial magnetic stimulation. *Brain.* (1998) 121:785–99. doi: 10.1093/brain/121.5.785
93. Aminoff EM, Kveraga K, Bar M. The role of the parahippocampal cortex in cognition. *Trends Cogn Sci.* (2013) 17:379–90. doi: 10.1016/j.tics.2013.06.009
94. Epstein R, Kanwisher N. A cortical representation of the local visual environment. *Nature.* (1998) 392:598–601. doi: 10.1038/33402
95. Mullally SL, Maguire EA. A new role for the parahippocampal cortex in representing space. *J Neurosci.* (2011) 31:7441–9. doi: 10.1523/JNEUROSCI.0267-11.2011
96. Kravitz DJ, Peng CS, Baker CI. Real-world scene representations in high-level visual cortex: it's the spaces more than the places. *J Neurosci.* (2011) 31:7322–33. doi: 10.1523/JNEUROSCI.4588-10.2011
97. Aguirre GK, D'Esposito M. Topographical disorientation: a synthesis and taxonomy. *Brain.* (1999) 122(Pt 9):1613–28. doi: 10.1093/brain/122.9.1613
98. Ploner CJ, Gaymard BM, Rivaud-Péchoux S, Baulac M, Clémenceau S, Samson S, et al. Lesions affecting the parahippocampal cortex yield spatial memory deficits in humans. *Cereb Cortex.* (2000) 10:1211–6. doi: 10.1093/cercor/10.12.1211
99. Bottini G, Sterzi R, Paulesu E, Vallar G, Cappa SF, Erminio F, et al. Identification of the central vestibular projections in man: a positron emission tomography activation study. *Exp Brain Res.* (1994) 99:164–9. doi: 10.1007/BF00241421
100. Dieterich M, Bense S, Lutz S, Drzezga A, Stephan T, Bartenstein P, et al. Dominance for vestibular cortical function in the non-dominant hemisphere. *Cereb Cortex.* (2003) 13:994–1007. doi: 10.1093/cercor/13.9.994
101. Frankland PW, Bontempi B. The organization of recent and remote memories. *Nat Rev Neurosci.* (2005) 6:119–30. doi: 10.1038/nrn1607
102. Baker CM, Burks JD, Briggs RG, Milton CK, Conner AK, Glenn CA, et al. A connectomic atlas of the human cerebrum-chapter 6: the temporal lobe. *Oper Neurosurg.* (2018) 15:S245–S94. doi: 10.1093/ons/opy260
103. Naya Y. Declarative association in the perirhinal cortex. *Neurosci Res.* (2016) 113:12–8. doi: 10.1016/j.neures.2016.07.001
104. Gill KP, Callaghan MJ. The measurement of lumbar proprioception in individuals with and without low back pain. *Spine.* (1998) 23:371–7. doi: 10.1097/00007632-199802010-00017
105. Lee AS, Cholewicki J, Reeves NP, Zazulak BT, Mysliwiec LW. Comparison of trunk proprioception between patients with low back pain and healthy controls. *Arch Phys Med Rehabil.* (2010) 91:1327–31. doi: 10.1016/j.apmr.2010.06.004
106. Fonti V, Belitser E. Feature selection using lasso. *VU Amsterdam Res Pap Bus Anal.* (2017) 30:1–25.
107. Meinshausen N, Bühlmann P. High-dimensional graphs and variable selection with the lasso. *Ann Stat.* (2006) 34:1436–62. doi: 10.1214/009053606000000281
108. Liu L, Zhang H, Wu J, Yu Z, Chen X, Rekik I, et al. Overall survival time prediction for high-grade glioma patients based on large-scale brain functional networks. *Brain Imaging Behav.* (2019) 13:1333–51. doi: 10.1007/s11682-018-9949-2

Disclaimer: The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2021 Lamichhane, Jayasekera, Jakes, Ray, Leuthardt and Hawasli. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Neurology

ORIGINAL RESEARCH
published: 03 August 2021
doi: 10.3389/fneur.2021.694310

Modulation of the Somatosensory Evoked Potential by Attention and Spinal Cord Stimulation

Guiomar Niso[1,2,3], *Marleen C. Tjepkema-Cloostermans*[4,5], *Mathieu W. P. M. Lenders*[4] *and Cecile C. de Vos*[1,4,6]*

[1] McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal, QC, Canada, [2] Psychological & Brain Sciences, Indiana University, Bloomington, IN, United States, [3] ETSI Telecomunicación, Universidad Politécnica de Madrid and Center for Biomedical Research Network CIBER-BBN, Madrid, Spain, [4] Department of Neurology and Neurosurgery, Medisch Spectrum Twente, Enschede, Netherlands, [5] Department of Clinical Neurophysiology, Institute for Technical Medicine, University of Twente, Enschede, Netherlands, [6] Center for Pain Medicine, Erasmus University Medical Center, Rotterdam, Netherlands

OPEN ACCESS

Edited by:
Marie-Eve Hoeppli,
Cincinnati Children's Hospital Medical Center, United States

Reviewed by:
Lucas Trambaiolli,
McLean Hospital, United States
Yann Quidé,
University of New South Wales, Australia

***Correspondence:**
Cecile C. de Vos
c.devos@erasmusmc.nl

Specialty section:
This article was submitted to Applied Neuroimaging, a section of the journal Frontiers in Neurology

Received: 12 April 2021
Accepted: 07 July 2021
Published: 03 August 2021

Citation:
Niso G, Tjepkema-Cloostermans MC, Lenders MWPM and de Vos CC (2021) Modulation of the Somatosensory Evoked Potential by Attention and Spinal Cord Stimulation. Front. Neurol. 12:694310. doi: 10.3389/fneur.2021.694310

Introduction: Spinal Cord Stimulation (SCS) is a last-resort treatment for patients with intractable chronic pain in whom pharmacological and other treatments have failed. Conventional tonic SCS is accompanied by tingling sensations. More recent stimulation protocols like burst SCS are not sensed by the patient while providing similar levels of pain relief. It has been previously reported that conventional tonic SCS can attenuate sensory-discriminative processing in several brain areas, but that burst SCS might have additional effects on the medial, motivational-affective pain system. In this explorative study we assessed the influence of attention on the somatosensory evoked brain responses under conventional tonic SCS as well as burst SCS regime.

Methods: Twelve chronic pain patients with an implanted SCS device had 2-weeks evaluation periods with three different SCS settings (conventional tonic SCS, burst SCS, and sham SCS). At the end of each period, an electro-encephalography (EEG) measurement was done, at which patients received transcutaneous electrical pulses at the tibial nerve to induce somatosensory evoked potentials (SEP). SEP data was acquired while patients were attending the applied pulses and while they were mind wandering. The effects of attention as well as SCS regimes on the SEP were analyzed by comparing amplitudes of early and late latencies at the vertex as well as brain activity at full cortical maps.

Results: Pain relief obtained by the various SCS settings varied largely among patients. Early SEP responses were not significantly affected by attention nor SCS settings (i.e., burst, tonic, and sham). However, late SEP responses (P300) were reduced with tonic and burst SCS: conventional tonic SCS reduced P300 brain activity in the unattended condition, while burst SCS reduced P300 brain activity in both attended and unattended conditions.

Conclusion: Burst spinal cord stimulation for the treatment of chronic pain seems to reduce cortical attention that is or can be directed to somatosensory stimuli to a

larger extent than conventional spinal cord stimulation treatment. This is a first step in understanding why in selected chronic pain patients burst SCS is more effective than tonic SCS and how neuroimaging could assist in personalizing SCS treatment.

Keywords: spinal cord stimulation, somatosensory evoked potential, neuromodulation, electro-encephalography, chronic pain, burst stimulation, attention

INTRODUCTION

Spinal Cord Stimulation (SCS) is a last-resort treatment for patients with intractable neuropathic pain in whom pharmacological and other treatments have failed. SCS is based on electrical stimulation of the nerve fibers in the spinal cord dorsal column (A-beta fibers) by an implanted electrode that is connected to an implanted pulse generator. Pain reduction occurs in the body area corresponding to the stimulated spinal segments. Conventional tonic SCS (i.e., single electrical pulses, given with a frequency of 30–120 Hz) is accompanied by tingling sensations (paresthesia). More recently developed stimulation protocols like burst stimulation (i.e., five pulses with intraburst frequency of 500 Hz, given with a frequency of 40 Hz) and other high-frequency stimulations (up to 10 kHz) are paresthesia-free while providing similar levels of pain relief (1–4). Although the absence of sensations is not necessarily preferred by all patients, it is an important improvement for research as it enables double-blind studies of SCS efficacy and mechanisms.

In addition to spinal action (5, 6) cerebral mechanisms are likely to contribute to the pain relieving effects of SCS (7–9), but this has not been thoroughly investigated yet. It has been suggested that tonic SCS normalizes thalamocortical dysrhythmia and overactivation (in the theta and low beta frequency range) in several pain processing cortical areas (10). In line with this hypothesis, a functional magnetic resonance imaging (fMRI) study indicated that conventional tonic SCS decreased connectivity between the thalamus and pain processing brain regions like the cingulate cortex, insula and sensorimotor cortex (11).

Burst SCS might even have effects on cortical regions outside the pain processing network: a resting state electro-encephalography (EEG) study in five patients who were trialing SCS, showed that compared with conventional tonic SCS, burst SCS led to increased synchronized alpha activity in the cingulate cortex and dorsolateral prefrontal cortex as well as behaviorally decreased attention to the pain. It was suggested that the analgesic effects of burst SCS are obtained by modulating both the lateral discriminatory and medial affective/attentional pain pathways (12). After a more thorough analysis of the data it was concluded that both tonic and burst SCS modulate the descending pain inhibitory system and the lateral pain pathway, but that burst SCS in addition modulates the activity in medial affective/attentional pain pathway (13).

One of the consequences of these findings reported by De Ridder et al. is that if reduction of cortical attention to pain is one of the working mechanisms of burst stimulation, burst might not only cause alterations in resting state activity, but also influences the capacity for attending and processing peripheral somatosensory input. In the present explorative study, we assessed the influence of attention on somatosensory evoked brain responses under conventional tonic SCS as well as burst SCS regime.

It has been previously reported that conventional tonic SCS can attenuate the somatosensory processing in SI, SII and the cingulate cortex [e.g., (8, 14–18)]. We expect that burst SCS will not only reduce the somatosensory evoked activity, but that it will also attenuate activity that is associated with attention to pain and that it will do that to a greater extent than conventional tonic SCS treatment. Insight in the various working mechanisms of action of burst SCS and other new SCS regimes will assist with better treatment selection, personalized SCS settings and optimized pain reduction for chronic pain patients.

MATERIALS AND METHODS

Subjects

Twelve chronic pain patients (6 men, 6 women), on average 57 years old, all with Failed Back Surgery Syndrome (FBSS) and pain in their low back as well as one or two legs participated in this study. Those 12 patients also participated in the larger Burst evaluation study described in a previous publication (19). The Burst evaluation study was designed to study the effects of burst SCS on the perceived pain and quality of life in 40 patients who were already familiar with spinal cord stimulation. The EEG measurements were an optional addition to this larger study and about one third of the chronic pain patients volunteered to undergo the three additional EEG recording sessions. The study conformed to the Declaration of Helsinki and received approval from the Twente Ethics Committee. Written informed consent was obtained from 12 patients to additionally participate in the EEG measurements. The study was registered in the Netherlands clinical trial register (www.trialregister.nl, NTR 4479).

All 12 participating patients had three EEG recording sessions between August 2014 and March 2015 (**Table 1**). Ten patients were using analgesic medication (either co-analgesic medication like antidepressants and anti-epileptic drugs, or opioids, or a combination of those) but did not change their medication intake during the study. All received adjuvant treatment for their pain with conventional tonic SCS (Eon stimulator, St Jude Medical, Plano, TX, USA) for on average 2.7 years. Before they received their stimulator they already had pain for on average 11 years, but this varied largely over the participants, from 1 up to 35 years. In the year(s) prior to the present study, stimulation settings had been optimized for each individual patient. Perceived pain was scored by the patients on a visual analog scale (VAS) ranging from 0 (no pain at all) to 100 (worst pain imaginable). Prior to implantation of their SCS system, the patients had an

TABLE 1 | Participants' demographics and their responses to the three different spinal cord stimulation (SCS) regimes: tonic SCS, sham SCS, and burst SCS.

#	Sex	Age (y)	Most affected side	Pain prior to SCS (y)	Duration SCS (y)	Pain prior to SCS (VAS)	Pain tonic SCS (VAS)	Pain sham SCS (VAS)	Pain burst SCS (VAS)	Preference
1	M	45	Left	3	0.5	80	90	71	65	Burst
2	M	55	Right	4	3	80	67	54	30	Burst
3	F	46	Left	17	2.5	90	67	60	40	Burst
4	F	45	Left	1	3	80	85	52	46	Burst
5	M	61	Right	4	1.5	80	55	51	49	Tonic
6	F	41	Left	18	2.5	80	67	67	79	Tonic
7	M	64	Right	3.5	2.5	80	64	54	17	Burst
8	F	66	Left	15	1	70	17	21	21	Tonic
9	M	66	Left	35	2.5	80	60	62	30	Burst
10	F	70	Left	5	6.5	80	61	50	69	Sham
11	M	65	Left	6	3	70	53	72	77	Tonic
12	F	65	Left	15	4	80	46	25	30	Sham

Pain scores are on a 0–100 visual analog scale (VAS) with 0 being no pain and 100 worst pain imaginable.

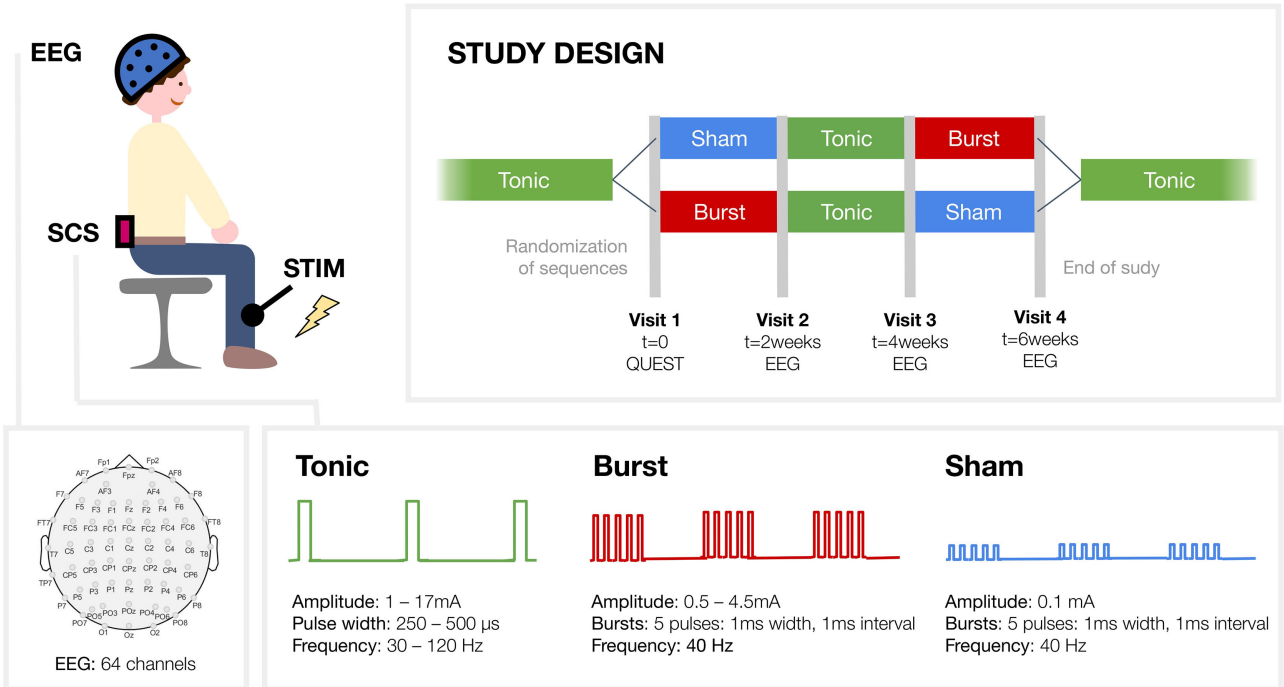


FIGURE 1 | Study design. Patients were evaluating three different spinal cord stimulation (SCS) regimes, each for 2 week: conventional tonic SCS, burst SCS and sham SCS. Participants were randomized to one of the two study arms. Tibial nerve stimulation was applied to elicit somatosensory evoked potentials that were recorded with electro-encephalography (EEG). Two different conditions were studied: the attended condition, where participants had to silently count the administered tibial stimuli, and the unattended condition, where they were asked to mind wander.

average VAS score for pain of 79 (range: 70–90). The participating patients were good, moderate as well as poor responders to conventional tonic SCS, reflected in an average VAS score of 61, with a range varying from 17 to 90.

All patients evaluated three different SCS settings, each for 2 weeks: conventional tonic SCS, burst SCS and sham SCS (**Figure 1**). Participants were randomized to either the "sham-tonic-burst" or "burst-tonic-sham" arm. Sham stimulation was a low amplitude burst stimulation intended to be non-therapeutically (19). However, the therapeutic range of burst stimulation was not known at the time this study was conducted and might be different for every patient. We can

therefore not rule out that in some patients in the present study burst stimulation with 0.1 mA (very low amplitude) was indeed at a therapeutic level. Nevertheless, as this stimulation setting was expected to be non-therapeutically, in the present study we refer to the "low amplitude burst stimulation" setting as "sham stimulation." Contrary to tonic SCS, both bust SCS and sham SCS are not sensed by the patient. So patients themselves knew when they received tonic SCS, but they did not know in which order they were evaluating burst or sham SCS.

EEG Acquisition

Electroencephalography (EEG) measurements were conducted during three sessions: at visits 2, 3 and 4 (**Figure 1**). EEG data was acquired using a 64-channel Ag/AgCl EEG placed according to the extended international 10–20 system (Waveguard EEG cap, ANT Neuro, the Netherlands) see channel layout in **Figure 1** and was recorded using ASA™ software (ANT Neuro, The Netherlands). The signals were amplified, low-pass filtered (digital FIR filter 1,350 Hz cut-off) and sampled at 5 kHz (TMSi-64 REFA, Twente Medical Systems International, the Netherlands). Impedance of the scalp electrodes was kept below 5 kOhm to reduce polarization effects.

Tibial Nerve Stimulation

Patients sat comfortably in an armchair in an electrically and sound-shielded room. They received transcutaneous electrical stimulation to induce Somatosensory Evoked Potentials (SEP). Stimulation was applied to the tibial nerve at the ankle of their affected leg in order to study the evoked potentials in several cortical areas (**Figure 1**). Square wave pulses of 0.2 ms duration (constant current stimulator model DS7A, Digitimer Limited, UK) were delivered through surface electrodes, with the anode positioned distal, fixed over the tibial nerve. Per run 190 to 210 electrical pulses were given, with the exact number varying per run. Stimuli were delivered at an average frequency of 1.1 Hz, with the inter stimulus intervals randomly varying from 0.6 to 1.6 s. The stimulation amplitude was adjusted for the individual patient until a level that elicited a twitch of the big toe. In all cases the pulses could be clearly felt without being painful.

Non-painful electrical stimulation of the tibial nerve evokes the first positive EEG activity after about 40 ms (P40) in the primary somatosensory cortex. This activation is generally measured at the vertex (20). P40 activation is followed by the P60, which also reflects somatosensory processing in the foot area of the SI (15, 20). The subsequent negative activity N90 is believed to be generated in the somatosensory cortices and reflect sensory-discriminative processes (20–22). Then there can be a large broad increase in activity around 250 ms which is generally measured at the vertex as a response to attentional processing of stimulus events (23). This late activation around 250 ms has been shown to be particularly strong to painful somatosensory stimuli and is identified to reflect activity in the somatosensory and cingulate cortices (15, 24) and insular and opercular cortices (25, 26).

Task

Each patient had three EEG recording sessions, one session with each of the three SCS regimes. During each session the spinal cord stimulator was still active with the same setting and intensity as it had been for the 2 weeks prior to the EEG recording. At each EEG session, a resting state EEG recording and two SEP recordings were made. Throughout the entire recording session the patients were asked to relax and keep their eyes open looking at a fixation cross. During one of the SEP recordings patients had to pay attention to the stimuli that were applied to their tibial nerve. They were asked to silently count them and afterwards report the number to the researcher. During the other SEP recording patients were asked to mind wander and not pay attention to the stimuli. The order in which stimuli had to be attended or not attended, was counterbalanced over the sessions and over the patients.

EEG Analysis

Preprocessing

Power-line external noise on EEG signals was removed using a notch around 50 Hz and its harmonics. Data was bandpass filtered between 0.6 and 100 Hz (stopband attenuation 60 dB). Cardiac and blinking artifacts were also detected using the ECG and EOG signals and corrected using the Signal-Space Projection approach (27). All the EEG preprocessing and analysis was performed using Brainstorm (http://neuroimage.usc.edu/brainstorm/) (28) following the indications for group analysis suggested in Tadel et al. (27). Data was then visually inspected by a specialist to manually discard bad channels and remove noisy segments (on average, one channel (TP8) and <2% of data segments per subject).

Source Reconstruction

Participants head model was estimated using the Symmetric Boundary Element Method from the open-source software OpenMEEG: Scalp 1.0000 1082V | Skull 0.0125 642V | Brain 1.0000 642V) (29, 30). We used a default brain template [Colin27-a stereotaxic average of 27 T1-weighted MRI scans of the same individual, MNI brain with a 1 mm resolution (31)]. Full noise covariance matrix was computed based on the EEG recordings baseline period −200 to −4 ms for every subject. EEG source reconstruction was subsequently completed using the sLORETA approach [standardized LOw Resolution brain Electromagnetic TomogrAphy (32)] implemented in Brainstorm: loose 0.2, SNR 3, pca 1, diagnoise 0, regnoise 1, eegreg 0.1, depth 1, weightexp 0.5, weightlimit 10 and fixed source orientation, obtaining a surface of 15,000 vertices.

Somatosensory Evoked Potentials

Approximately 200 SEP epochs from −200 to 500 ms were averaged per participant, with time = 0 ms being the time of delivery of the electrical stimulation at the tibial nerve. Each epoch was DC offset corrected (i.e., for each signal, the mean of the baseline from −200 to −4 ms was computed, and then subtracted from each time sample) and the stimulation artifact [−4, 6 ms] was cut. Source data was Z-scored with respect to the baseline [−200, −4 ms] and individual cortical maps were smoothed using a circularly symmetric Gaussian surface kernel with a full width half maximum size of 10 mm (27). In order to

compare our results with previous literature we obtain the SEP from a source defined at the vertex.

Statistics

Differences between SCS regimes (burst, tonic, sham) were evaluated on the different SEP amplitudes at latencies of interest at the vertex (i.e., 40, 60, 90, and 250 ms) using two sided non parametric Wilcoxon signed rank tests and a two-way analysis of variance (ANOVA) test, including SCS regime (burst, tonic, sham) and participants attention condition (attended, unattended). In addition, whole brain source differences between conditions were estimated correcting for multiple comparisons using a non-parametric cluster based permutation test (paired t-test, 1,000 permutations, $p < 0.05$, cluster alpha 0.05) (33).

RESULTS

Subjects

Clinically, the 12 participants responded differently to the three spinal cord stimulation regimes they evaluated. The amount of pain relief by the three different SCS regimes varied largely for the individual patients. The average VAS scores for pain were 46 (range: 17–79) for burst SCS, 61 (range: 17–90) for tonic SCS, and 53 (range: 21–72) for sham SCS (**Table 1**). Six patients preferred burst SCS, four patients preferred tonic SCS, two patients preferred sham SCS. Preference was mainly based on the largest pain relief, but was also influenced by the perception of the paresthesia: five patients liked the absence of paresthesia, while one patient mentioned he really missed the paresthesia sensations, and two patients missed reassurance that the stimulation was active and that they could feel changes in stimulation intensity when they used their remote control. Both sham and burst SCS were not sensed by any the patients, while all of them could feel at least some paresthesia with tonic SCS. During the study, patients did not know in which phase they had sham SCS or burst SCS.

Somatosensory Evoked Potential

All participants could clearly feel and count the applied stimuli at their tibial nerve in all three SCS conditions. Average stimulation amplitude was 27 mA (range: 10–75 mA). The individual's stimulation amplitude was stable over the three EEG recording sessions (<10% variation for each subject) and so was the perceived intensity of the applied stimuli, which was non-painful but clearly sensed by all participants. All participants were therefore able to focus on the applied stimuli and could count them correctly, with an average accuracy of 98% for all three SCS conditions. Since none of the participants perceived the stimuli as painful in either of the three conditions, all reported that they were capable of shifting their attention away from the stimuli during the trials in which they were asked to mind wander.

Neither attention nor SCS setting had a statistically significant effect on the amplitudes of the early SEP latencies (P40, P60, N90). Which corresponds with the similar intensity scores that were reported for the applied stimuli by the participants during all three SCS settings.

Effect of Attending the Applied Stimuli

Sham SCS was intended to have no therapeutic effect. Attending the electrical stimuli applied at the tibial nerve during sham SCS caused no statistically significant differences in P300 amplitude as when the stimuli were not attended (**Figure 2A**). Comparing the evoked activity in time window 250–300 ms between the attended and unattended condition revealed increased activity in the right somatosensory, motor and cingulate cortices, and in occipital and temporal areas during attention (**Figure 2B**).

When the participants were asked to mind wander during tonic SCS and did not attend the applied stimuli, the P300 amplitude decreased substantially in comparison to the attended condition (**Figure 2A**). The right prefrontal cortex showed significantly more activity in the attended condition as compared with the unattended condition (**Figure 2B**).

During burst SCS, paying attention to the applied stimuli or not attending them did not change the P300 amplitude of the SEP (**Figure 2**).

Effect of Spinal Cord Stimulation Setting

When the applied stimuli were attended by the participants, only the burst SCS regime reduced the P300 amplitude as compared with sham SCS (**Figure 3**). When the stimuli applied to the tibial nerve were not attended, because the participants were mind wandering, both the tonic and the burst SCS regime reduced the P300 amplitude as compared to sham SCS, with the lowest P300 amplitude during burst SCS (**Figure 3**). The largest difference, however, between the attended and unattended condition was obtained under tonic SCS regime (**Figure 2A**).

In both the attended and unattended condition, the amplitude of the P300 was significantly smaller ($p < 0.03$) during burst SCS in comparison to sham SCS (**Figure 4**). In the attended condition this was the case for all latencies from 200 to 300 ms after the electrical pulse was applied to the tibial nerve. No significant differences were found between tonic and sham SCS.

Comparing at source level, the evoked activity in the time window 250–300 ms between burst SCS and sham SCS revealed decreased activity during burst SCS in the right supplementary motor area (SMA), somatosensory, mid cingulate, and left and right insular cortices (**Figure 4B**).

DISCUSSION

Attention can modulate the amplitude of the P300 in chronic pain patients treated with spinal cord stimulation. When patients either silently counted the applied electrical stimuli or were mind wandering, this modulated the SEP amplitude of the P300, but not the evoked potentials at earlier latencies and neither the perceived intensity of the applied stimuli.

Previous findings by De Ridder et al. (12) and De Ridder and Vanneste (13) have related the analgesic effect of burst spinal cord stimulation to reduced attention to pain. If burst SCS indeed reduces the capacity for attention to be directed to pain, then this should be reflected in reduced amplitudes of the attention-related component of the SEP, the P300 (23). In this explorative study, we have measured SEPs in 12 chronic pain patients who had 2-week evaluation periods with conventional tonic SCS, burst

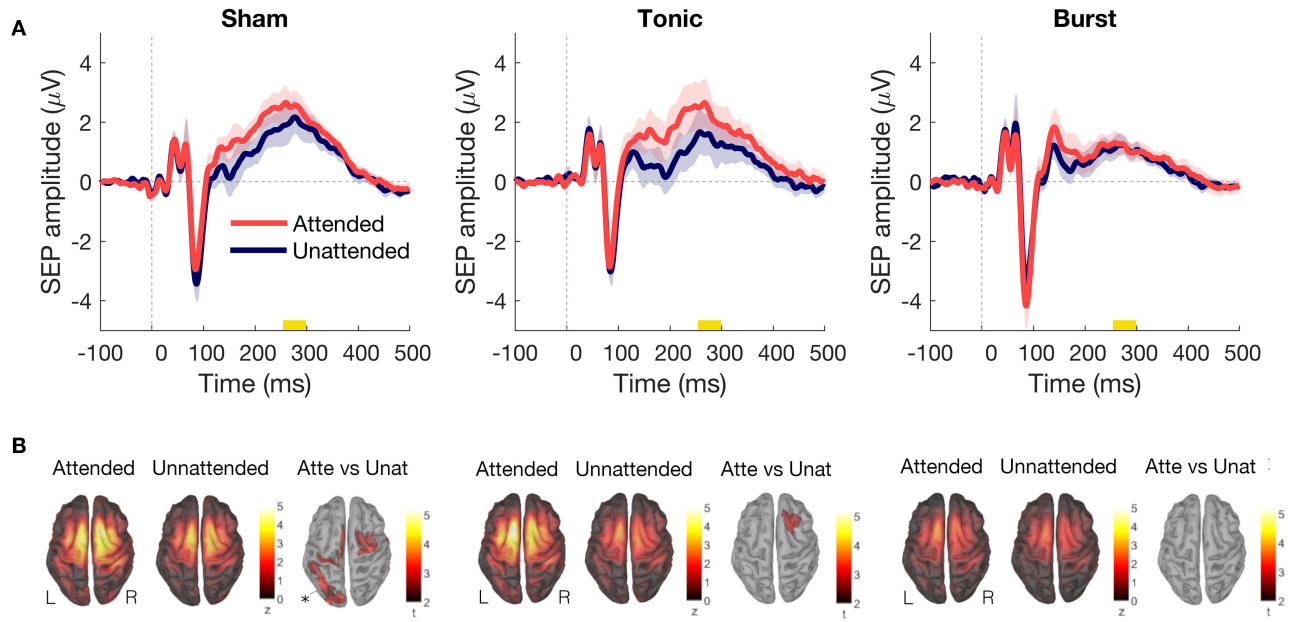


FIGURE 2 | (A) Difference in somatosensory evoked potential between attended (red) and unattended (blue) conditions on the vertex for each type of spinal cord stimulation (SCS): sham SCS (left), tonic SCS (middle), and burst SCS (right). Shadows indicate standard error of the mean (200 epochs per condition, $n = 12$ subjects). **(B)** P300 source activation (from 250 to 300 ms), for each type of SCS and condition. Statistical results with non-parametric cluster based permutation tests. All results showed Attended > Unattended.

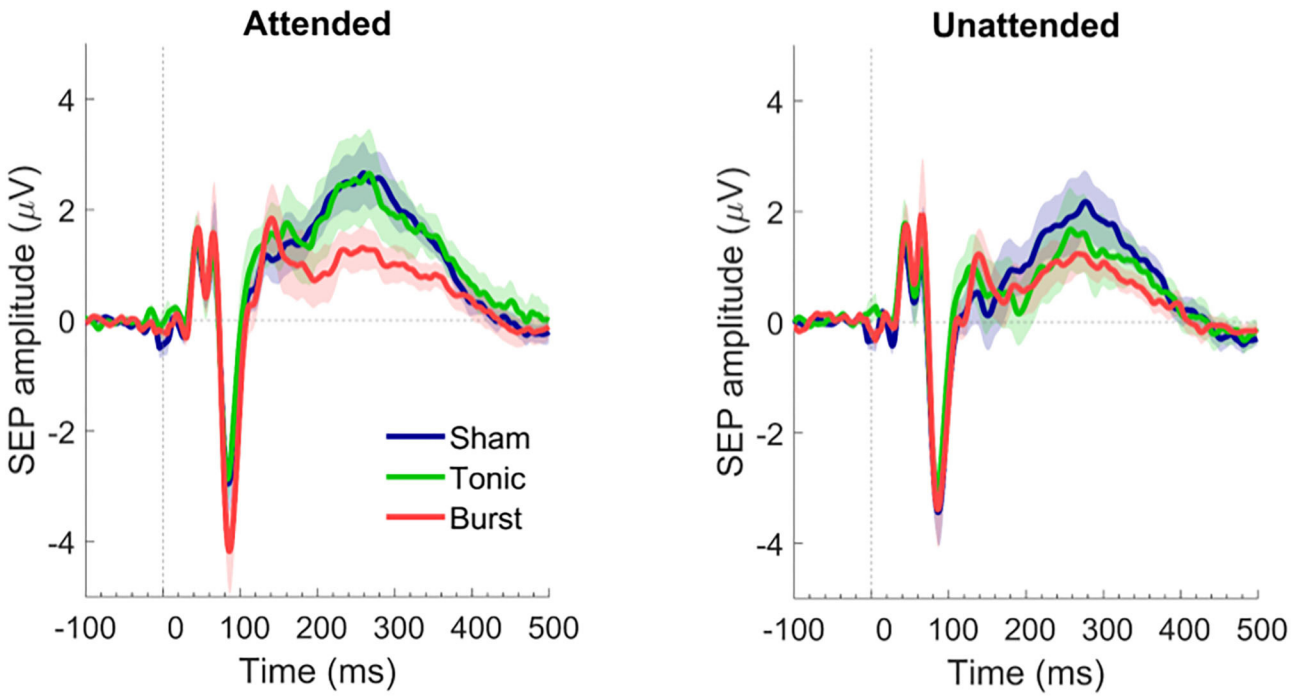


FIGURE 3 | Somatosensory evoked potential in attended **(left)** and unattended **(right)** conditions on the vertex for each type of spinal cord stimulation: sham SCS (blue), tonic SCS (green), and burst SCS (red). Shadows indicate standard error of the mean (200 epochs per condition, $n = 12$ subjects).

SCS and sham SCS, and who did not know at which moment they had sham SCS or burst SCS. When patients were asked to actively attend the electrical stimuli applied at their tibial nerve, there was a significant reduction in P300 amplitude when patients were under burst SCS regime as compared with sham and tonic SCS regimes (**Figure 3**). Even though both burst and sham SCS

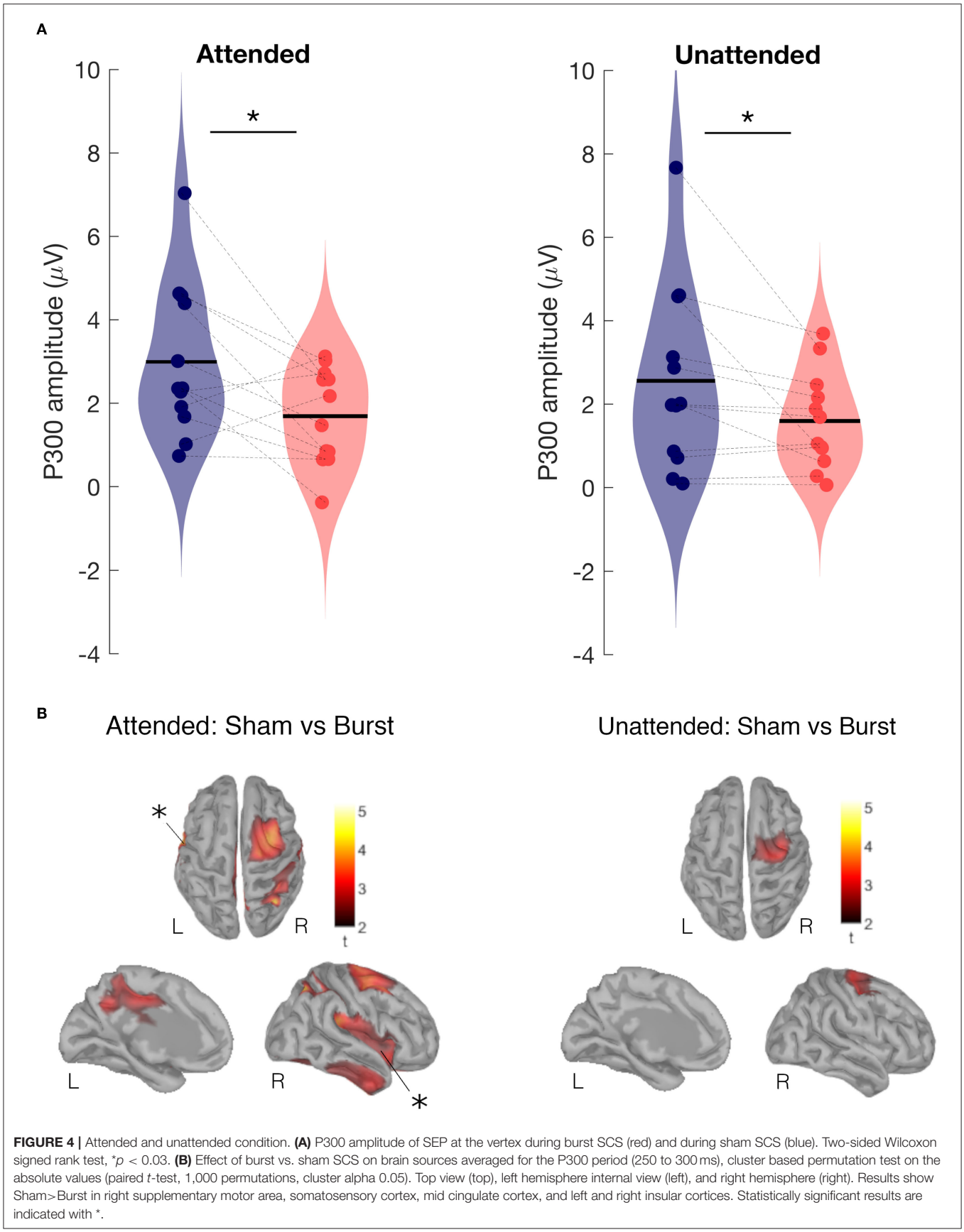


FIGURE 4 | Attended and unattended condition. **(A)** P300 amplitude of SEP at the vertex during burst SCS (red) and during sham SCS (blue). Two-sided Wilcoxon signed rank test, $^*p < 0.03$. **(B)** Effect of burst vs. sham SCS on brain sources averaged for the P300 period (250 to 300 ms), cluster based permutation test on the absolute values (paired *t*-test, 1,000 permutations, cluster alpha 0.05). Top view (top), left hemisphere internal view (left), and right hemisphere (right). Results show Sham>Burst in right supplementary motor area, somatosensory cortex, mid cingulate cortex, and left and right insular cortices. Statistically significant results are indicated with *.

settings were not sensed by the patients, and patients did not know which of those two SCS regimes was active at the moment of the measurement.

During sham SCS, attending or not attending the peripherally applied stimuli only caused a small difference in P300 amplitudes, indicating that even while the patients were mind wandering, somatosensory stimuli were still processed to almost the same amount as if they were attended. Attending the applied stimuli while receiving tonic SCS showed a P300 amplitude similar to the sham conditions. However, when the stimuli were not attended, the amplitude decreased substantially. During burst SCS, not attending the stimuli caused an even lower P300 than not attending them during tonic SCS. Attending the stimuli during burst SCS however, did not cause an increase in the P300 amplitude, indicating that burst SCS might affect the attention that could be directed to the applied somatosensory stimuli.

Subjects

The 12 participants in this study are not healthy subjects, but chronic pain patients who have been suffering neuropathic pain for years and are treated with analgesic medication and SCS therapy. SEP amplitudes and latencies in chronic pain patients vary from healthy subjects, as amplitudes have been reported larger and certain latencies to be delayed (34). Therefore, in this study, aimed to specifically assess the effects of both conventional and burst SCS therapy on somatosensory processing, the participating patients were their own controls and we had one condition with sham SCS, which was intended to be a non-therapeutic SCS intensity.

Besides SCS therapy, most of the patients were also using analgesic medication. Although high dose opioids can induce an increase in low frequency (delta band) brain activity and a decrease in amplitude of potentials evoked by painful stimuli, opioids have been reported to not influence the amplitudes of the non-painful SEPs (35). Paracetamol and pregabalin have been reported to not alter painful SEPs (36, 37). NSAIDs have been reported to alter amplitudes and latencies of painful SEPs, but there are no reports on their influence on non-painful SEPs (35). Even if analgesic medication has influenced the SEP in some participants, it has done that in equal amounts for all three SCS conditions, as none of the patients changed their dose or type of medication over the course of this study.

Spinal Cord Stimulation

In our study, the participants had their spinal cord stimulator for at least half a year, so all of them were familiar with tonic SCS and the paresthesia it caused. This means we have a different population than De Ridder et al. reported on (12, 13). Their five patients were completely new to SCS and still trialing SCS with an external pulse generator. The sensation of (tonic) SCS was new to the participants in the study by De Ridder et al., while for our patients it was the absence of sensations during sham and burst SCS which was a new experience. We have therefore conducted our SEP measurements after 2-weeks evaluation periods with burst SCS and sham SCS, with a 2-weeks period with tonic SCS in between the burst and the sham SCS.

For each participant the amplitude and the perceived intensity of the applied tibial nerve stimuli did not vary during the three study conditions. However, the effects of the three SCS regimes (burst, tonic, and sham) on their own ongoing pain varied largely over the participants, as did their preference for specific SCS settings. Preference was also influenced by other aspects than pain reduction, like the presence or absence of paresthesia (19). The number of participants in the present study is too small to separately analyze effects by either preference or pain relief. Therefore, effects that we report on brain activity are independent of the clinical effects of the SCS regimes.

Somatosensory Evoked Potential

To make sure that the participants actively attended the applied electrical stimuli at their tibial nerve, we asked them to silently count the stimuli and report the number at the end of the measurement. To avoid them just remembering the number of applied stimuli from previous measurements, we randomly varied the number of stimuli of every SEP recording. Since the patients reported the correct numbers in all attention conditions, it is very likely they were indeed counting and paying attention. In the mind wandering condition, we can never be completely certain that patients were indeed not counting or otherwise attending the stimuli when we asked them not to do so. However, the differences in P300 amplitude between the attended and unattended stimuli in the sham and tonic SCS conditions suggest that patients were again compliant and were not attending the stimuli during these recordings.

Tonic SCS is accompanied by paresthesia, generally by the patients described as constant tingling sensations. When we applied electrical stimuli to the tibial nerve, these electrical stimuli and the paresthesia are concurrent sensations that need to be processed by the brain, in addition to the patient's ongoing pain. When the patients were asked to not attend the applied stimuli under tonic SCS, it led to a decreased P300 amplitude and reduced activity in somatosensory and motor cortices (**Figure 2**), which did not happen during sham or burst SCS regimes. The concurrent processing of paresthesia seems to allow the participants to pay less attention to somatosensory stimuli when they are asked to.

Other studies have found that conventional tonic SCS inhibits the early SEP latencies that are generated in the primary somatosensory cortex (18, 38). One case report even showed complete inhibition of the early SEP during conventional tonic SCS as well as during high frequency SCS and high density tonic SCS (17). We have not found complete inhibition nor statistically significant decreases in early peaks with either burst or tonic SCS as compared to sham SCS. However, our sham SCS was probably not at a subtherapeutic intensity for every participant, so there is a chance that all three SCS regimes reduced the early SEP amplitudes to the same amount. Still, our **Figures 2**, **3** show early latency peaks P40, P60, and N90 with amplitudes similar to the "no stimulation" conditions reported previously (17, 38). No statistical differences in early amplitudes between the SCS regimes or attention conditions were found in the present study.

One other study also reported reduced late SEP (P300) amplitudes in response to non-painful tibial nerve stimulation

during tonic SCS as compared with no SCS (15). In that study, participants were not specifically asked to attend or not-attend the applied stimuli and the SEP was obtained directly after tonic SCS was switched ON or OFF. Therefore, it is difficult to disentangle the effects of the different conditions and it is possible that some participants were attending the stimuli while others were not. In addition, the effects of the previous SCS setting might not have ceased completely when they already did their next measurements, which could explain the smaller amplitude difference in their results. The time period during which SCS effects maintain after a setting has been changed, can vary largely among patients and can last up to hours for some individuals (39). Therefore, in the present study, the SEP measurements were conducted at the end of the 2-weeks evaluation period of an SCS regime.

Polácek et al. (15) applied source dipole fitting on their SEP data and calculated the main origin of their P300 at the midcingulate cortex. The P300 peak is believed to consist of an earlier component P3a (generated in frontal areas) and a later component P3b (generated in temporal-parietal areas). The P300 (P3a) and activation of the mid cingulate cortex is larger in amplitude when a stimulus is novel and attentional focus is oriented to sensory stimuli (23, 40). In the P300 latency range, we find differences between burst SCS and sham SCS in activation, not only in the mid cingulate cortex, but also in insular cortex, somatosensory cortex and SMA (**Figure 4B**). Similar areas show differences in activation when comparing the attended condition with the unattended condition during sham SCS (**Figure 2B**). Attention to pain tends not only to increase the perceived intensity of pain, but also the magnitude of the insular activity. The insula plays a role in the detection of salient stimuli and modulation of the reaction to these stimuli (40, 41). Decreased activity in mid cingulate and insular cortices during burst SCS as compared with sham SCS suggests that the salience network is less engaged when a patient receives burst stimulation. In addition, we found decreased activity with burst SCS in the supplementary motor area and somatosensory cortices, which are part of the dorsal attentional network that is involved in the top-down selection of which stimuli are attended and how to respond to them.

Limitations

Our EEG study is an explorative study, with a small number of participants to search for potential differences in effects and working mechanisms between tonic and burst spinal cord stimulation. In addition we compared burst and tonic SCS with sham SCS. Only 12 chronic pain patients with an implanted SCS device participated in our study that was underpowered. Interpreting the statistical results has to be done carefully, but since the effects of tonic and burst SCS happen in those 12 patients regardless of the effect of SCS on their pain, our results are interesting to further test in an properly powered study.

A major limitation of our present study, however, is that sham SCS might not have been real sham stimulation for every participant and some patients might have actually received sufficient energy to perceive therapeutic effects. Two patients reported their lowest pain scores under sham SCS regime. The therapeutic range of burst SCS is still unknown and this range might vary to a great extent per patient, similar to how the therapeutic range of conventional tonic SCS varies per patient and is among others dependent on the individual's anatomy of the spinal cord and the position of the electrode lead in the epidural space (42, 43). However, defining the therapeutic range of burst is largely complicated by the fact that burst SCS is not sensed, which hinders (direct) feedback from the patient. Studies conducted after we collected our data indicate that the therapeutic range of burst SCS might go as low as 0.1 mA for individual patients (44).

CONCLUSION

Burst stimulation is one of the relatively new developments in spinal cord stimulation regimes. Several aspects of the working mechanisms of burst stimulation and other new paresthesia-free regimes are still unknown and require further research, as they seem to affect different or additional cortical areas than tonic SCS. The present study showed that burst SCS reduced the P300 amplitude of the somatosensory evoked potential. A similar reduction was also obtained during tonic SCS when patients were instructed to not attend peripherally applied pulses. Which suggests that burst SCS reduced the capacity for attention directed to somatosensory stimuli.

Our findings support the hypothesis posed by De Ridder and Vanneste (13) that burst SCS modulates activity in pain processing brain areas in a similar manner as when somatosensory stimuli are not attended. This effect of burst SCS was present in general, even when the participants were instructed to pay attention to the applied somatosensory stimuli. Overall, burst SCS acted without reducing the perceived intensity of the peripherally applied stimuli and regardless of the analgesic effect of burst SCS on the patient's own pain. In conclusion, burst spinal cord stimulation for the treatment of chronic pain seems to reduce the attention that is or can be directed to somatosensory stimuli, probably to a larger extent than conventional tonic spinal cord stimulation treatment. This is a first step in understanding why in selected chronic pain patients burst SCS is more effective than tonic SCS and how neuroimaging could assist in personalizing SCS treatment.

DATA AVAILABILITY STATEMENT

The data and code supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Twente Ethics Committee, Enschede, the Netherlands. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

The conception was originated from CdV and ML. Data collection was done by MT-C and CdV. Data analysis and interpretation was performed by GN and CdV. The first draft was written by GN and CdV and further input was provided by ML and MT-C. All authors contributed to the article and approved the submitted version.

FUNDING

GN received financial support through a postdoctoral fellowship from the AXA Research Fund and CdV through a postdoctoral fellowship from the Canadian Institutes of Health Research (CIHR) and operating money from Stichting the Neurobionics Foundation.

REFERENCES

1. De Ridder D, Vanneste S, Plazier M, van der Loo E, Menovsky T. Burst spinal cord stimulation: toward paresthesia-free pain suppression. *Neurosurgery.* (2010) 66:986–90. doi: 10.1227/01.NEU.0000368153.44883.B3
2. de Vos C, Bom MJ, Vanneste S, Mathieu WP, de Ridder D. Burst spinal cord stimulation evaluated in patients with failed back surgery syndrome and painful diabetic neuropathy. *Neuromodul Technol Neural Interface.* (2014) 17:152–9. doi: 10.1111/ner.12116
3. Perruchoud C, Eldabe S, Batterham AM, Madzinga G, Brookes M, Durrer A, et al. Analgesic efficacy of high-frequency spinal cord stimulation: a randomized double-blind placebo-controlled study. *Neuromodulation.* (2013) 16:363–9; discussion 369. doi: 10.1111/ner.12027
4. Van Buyten JP, Al-Kaisy A, Smet I, Palmisani S, Smith T. High-frequency spinal cord stimulation for the treatment of chronic back pain patients: results of a prospective multicenter european clinical study. *Neuromodul Technol Neural Interface.* (2013) 16:59–66. doi: 10.1111/ner.12006
5. Cui JG, Linderoth B, Meyerson BA. Effects of spinal cord stimulation on touch-evoked allodynia involve GABAergic mechanisms. An experimental study in the mononeuropathic rat. *Pain.* (1996) 66:287–95. doi: 10.1016/0304-3959(96)03069-2
6. Schechtmann G, Song Z, Ultenius C, Meyerson BA, Linderoth B. Cholinergic mechanisms involved in the pain relieving effect of spinal cord stimulation in a model of neuropathy. *Pain.* (2008) 139:136–45. doi: 10.1016/j.pain.2008.03.023
7. Zhang TC, Janik JJ, Grill WM. Mechanisms and models of spinal cord stimulation for the treatment of neuropathic pain. *Brain Res.* (2014) 1569:19–31. doi: 10.1016/j.brainres.2014.04.039
8. Bentley LD, Duarte RV, Furlong PL, Ashford RL, Raphael JH. Brain activity modifications following spinal cord stimulation for chronic neuropathic pain: a systematic review. *Eur J Pain.* (2016) 20:499–511. doi: 10.1002/ejp.782
9. Sivanesan E, Maher DP, Raja SN, Linderoth B, Guan Y. Supraspinal mechanisms of spinal cord stimulation for modulation of pain: five decades of research and prospects for the future. *Anesthesiology.* (2019) 130:651–65. doi: 10.1097/ALN.0000000000002353
10. Schulman JJ, Ramirez RR, Zonenshayn M, Ribary U, Llinas R. Thalamocortical dysrhythmia syndrome: MEG imaging of neuropathic pain. *Thalamus Relat Syst.* (2005) 3:33. doi: 10.1017/S1472928805000063
11. Moens M, Sunaert S, Mariën P, Brouns R, De Smedt A, Droogmans S, et al. Spinal cord stimulation modulates cerebral function: an fMRI study. *Neuroradiology.* (2012) 54:1399–407. doi: 10.1007/s00234-012-1087-8
12. De Ridder D, Plazier M, Kamerling N, Menovsky T, Vanneste S. Burst spinal cord stimulation for limb and back pain. *World Neurosurg.* (2013) 80:642–9.e1. doi: 10.1016/j.wneu.2013.01.040
13. De Ridder D, Vanneste S. Burst and tonic spinal cord stimulation: different and common brain mechanisms. *Neuromodulation.* (2016) 19:47–59. doi: 10.1111/ner.12368
14. Bocci T, De Carolis G, Paroli M, Barloscio D, Parenti L, Tollapi L, et al. Neurophysiological comparison among tonic, high frequency, and burst spinal cord stimulation: novel insights into spinal and brain mechanisms of action. *Neuromodulation.* (2018) 21:480–8. doi: 10.1111/ner.12747
15. Polácek H, Kozák J, Vrba I, Vrána J, Stancák A. Effects of spinal cord stimulation on the cortical somatosensory evoked potentials in failed back surgery syndrome patients. *Clin Neurophysiol.* (2007) 118:1291–302. doi: 10.1016/j.clinph.2007.02.029
16. Theuvenet PJ, Dunajski Z, Peters MJ, van Ree JM. Responses to median and tibial nerve stimulation in patients with chronic neuropathic pain. *Brain Topogr.* (1999) 11:305–13. doi: 10.1023/A:1022210704505
17. Buonocore M, Demartini L. Inhibition of somatosensory evoked potentials during different modalities of spinal cord stimulation: a case report. *Neuromodulation.* (2016) 19:882–4. doi: 10.1111/ner.12380
18. Buonocore M, Bodini A, Demartini L, Bonezzi C. Inhibition of somatosensory evoked potentials during spinal cord stimulation and its possible role in the comprehension of antalgic mechanisms of neurostimulation for neuropathic pain. *Minerva Anestesiol.* (2012) 78:297–302.
19. Tjepkema-Cloostermans MC, de Vos CC, Wolters R, Dijkstra-Scholten C, Lenders MWPM. Effect of burst stimulation evaluated in patients familiar with spinal cord stimulation. *Neuromodulation.* (2016) 19:492–7. doi: 10.1111/ner.12429
20. Kakigi R, Koyama S, Hoshiyama M, Shimojo M, Kitamura Y, Watanabe S. Topography of somatosensory evoked magnetic fields following posterior tibial nerve stimulation. *Electroencephalogr Clin Neurophysiol.* (1995) 95:127–34. doi: 10.1016/0013-4694(95)00053-2
21. Kany C, Treede RD. Median and tibial nerve somatosensory evoked potentials: middle-latency components from the vicinity of the secondary somatosensory cortex in humans. *Electroencephalogr Clin Neurophysiol.* (1997) 104:402–10. doi: 10.1016/S0168-5597(97)00045-2
22. Roosink M, Buitenweg JR, Renzenbrink GJ, Geurts ACH, Ijzerman MJ. Altered cortical somatosensory processing in chronic stroke: a relationship with post-stroke shoulder pain. *Neurorehabilitation.* (2011) 28:331–44. doi: 10.3233/NRE-2011-0661
23. Polich J. Updating P300: an integrative theory of P3a and P3b. *Clin Neurophysiol.* (2007) 118:2128–48. doi: 10.1016/j.clinph.2007.04.019
24. Kitamura Y, Kakigi R, Hoshiyama M, Koyama S, Shimojo M, Watanabe S. Pain-related somatosensory evoked magnetic fields. *Electroencephalogr Clin Neurophysiol.* (1995) 95:463–74. doi: 10.1016/0013-4694(95)00139-5
25. Garcia-Larrea L, Frot M, Valeriani M. Brain generators of laser-evoked potentials: from dipoles to functional significance. *Neurophysiol Clin.* (2003) 33:279–92. doi: 10.1016/j.neucli.2003.10.008
26. Frot M, Faillenot I, Mauguière F. Processing of nociceptive input from posterior to anterior insula in humans. *Hum Brain Mapp.* (2014) 35:5486–99. doi: 10.1002/hbm.22565
27. Tadel F, Bock E, Niso G, Mosher JC, Cousineau M, Pantazis D, et al. MEG/EEG group analysis with brainstorm. *Front Neurosci.* (2019) 13:76. doi: 10.3389/fnins.2019.00076
28. Tadel F, Baillet S, Mosher JC, Pantazis D, Leahy RM. Brainstorm: a user-friendly application for MEG/EEG analysis. *Comput Intell Neurosci.* (2011) 2011:879716. doi: 10.1155/2011/879716
29. Gramfort A, Papadopoulo T, Olivi E, Clerc M. Forward field computation with OpenMEEG. *Comput Intellig Neurosci.* (2011) 2011:1–13. doi: 10.1155/2011/923703
30. Kybic J, Clerc M, Abboud T, Faugeras O, Keriven R, Papadopoulo T. A common formalism for the integral formulations of the forward EEG problem. *IEEE Trans Med Imaging.* (2005) 24:12–28. doi: 10.1109/TMI.2004.837363
31. Holmes CJ, Hoge R, Collins L, Woods R, Toga AW, Evans AC. Enhancement of MR images using registration for signal averaging. *J Comput Assist Tomogr.* (1998) 22:324–33. doi: 10.1097/00004728-199803000-00032
32. Pascual-Marqui RD. Standardized low-resolution brain electromagnetic tomography (sLORETA): technical details. *Methods Find Exp Clin Pharmacol.* (2002) 24:5–12.

33. Maris E, Oostenveld R. Nonparametric statistical testing of EEG- and MEG-data. *J Neurosci Methods.* (2007) 164:177–90. doi: 10.1016/j.jneumeth.2007.03.024
34. Kuttikat A, Noreika V, Chennu S, Shenker N, Bekinschtein T, Brown CA. Altered neurocognitive processing of tactile stimuli in patients with complex regional pain syndrome. *J Pain.* (2018) 19:395–409. doi: 10.1016/j.jpain.2017.11.008
35. Malver LP, Brokjaer A, Staahl C, Graversen C, Andresen T, Drewes AM. Electroencephalography and analgesics. *Br J Clin Pharmacol.* (2014) 77:72–95. doi: 10.1111/bcp.12137
36. Moore UJ, Marsh VR, Ashton CH, Seymour RA. Effects of peripherally and centrally acting analgesics on somato- sensory evoked potentials [see comments]. *Br J Clin Pharmacol.* (1995) 40:111–7. doi: 10.1111/j.1365-2125.1995.tb05766.x
37. Olesen SS, Graversen C, Olesen AE, Frøkjaer JB, Wilder-Smith O, van Goor H, et al. Randomised clinical trial: pregabalin attenuates experimental visceral pain through sub-cortical mechanisms in patients with painful chronic pancreatitis. *Aliment Pharmacol Ther.* (2011) 34:878–87. doi: 10.1111/j.1365-2036.2011.04802.x
38. Wolter T, Kieselbach K, Sircar R, Gierthmuehlen M. Spinal cord stimulation inhibits cortical somatosensory evoked potentials significantly stronger than transcutaneous electrical nerve stimulation. *Pain Phys.* (2013) 16:405–14. doi: 10.36076/ppj.2013/16/405
39. Wolter T, Winkelmüller M. Continuous versus intermittent spinal cord stimulation: an analysis of factors influencing clinical efficacy. *Neuromodul Technol Neural Interface.* (2012) 15:13–20. doi: 10.1111/j.1525-1403.2011.00410.x
40. Torta DM, Legrain V, Mouraux A, Valentini E. Attention to pain! A neurocognitive perspective on attentional modulation of pain in neuroimaging studies. *Cortex.* (2017) 89:120–34. doi: 10.1016/j.cortex.2017.01.010
41. Menon V, Uddin LQ. Saliency, switching, attention and control: a network model of insula function. *Brain Struct Funct.* (2010) 214:655–67. doi: 10.1007/s00429-010-0262-0
42. Holsheimer J. Which neuronal elements are activated directly by spinal cord stimulation. *Neuromodulation.* (2002) 5:25–31. doi: 10.1046/j.1525-1403.2002._2005.x
43. Holsheimer J, Khan YN, Raza SS, Khan EA. Effects of electrode positioning on perception threshold and paresthesia coverage in spinal cord stimulation. *Neuromodulation.* (2007) 10:34–41. doi: 10.1111/j.1525-1403.2007.00085.x
44. Ridder DD, De Ridder D, Vanneste S, Plazier M, Vancamp T. Mimicking the brain: evaluation of St Jude Medical's Prodigy Chronic Pain System with Burst Technology. *Expert Rev Med Devices.* (2015) 12:143–50. doi: 10.1586/17434440.2015.985652

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2021 Niso, Tjepkema-Cloostermans, Lenders and de Vos. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Neurology

ORIGINAL RESEARCH
published: 04 August 2021
doi: 10.3389/fneur.2021.694271

Spinal Cord Resting State Activity in Individuals With Fibromyalgia Who Take Opioids

Katherine T. Martucci[1]*, *Kenneth A. Weber II*[2] *and Sean C. Mackey*[2]

[1] *Human Affect and Pain Neuroscience Laboratory, Center for Translational Pain Medicine, Department of Anesthesiology, Duke University Medical Center, Durham, NC, United States,* [2] *Systems Neuroscience and Pain Laboratory, Division of Pain Medicine, Department of Anesthesiology, Perioperative, and Pain Medicine, Stanford University, Palo Alto, CA, United States*

Chronic pain coincides with myriad functional alterations throughout the brain and spinal cord. While spinal cord mechanisms of chronic pain have been extensively characterized in animal models and *in vitro*, to date, research in patients with chronic pain has focused only very minimally on the spinal cord. Previously, spinal cord functional magnetic resonance imaging (fMRI) identified regional alterations in spinal cord activity in patients (who were not taking opioids) with fibromyalgia, a chronic pain condition. Here, in patients with fibromyalgia who take opioids ($N = 15$), we compared spinal cord resting-state fMRI data vs. patients with fibromyalgia not taking opioids ($N = 15$) and healthy controls ($N = 14$). We hypothesized that the opioid (vs. non-opioid) patient group would show greater regional alterations in spinal cord activity (i.e., the amplitude of low frequency fluctuations or ALFF, a measure of regional spinal cord activity). However, we found that regional spinal cord activity in the opioid group was more similar to healthy controls, while regional spinal cord activity in the non-opioid group showed more pronounced differences (i.e., ventral increases and dorsal decreases in regional ALFF) vs. healthy controls. Across patient groups, self-reported fatigue correlated with regional differences in spinal cord activity. Additionally, spinal cord functional connectivity and graph metrics did not differ among groups. Our findings suggest that, contrary to our main hypothesis, patients with fibromyalgia who take opioids do not have greater alterations in regional spinal cord activity. Thus, regional spinal cord activity may be less imbalanced in patients taking opioids compared to patients not taking opioids.

Keywords: chronic pain, opiate, ALFF, low frequency power, cervical spinal cord, fatigue, fMRI, widespread pain

OPEN ACCESS

Edited by:
Flavia Di Pietro,
Curtin University, Australia

Reviewed by:
Nicole N. Scheff,
University of Pittsburgh, United States
Edita Navratilova,
University of Arizona, United States
Marieke Niesters,
Leiden University Medical Center, Netherlands

***Correspondence:**
Katherine T. Martucci
katherine.martucci@duke.edu

Specialty section:
This article was submitted to Applied Neuroimaging, a section of the journal Frontiers in Neurology

Received: *12 April 2021*
Accepted: *28 June 2021*
Published: *04 August 2021*

Citation:
Martucci KT, Weber KA II and Mackey SC (2021) Spinal Cord Resting State Activity in Individuals With Fibromyalgia Who Take Opioids. Front. Neurol. 12:694271. doi: 10.3389/fneur.2021.694271

INTRODUCTION

Chronic pain states and opioid medication use both can alter the central nervous system (CNS) via effects on neurophysiologic mechanisms within the brain and spinal cord. While spinal cord mechanisms of chronic pain have been extensively studied in animal models and *in vitro*, to date, research in patients with chronic pain has focused only minimally on the spinal cord. Measurement of spinal cord activity in human chronic pain patients is essential for our understanding of chronic pain because the spinal cord represents the CNS nexus where peripheral inputs, local spinal cord circuits, as well as descending modulatory circuits from supraspinal and brainstem areas all intersect. Further, the spinal cord is a key region where interacting effects would presumably occur

from both chronic pain and opioid use. Opioid analgesics exert their pain-relieving effects by acting both locally within the spinal cord dorsal horn and in the brain, which in turn, activates descending inhibition of pain via brainstem to spinal cord projections (1). Thus, investigating the CNS, and specifically the spinal cord, in patients taking opioids may provide insight to how long-term opioid use influences neurophysiology, and thereby provide an additional marker to identify concerns and/or assess appropriateness of opioid use.

Currently, our understanding is limited regarding the effects of long-term opioid use on clinical outcomes in patients with chronic pain. While opioids are a mainstay of perioperative, cancer, and palliative care, the appropriateness of opioid use for long-term treatment of chronic pain is highly debated and controversial. This controversy is due to the potential for adverse effects such as sedation, dizziness, nausea, vomiting, constipation, physical dependence, tolerance, and respiratory depression; as well as the risk for development of opioid use disorder (2, 3). Opioid use is not superior to non-opioid therapy for long-term (i.e., 12-months) treatment of chronic pain (e.g., chronic back pain and knee osteoarthritis) (4). For the chronic pain condition of fibromyalgia, opioid use is particularly controversial, and long-term opioid use vs. non-opioid medication use does not improve physical function or reduce pain interference (5). Patient reports and clinically observed outcomes such as physical function and pain interference inform the limited current understanding of how long-term opioid use affects chronic pain, however, underlying effects of opioid use on neurophysiology remains generally unknown.

Few neuroimaging studies include individuals with chronic pain who take opioids, yet from these studies, it is apparent that opioid-related effects on brain neurophysiology occur rapidly and extensively. For example, structural changes in the brain occur in individuals who take opioids for 1 month for chronic low back pain, and these changes persist for several months after opioid treatment is terminated (6, 7). Similar effects on cortical and subcortical structure and function have been observed in pain-free individuals with opioid use disorder (8). Additionally, chronic pain patients taking opioids show altered frontostriatal functional connectivity (9) and altered brain response to noxious stimulation (10). Further, we have shown that compared to patients not taking opioids, chronic pain patients taking opioids show differential response to reward processing in the brain (11). However, to our knowledge, no studies in patients with chronic pain who take opioid medications have investigated spinal cord activity.

By investigating spinal cord activity, new information can be gained regarding CNS activity in patients with chronic pain who take opioids. Spinal cord activity can be non-invasively and, as demonstrated through technological improvements over the last decade, reliably measured in human clinical research using functional magnetic resonance imaging (fMRI) (12). While fMRI of the brain has been used extensively to identify altered activity within the central nervous system to help elucidate the etiology of the chronic pain condition, fibromyalgia, alterations have also been shown in the periphery (13–15). Thus, to link these peripheral and central nervous system findings, we have extended this evidence to the spinal cord and previously showed regional differences in spinal cord activity in patients with fibromyalgia vs. healthy controls (16). However, none of the patients in the previous study were taking opioid medications. Importantly, individuals with fibromyalgia who take opioids do not tend to do better than their counterparts who take non-opioid medications (5), and use of opioid medications may produce opioid-induced hyperalgesia (2). Opioid-induced hyperalgesia has been documented in clinical populations, and occurs in part, via enhanced spinal cord activity [i.e., increased descending facilitation (17, 18)]. Therefore, we hypothesized that patients with fibromyalgia who take opioids (vs. patients with fibromyalgia who do not take opioids) would show greater regional alterations in spinal cord activity (i.e., enhanced central sensitization).

To test this hypothesis, in the present pilot study, we analyzed resting-state (task-free) fMRI data from the spinal cord in a cohort of patients with fibromyalgia who take opioids. We focused our analysis on the cervical spinal cord based on technological availability (i.e., head and neck coil and fMRI protocol for this region). We compared cervical spinal cord activity (i.e., the amplitude of low frequency fluctuations, ALFF) from the cohort of patients with fibromyalgia who take opioids (i.e., opioid group) to previously analyzed data sets of patients with fibromyalgia who do not take opioids (i.e., non-opioid group) and healthy pain-free controls. Lastly, we tested for behavioral/clinical correlations and compared functional connectivity and graph metrics from the resting-state fMRI data to understand functional network characteristics within the spinal cord that may be differentially altered in patients taking opioids.

METHODS

Participants

Patients with fibromyalgia not taking opioids ($N = 17$), patients with fibromyalgia taking opioids ($N = 16$) and pain-free healthy controls ($N = 17$) participated in the study. Recruitment and data collection were conducted from May through August 2016. All patients were female and met the following inclusion criteria: modified American College of Rheumatology (ACR) 2011 criteria for fibromyalgia [widespread pain index (WPI) ≥ 7 + symptom severity (SS) ≥ 5, or WPI 3-6 + SS ≥ 9; with symptoms present at the same level for > 3 months; no disorder to otherwise explain the pain] (19), pain in all four body quadrants, average pain over the previous month > 2, not pregnant or nursing, no MRI contraindications, and no depression or anxiety disorder. Patients took their usual medications during the study (**Table 1**). To reduce potential bias of subject data inclusion within the three groups, the groups were recruited separately using three pre-defined sets of eligibility criteria as follows: The non-opioid fibromyalgia group was required to not have taken any opioid medications within the last 90 days and not have taken opioid medications for >30 days in their lifetime. The opioid fibromyalgia group was required to have taken opioid medications for at least the

TABLE 1 | Demographic and clinical symptom measures are shown for each group with three group *t*-test comparisons between groups.

	Healthy controls			FMN patients			FMO patients			HC vs. FMN	HC vs. FMO	FMN vs. FMO
	N	Mean	Std Dev	*N*	Mean	Std Dev	*N*	Mean	Std Dev	*t*-test *P*-value	*t*-test *P*-value	*t*-test *P*-value
Age	14	48.71	11.10	15	47.13	9.82	15	53.27	6.73	0.687	0.200	0.056
WPI score	14	0.00	0.00	15	13.80	3.53	14	13.36	3.52	<0.001*	<0.001*	0.738
SS score	14	0.00	0.00	15	8.27	1.94	11	8.27	1.85	<0.001*	<0.001*	0.994
SHS	14	72.50	13.50	15	103.13	13.27	15	100.27	14.35	<0.001*	<0.001*	0.574
Fatigue	14	48.19	5.36	15	65.10	6.73	14	69.34	5.28	<0.001*	<0.001*	0.072
BPI severity	14	0.23	0.49	15	5.14	1.82	15	5.82	1.61	<0.001*	<0.001*	0.290
BPI interference	10	0.61	1.07	15	5.05	2.52	15	6.19	1.91	<0.001*	<0.001*	0.184

*Portions reused and modified with permission from Martucci et al. (16). BPI, brief pain inventory; HC, healthy controls; FMN, fibromyalgia non-opioid; FMO, fibromyalgia opioid; N, number of subjects, SHS, sensory hypersensitivity scale; SS, symptom severity; Std Dev, standard deviation; WPI, widespread pain index; P-value, significance (two-tailed independent samples t-test); *p < 0.05.*

past 90 days. Control participants were pain-free, free of any depression or anxiety disorder, and not taking pain or mood-altering medications. Data from the non-opioid and healthy control groups were analyzed and published previously (16).

Study Procedures

All procedures were approved by the Stanford University Institutional Review Board, were carried out in accordance with the approved protocols, and were conducted at the Stanford University Richard M. Lucas Center for Imaging. All participants signed written and informed consent acknowledging their willingness to participate in the study, understanding of all study procedures, and understanding that they were free to withdraw their study participation at any time.

Participants completed questionnaires including the Fibromyalgia 2011 Diagnostic Criteria (19) for Widespread Pain Index (WPI) and Symptom Severity (SS) scores, Fibromyalgia Assessment Questionnaire, the Sensory Hypersensitivity Scale (SHS) (20), the Short Form Brief Pain Inventory (BPI) (21), and PROMIS Fatigue (bank v1.0, adaptive) (22). The PROMIS Fatigue bank have been developed, calibrated, and validated in the general and diverse patient populations (M = 50, SD = 10) and are available for public use (www.healthmeasures.net/). Additional questionnaires and brain scans collected were not included in the present analysis.

MRI Scanning Procedures

A 3T General Electric Signa Discovery MR750 scanner with a 16-channel head and neck neurovascular coil (GE Systems, Chicago, Illinois) was used for MRI scanning. The scan session included initial preparatory localizer scans, ASSET calibration scan, high-order shimming using the whole body coil of the scanner, a resting state functional scan, and structural scan sequences. The entire imaging session took 30–45 min. Participants were asked for verbal pain ratings via the scanner's intercom and their comfort was ensured throughout the MRI scanning session.

Functional magnetic resonance imaging (fMRI) scans of the cervical spinal cord were acquired using a 2D gradient-echo (GE) echo-planar-imaging (EPI) sequence [14 oblique slices, 4 mm slice thickness, repetition time (TR) 2,500 ms, interleaved acquisition, echo time (TE) 30 ms, flip angle 75°, FOV 160 × 160 mm^2, with matrix size 128 × 128, and in-plane resolution 1.25 × 1.25 mm^2, total of 264 volumes]. The field-of-view was centered at the middle of the C6 vertebra and extended from the most superior part of the C5 vertebra to the most inferior part of the C7 vertebra. One control subject's fMRI scan parameters differed slightly (flip angle 70°, 17 oblique slices, FOV 220 × 220 mm^2 in-plane resolution 1.7 × 1.7 mm^2, 3 mm slice thickness, 1 mm gap); exclusion of this subject did not change the results, therefore the final results include this subject's data. Verbal pain ratings (0–10 scale, with verbal descriptive anchors of "no pain" and "worst pain imaginable") were obtained before and after the fMRI scans.

A high-resolution structural MRI scan was acquired using a single slab 3D fast spin-echo (FSE) T2-weighted sequence (Cube) [TR 2,500 ms, TE 85 ms (maximum), echo train length 70, slice thickness = 1.4 mm, FOV 240 × 240 mm^2, matrix size 256 × 256, effective resolution 1.4 × 0.94 × 0.94 mm^3, interpolated resolution 0.7 × 0.47 × 0.47 mm^3, number of averages 2]. This scan was used for registration of fMRI images to the PAM50 T2-weighted spinal cord template De Leener et al. (23).

An additional structural scan with optimized spinal cord gray matter–white matter contrast was acquired using a 2D axial multi-echo recombined GE (MERGE) sequence (32 oblique slices, 3 mm slice thickness, 0.5 mm spacing, TR 525 ms, TE 5.4 ms, number of echoes 3, flip angle 20°, FOV 180 × 144 mm^2, FOV centered at C6 vertebra, matrix size 320 × 192, in-plane resolution 0.35 × 0.35 mm^2, and number of averages 2). The MERGE sequence images were used to assist with registration of internal spinal cord structures (i.e., gray vs. white matter) to the PAM50 template.

Image Processing

We preprocessed the functional images as performed previously (24, 25) using customized in-house scripts, Oxford Center for Functional MRI of the Brain's (FMRIB) Software Library (FSL), and the Spinal Cord Toolbox version 3.0 (26, 27).

Motion Correction

We applied motion correction to the resting state fMRI data using a two-phase design calling FSL's Linear Image Registration Tool (FLIRT) with normalized correlation cost function and spline interpolation (28). First, a binary mask was manually drawn for each data set, which included the vertebral column, to create the reference image and exclude any regions of non-rigid motion from respiration and swallowing. In the first phase of motion correction, we used two-step 3D rigid body realignment: (1) We realigned the fMRI time series volumes to the middle time point reference volume, (2) we calculated the mean time series image and repeated realignment using the mean image new reference volume. In the second phase of motion correction, we used 2D rigid realignment to correct slice-independent motion; we realigned each axial slice independently using the mean image reference volume.

Registration to Template Space

We performed spatial registration to the PAM50 T2-weighted spinal cord template (resolution $0.5 \times 0.5 \times 0.5$ mm^3) to bring the fMRI images into the same image space (27). First, we cropped the T2-weighted structural image to include only C2 to T1 vertebrae. To create a structural segmentation mask, we segmented the spinal cord from the T2-weighted structural image. To create a vertebral landmarks mask, we marked the C2 and T1 vertebrae using the drawing feature in FSLview. Then, we straightened the T2-weighted structural image along the spinal cord using the structural segmentation mask and registered it to the template using the landmarks mask to guide registration along the superior-inferior (z) axis. Next, to initialize registration, we manually segmented the spinal cord from the MERGE (structural image with increased gray matter and white matter contrast) image, and used the template to T2-weighted image transformation to co-register the template to the MERGE image and the structural segmentation mask. Then, we segmented the spinal cord gray matter from the MERGE image, and used this to more precisely register the template to the internal spinal cord structures (i.e., white matter and gray matter). We then segmented the spinal cord from the mean motion-corrected fMRI image to create a functional segmentation mask, and co-registered the template to the mean fMRI image using the template to MERGE image transformation and functional segmentation masks to initialize the registration. This step was followed by non-linear registration in the axial plane only. Lastly, we concatenated the transformations from each of the above steps to allow for forward transformation of fMRI images to template space, as well as reverse transformation of the template masks into fMRI space (29).

Image Denoising

Spinal cord fMRI data are susceptible to noise from subject movement, cardiac and respiratory cycles, and cerebrospinal fluid (CSF) pulsations (30). To reduce the impact of physiological noise, we used FSL's physiological noise modeling (PNM) tool (31, 32) to create 16 slice-specific cardiac and respiratory noise regressors using physiologic data collected by the MRI scanner (sine and cosine terms with principal frequency and next three harmonics). Our rationale for this approach was based on retrospective correction of physiologic noise and motion effects (RETROICOR) (33) used previously in resting state spinal cord fMRI analysis (25). We generated additional multiplicative terms to account for interactions between the cardiac and respiratory cycles (total of 32 regressors). For CSF signal regression, we manually created CSF masks on the mean motion-corrected fMRI images and we used these to generate a slice-specific CSF noise regressor based on each slice's mean CSF signal. For white matter signal regression, as advised for spinal cord resting state fMRI analyses (34), we used the PAM50 template white matter probability map by warping to functional space, thresholding at 0.5 ($\geq$50% probability), and eroding (to ensure no overlap with gray matter) to generate a slice-specific white matter noise regressor based on the mean white matter signal for each slice. In summary, our generated regressors included motion correction parameters (i.e., x, y, z rotations and translations from the first phase of motion correction), physiologic noise regressors (cardiac and respiratory), and tissue-specific noise (white matter and CSF). We regressed all of these from the motion-corrected fMRI time series using FSL's Improved Linear Model (FILM) (35).

Normalization of Functional Images, Spatial Smoothing, Quality Control

The denoised functional images were subsequently warped to the PAM50 template space. Spatial smoothing of the normalized fMRI images was performed with a $2 \times 2 \times 4$ mm^3 full-width half maximum (FWHM) gaussian kernel prior to the ALFF analyses. Lastly, visual inspection of the fMRI preprocessed data was performed for quality control.

Mean ALFF Analysis

Amplitude of low frequency fluctuations (ALFF) is a measurement of low frequency oscillatory power based on the blood oxygen level dependent (BOLD) fMRI signal. It can be used as a general measure of CNS activity for resting-state fMRI data analysis. ALFF is advantageous for studying CNS activity because it is not dependent on the correlation of activity across selected regions of interest, but rather can provide independent measures of activity on a per-voxel basis. ALFF measures are calculated per subject and allow for comparison between patients and controls. It has been reported that ALFF has high test-retest reliability and, as compared with fractional ALFF (i.e., fALFF), ALFF has been shown to be more sensitive to individual and group-level differences (36). Thus, Mean ALFF was our primary measure to compare spinal cord resting state fMRI activity in patients with fibromyalgia taking vs. not taking opioids.

To calculate Mean ALFF for each voxel in each subject's preprocessed fMRI data, the Data Processing Assistant for Resting-State fMRI Advance Edition (DPARSFA) Toolbox (37) was used, running in Matlab R2015b on Windows 10 Pro. Initially, Mean ALFF was calculated across all low frequencies of 0.01–0.198 Hz and then tested for between-group differences. The Mean ALFF data were normalized (z-transformed) prior to statistical analysis.

To determine group differences in Mean ALFF, we analyzed normalized ALFF images to identify between-group differences

using FSL's randomize tool. First, the normalized ALFF images (i.e., one per subject) were concatenated into a single multi-volume image. Then, the multi-volume image (i.e., 1 volume per subject) was processed using randomize to conduct a two-sample unpaired t-test of the images in each volume (38). Lastly, the significance level of between-group differences was evaluated with threshold-free cluster enhancement (TFCE) at both an uncorrected and corrected $p < 0.05$ (using 5,000 permutations).

fMRI and Symptom Measures Correlation Analysis

For the correlation analyses of Mean ALFF values with symptom measures, we first extracted Mean ALFF values for each individual patient using regions of greater Mean ALFF and lesser Mean ALFF for frequencies 0.01–0.198 Hz (uncorrected $p < 0.05$) from the comparison of opioid and non-opioid patient groups. We then used these extracted Mean ALFF values to evaluate relationships with symptom measures across the two patient groups, and each patient group vs. healthy controls (IBM, SPSS Statistics, version 26). We included the following symptom measures from questionnaires in our analyses: average scan pain (mean of pre and post scan ratings), ACR fibromyalgia criteria widespread pain index (WPI) score, ACR fibromyalgia criteria symptom severity (SS) score, sensory hypersensitivity (SHS), fatigue (PROMIS Fatigue T-score metric, calculated using REDCap item response theory (IRT) scoring), pain severity (BPI), and pain interference (BPI). These symptom measures broadly represent sensory aspects of chronic pain (e.g., distribution of pain across the body, severity of other bodily symptoms, hypersensitivity to multiple types of sensory stimuli, sensation and experience of fatigue, pain intensity experienced on average, and pain interference experienced on average, respectively). The correlational analyses between fMRI data and questionnaire data were exploratory, selected for aspects of symptoms typically important for characterization of the clinical presentation of fibromyalgia (e.g., fatigue), and not corrected for multiple comparisons.

Functional Connectivity and Graph Metrics Analysis

Functional connectivity is a measure of temporal correlation of signals between CNS regions, and provides a tool to understand the functional organization of brain networks and, more recently, spinal cord networks. Bilateral motor (i.e., right and left ventral horn) and bilateral sensory (i.e., right and left dorsal horn) resting state fMRI spinal cord networks exist (39–41) and have been shown to be altered after spinal cord injury and during thermal stimulation when applied unilaterally (25, 42). Therefore, because altered spinal cord processing may partially contribute to fibromyalgia, in the present study we also investigated spinal cord networks using functional connectivity analysis. We used a seed-based region of interest (ROI) approach as recently reported by our group (16, 25).

Functional connectivity strength was measured between left-ventral, left-dorsal, right-dorsal, and right-ventral horns at five levels (4.0 mm thick ROIs) which were vertically distributed (4.0 mm gap between ROIs) within the cervical spinal cord FOV (20 ROIs total). We generated the ROIs using the corresponding PAM50 spinal cord template probabilistic gray matter mask (0.5 thresholded) (23). We then extracted the mean time series from the preprocessed bandpass filtered (0.01–0.198 Hz) functional images for each ROI and for each participant, and created correlation matrices by calculating Fisher-transformed Pearson correlation coefficients between each ROI pair. We then calculated the mean ventral-ventral (V-V), dorsal-dorsal (D-D), ventral-dorsal within hemi-cord (V-D within), and ventral-dorsal between hemi-cord (V-D between) functional connectivity across the five levels. We compared functional connectivity strength to no connectivity ($r = 0$) within each group (one-sample t-test) and between groups (two-sample t-test).

Graph Metrics Analysis

Lastly, we calculated weighted, undirected global graph metrics of modularity, efficiency, and small worldness to estimate topological properties of functional networks across the 20 ROIs. We calculated the graph metrics with GraphVar software and the Brain Connectivity Toolbox, and we used the absolute value of weights and relative thresholds over varied link densities (10, 20, 30, 40, and 50%) (43, 44). We normalized our graph metrics to metrics from 100 participant-specific random generated (5,000 iterations). We identified between group differences in graph metrics using a repeated measures general linear model (i.e., repeated measures ANOVA with between-group effects) across link densities for each of three group comparisons (1) healthy controls vs. non-opioid patients, (2) healthy controls vs. opioid patients, and (3) non-opioid patients vs. opioid patients.

RESULTS

Patients with fibromyalgia not taking opioids ($N = 17$), patients with fibromyalgia taking opioids ($N = 16$) and pain-free healthy controls ($N = 17$) participated in the study. We excluded data from six participants due to issues of poor resting-state fMRI image quality (one non-opioid patient, one opioid patient, two controls), scan artifacts (one non-opioid patient), and incorrect resting-state fMRI scanner sequence prescription (one control). Thus, we included in the analysis a total data set from 15 non-opioid patients, 15 opioid patients, and 14 healthy controls. Patients continued their usual prescribed non-opioid and opioid medications during the study (see **Supplementary Table 1** and **Supplementary Figure 1**). Each patient underwent an MRI session of the cervical spinal cord (spanning the C5, C6, and C7 vertebrae) which included a fMRI scan to measure spinal cord activity at rest, and both sagittal and axial structural MRI scans for registration of the fMRI images to a standard template.

Participant Symptom Measures

All participants reported their pain ratings before and after the fMRI scan and completed questionnaires measuring their pain distribution across the body, symptom severity, sensory hypersensitivity, and fatigue. Symptom measures of pain (WPI, SS, BPI), fatigue (PROMIS Fatigue, total converted T score), and sensory hypersensitivity (SHS) were greater in

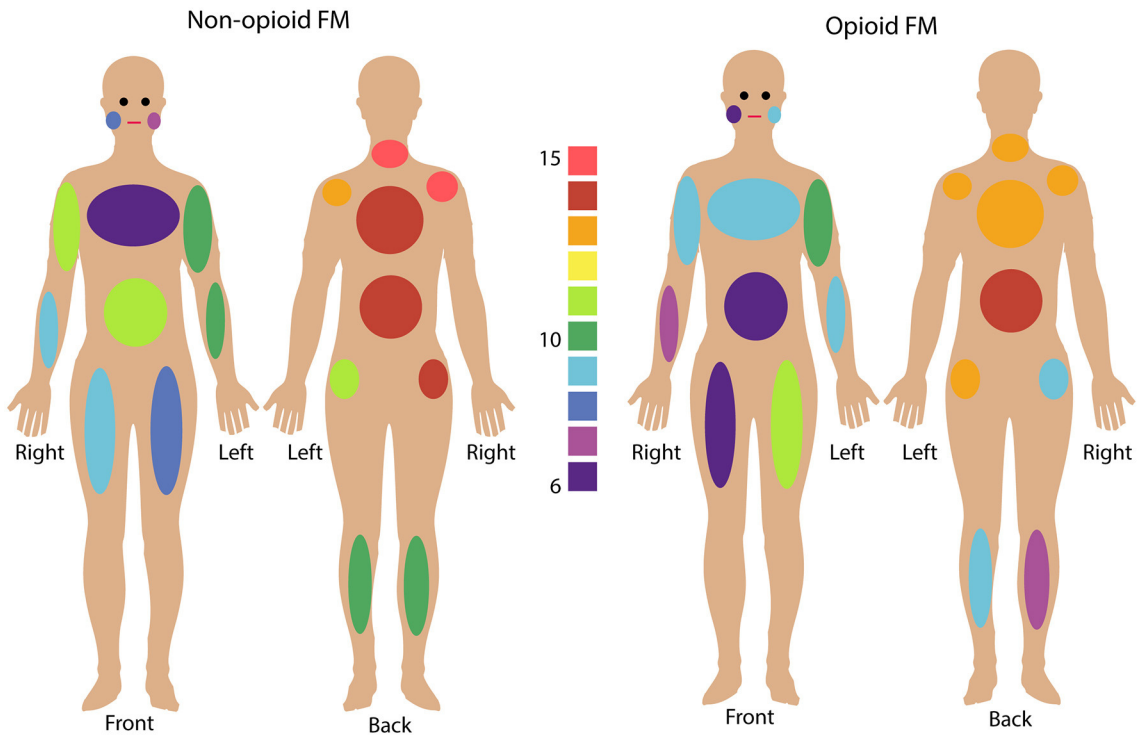


FIGURE 1 | Fibromyalgia pain distribution across the body. Non-opioid patients (left) and opioid patients (right) are shown. Colors indicate the number of patients in each group who reported pain in any given body area using the Fibromyalgia Assessment Questionnaire. Bilateral body areas include right and left shoulder, upper arm, lower arm, hip, upper leg, lower leg, and jaw; and axial areas include chest, abdomen, upper back, lower back, and neck. (See **Supplementary Table 5** for details on individual patient reported pain locations).

both opioid and non-opioid patient groups compared to the healthy control group, however, no symptom measures were significantly different between non-opioid and opioid groups (**Table 1**). Additionally, both opioid and non-opioid patients reported widespread pain distribution across the body, which is characteristic of fibromyalgia (**Figure 1**, individual patient details in **Supplementary Table 5**).

Altered Regional Spinal Cord Mean ALFF in Opioid and Non-Opioid Patients

To characterize spinal cord activity in fibromyalgia patients who take opioids, resting-state fMRI images were analyzed and compared between groups of opioid patients and non-opioid patients, and healthy controls. The fMRI images were analyzed using standard preprocessing scripts and published methods to calculate the mean amplitude of low frequency fluctuations (ALFF) for each participant's data set. ALFF provides a measure of low frequency oscillatory activity (0.01–0.198 Hz) that occurs at rest in the CNS and is related to the BOLD fMRI signal.

In opioid patients as compared with healthy controls, we observed distributed regions of greater Mean ALFF and regions of lesser Mean ALFF, but only at the uncorrected threshold (uncorrected $p < 0.05$) (**Figure 2**). Comparing non-opioid patients to healthy controls, we observed more robust distributed regions of greater and lesser Mean ALFF (uncorrected $p < 0.05$), and a small region of greater Mean ALFF (corrected $p < 0.05$) [data published previously (16)] (**Figure 2**). Contrasting the two patient groups resulted in similar regional differences as observed between non-opioid patients and healthy controls (**Figure 3**). These regions overlapped with regional Mean ALFF group differences for non-opioid patients vs. healthy controls, and opioid patients vs. healthy controls. In summary, when comparing each patient group to healthy controls, opioid patients showed fewer regions of Mean ALFF differences than non-opioid patients (for cluster details see **Supplementary Table 2**). Additionally, individual patients' Mean ALFF values, extracted from non-opioid fibromyalgia greater than healthy controls (i.e., greater Mean ALFF, FMN > HC) vs. FMN < HC (i.e., lesser Mean ALFF) regions, were inversely correlated across patient groups ($N = 30$, Pearson correlation, $r = -0.817$, $p < 0.001$).

For the correlation analyses of Mean ALFF values with symptom measures, we first extracted Mean ALFF values for each individual patient using masks of the regions of greater Mean ALFF and lesser Mean ALFF for frequencies 0.01–0.198 Hz (uncorrected $p < 0.05$) from the comparison map of opioid and non-opioid patient groups (see **Figure 4**). We then used these extracted Mean ALFF values to evaluate relationships with symptom measures across the two patient groups, and all three groups. Across patient groups, fatigue (PROMIS Fatigue T score) positively correlated with Mean

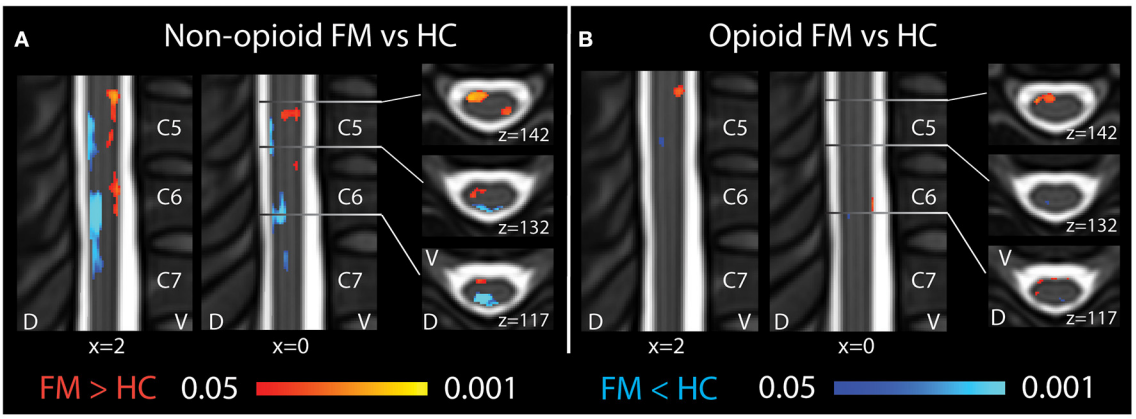


FIGURE 2 | Spinal cord regional mean ALFF differences among patients taking and not taking opioids vs. healthy controls. **(A)** Compared to healthy controls, fibromyalgia patients who were not taking opioids (non-opioid FM) showed several spinal cord regions of ventral increases and dorsal decreases in Mean ALFF. Images reused and modified with permission from Martucci et al. (16). **(B)** Compared to healthy controls, opioid fibromyalgia patients (opioid FM) showed few regions of altered Mean ALFF. Red shading indicates regions of greater Mean ALFF and blue shading indicates regions of lesser Mean ALFF in patient groups vs. healthy controls. Sagittal images are indicated with "x" coordinate locations and axial images are indicated with "z" coordinate locations based on the PAM50 template (23). D, dorsal; FM, fibromyalgia; HC, healthy controls; L, left; R, right; V, ventral. *P*-values are uncorrected <0.05.

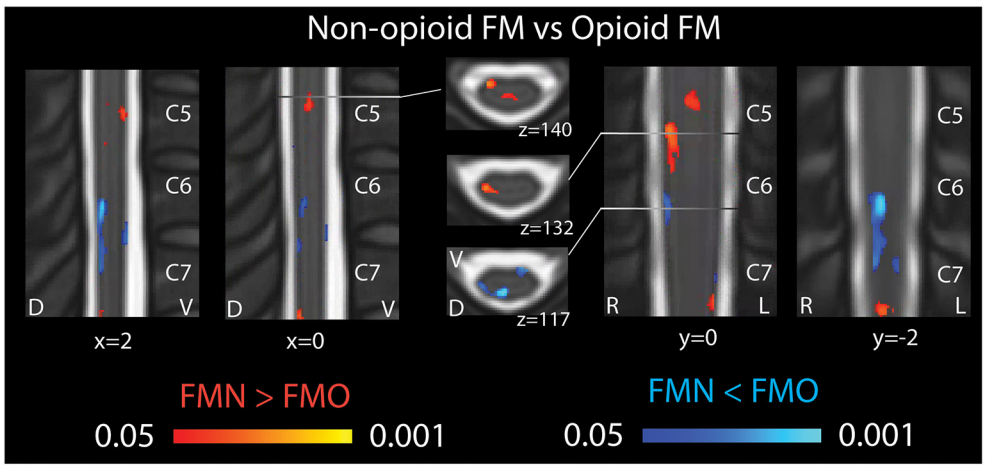


FIGURE 3 | Spinal cord regional mean ALFF differences in patients not taking opioids vs. patients taking opioids. Fibromyalgia patients who were not taking opioids (non-opioid FM) showed several spinal cord regions of greater Mean ALFF vs. patients taking opioids (opioid FM) (regions of red shading, FMN > FMO). Non-opioid fibromyalgia patients showed several spinal cord regions of lesser Mean ALFF vs. patients taking opioids (regions of blue shading, FMN < FMO). Sagittal images are indicated with "x" coordinate locations, coronal images are indicated with y coordinate locations, and axial images are indicated with "z" coordinate locations based on the PAM50 template (23). D, dorsal; FM, fibromyalgia; FMN, non-opioid FM; FMO, opioid FM; L, left; R, right; V, ventral. *P*-values are uncorrected <0.05.

ALFF values extracted from regions of greater Mean ALFF in patients taking opioids; and fatigue negatively correlated with Mean ALFF values extracted from regions of lesser Mean ALFF in patients taking opioids (**Figure 4**). The relationships between Mean ALFF and fatigue were exploratory and not corrected for multiple comparisons. No other correlations of extracted Mean ALFF values were found with any other symptom measure (**Table 2**).

We additionally conducted a *post-hoc* analysis, within the group of patients taking opioids, that identified no correlations between the Mean ALFF values and opioid dose ($r = -0.015$, $p = 0.706$; $r = 0.023$, $p = 0.936$; for values extracted from regions of greater and lesser Mean ALFF, respectively) (**Supplementary Figure 2**).

Altered Functional Connectivity in Patients Taking Opioids

In addition to Mean ALFF values as a measure of regional activity within the spinal cord, we hypothesized that patients taking opioids would show altered functional connectivity between ventral and dorsal regions of the spinal cord. Bilateral motor (V-V) and sensory (D-D) functional spinal cord networks are found

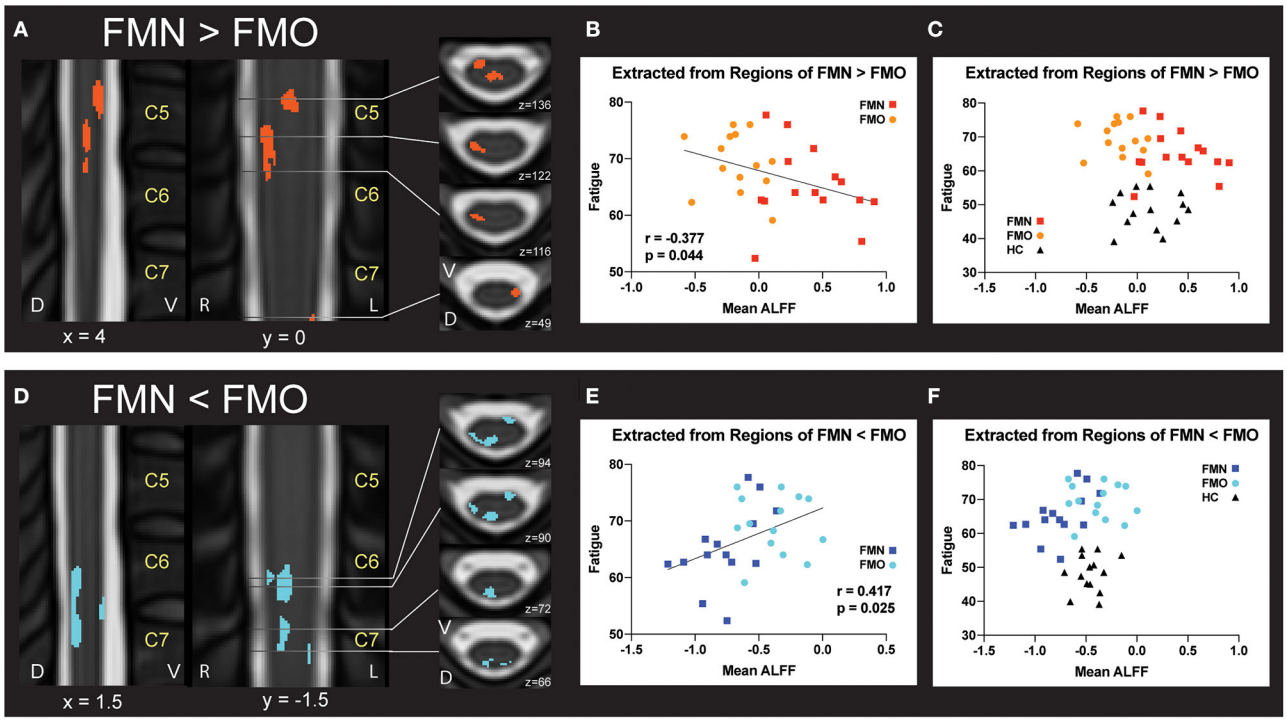


FIGURE 4 | Correlations between regional mean ALFF and fatigue. **(A)** Regions of greater Mean ALFF were identified in fibromyalgia patients who were not taking opioids (non-opioid FM, FMN) vs. patients taking opioids (opioid FM, FMO). **(B)** Individually extracted regional Mean ALFF values were negatively correlated with fatigue across patient groups. **(C)** Healthy control values are plotted for visual comparison only. **(D)** Regions of lesser Mean ALFF were identified in fibromyalgia patients who were not taking opioids (non-opioid FM, FMN) vs. patients taking opioids (opioid FM, FMO). **(E)** Individually extracted regional Mean ALFF values from FMN < FMO regions were positively correlated with fatigue across patient groups. **(F)** Healthy control values are plotted for visual comparison only. Sagittal images are indicated with "x" coordinate locations, coronal images are indicated with "y" coordinate locations, and axial images are indicated with "z" coordinate locations based on the PAM50 template (23). ALFF, amplitude of low frequency fluctuations; D, dorsal; FM, fibromyalgia; FMN, non-opioid FM; FMO, opioid FM; HC, healthy controls, L, left; R, right; V, ventral. *P*-values are uncorrected <0.05.

TABLE 2 | Pearson correlations between region extracted Mean ALFF (0.01–0.198 Hz) and symptom measures across non-opioid FM patients ($N = 15$) and opioid FM patients ($N = 15$).

	ALFF FMN > FMO			ALFF FMN < FMO		
	N	***r***	***p***	***N***	***r***	***p***
Average scan pain	28	−0.074	0.708	28	0.155	0.431
WPI score	29	0.143	0.460	29	−0.185	0.337
SS score	26	−0.061	0.766	26	0.115	0.577
Sensory Hypersensitivity (SHS)	30	−0.112	0.556	30	−0.112	0.556
Fatigue (PROMIS)	29	0.417*	0.025	29	−0.377*	0.044
Pain Severity (BPI)	30	0.263	0.159	30	−0.189	0.318
Pain Interference (BPI)	29	0.196	0.308	29	−0.114	0.554

*ALFF, amplitude of low frequency fluctuations; BPI, brief pain inventory; PROMIS, patient-reported outcomes measurement information system; SS, symptom severity; SHS, sensory hypersensitivity scale; WPI, widespread pain index; r, Pearson correlation; p, significance (two-tailed). *p < 0.05.*

in healthy individuals (25, 39–41, 45). Thus, we analyzed mean ventral-ventral (V-V), dorsal-dorsal (D-D), ventral-dorsal within hemi-cord (V-D within), and ventral-dorsal between hemi-cord (V-D between) functional connectivity among the opioid patient group, non-opioid patient group, and healthy control group. We observed that V-V connectivity was significant ($r > 0$) for the opioid patient group (mean $r \pm 1$ SE $= 0.148 \pm 0.026$, $p < 0.001$), as well as for healthy controls ($r = 0.104 \pm 0.033$, $p = 0.008$) and non-opioid patients (mean $r \pm 1$ SE $= 0.078 \pm 0.018$, $p < 0.001$). Additionally, we observed that D-D connectivity only trended toward significant for the opioid patient group ($r = 0.041 \pm 0.022$, $p = 0.075$), and was significant for healthy controls ($r =$

0.087 ± 0.030, $p = 0.013$) and non-opioid patients ($r = 0.065 \pm 0.014$, $p < 0.001$). We observed that V-D within connectivity was not significant for the opioid patient group ($r = 0.006 \pm 0.013$, $p = 0.629$) nor other groups (healthy controls $r = 0.031 \pm 0.027$, $p = 0.266$; non-opioid patients $r = -0.012 \pm 0.013$, $p = 0.360$) (**Figure 5**). We observed that V-D between connectivity was significant for the opioid patient group (mean $r \pm 1$ SE $= 0.044 \pm 0.015$, $p = 0.011$), but was not significant for non-opioid patients ($r = 0.017 \pm 0.017$, $p = 0.325$) nor healthy controls ($r = 0.040 \pm 0.021$, $p = 0.080$). Please Note: Connectivity strength for non-opioid patients and healthy controls were reported previously (16) and are mentioned here for context in comparison to the opioid patient group.

We also tested for group differences in functional connectivity by comparing across each set of groups. Group differences between healthy controls vs. opioid patients were not significant for V-V ($p = 0.302$), D-D ($p = 0.228$), V-D within ($p = 0.397$), or V-D between ($p = 0.873$) functional connectivity. These results were similar to previously reported results of group differences between healthy controls vs. non-opioid patients which were not significant for V-V ($p = 0.503$), D-D ($p = 0.514$), V-D within ($p = 0.149$), or V-D between ($p = 0.409$) functional connectivity (16). The group difference between non-opioid patients vs. opioid patients was significant for V-V functional connectivity, with greater V-V functional connectivity for the opioid patient group ($p = 0.038$), but group differences were not significant for D-D ($p = 0.362$), V-D within ($p = 0.318$), or V-D between ($p = 0.253$) functional connectivity. Across the patient groups, no relationships were significant between functional connectivity measures and spinal cord Mean ALFF values (**Supplementary Table 3**).

Unaltered Graph Metrics Among Patient and Healthy Control Groups

Graph metrics describe the topological properties of the connectivity of resting state functional networks (43), therefore, to evaluate opioid effects on spinal cord properties of connectivity we analyzed graph metrics of small worldness, efficiency, and modularity. Consistent with previous reports of graph metrics analysis (25, 46), we did not observe differences in small world properties at the lower link densities (all $p > 0.05$). Mean small worldness at the 10% link density was 2.240 ± 0.302 for healthy controls, 2.354 ± 0.365 for non-opioid patients, 2.038 ± 0.433 for opioid patients. We did not find any group differences to be significant (healthy controls vs. opioid patients $p = 0.708$; healthy controls vs. non-opioid patients $p = 0.814$; opioid vs. non-opioid patients $p = 0.582$). Additionally, we did not find any group differences across the range of link densities for graph metrics of small worldness, efficiency, and modularity (all $p > 0.05$) (**Figure 5**; **Supplementary Table 4**).

DISCUSSION

In the present study, we measured spinal cord resting-state fMRI-associated low frequency power, network functional connectivity, and graph metrics to compare spinal cord activity and networks in patients with fibromyalgia taking opioids, patients with fibromyalgia not taking opioids, and healthy controls. Importantly, our groups of patients with fibromyalgia taking vs. not taking opioids reported similar levels of pain and clinical symptoms. Despite this, we found that, compared to non-opioid patients vs. healthy controls, our opioid patients demonstrated fewer regional differences in spinal cord low frequency power (ALFF) compared to healthy controls. In addition, individual differences in regional Mean ALFF, across opioid and non-opioid patients, were correlated with self-reported levels of fatigue. Lastly, compared to the other groups, the opioid patient group showed slight differences in functional connectivity. Overall, compared to previously reported results contrasting non-opioid patients with fibromyalgia vs. healthy controls, patients with fibromyalgia taking opioids showed less altered spinal cord low frequency power, unique differences in functional connectivity, and these changes appeared to be related to self-reported fatigue.

Differences in ALFF in the patient groups were observed primarily as more activity in ventral regions and less activity in dorsal regions of the spinal cord. The regions of altered activity were predominantly within white matter regions of the spinal cord. These observed signal differences, while apparent in the white matter, could in fact, have occurred within the spinal cord gray matter because the BOLD fMRI signal may parallel spinal cord blood flow and diffuse outward from the center of the spinal cord. However, assuming that these activity differences occur predominantly in white matter, our results may relate to potential differences in transmission of sensory and pain-related information in patients not taking opioids, and to a lesser extent in patients taking opioids. The differences observed in ventral spinal cord were localized to regions of the right spinothalamic tract, which transmits thermal and pain-related information; thus, increased ventral activity in patients who were not taking opioids, and to some extent in patients who were taking opioids, indicates potential increased transmission of pain-related information in fibromyalgia. Conversely, the differences observed in the dorsal spinal cord were localized to regions of the dorsal columns / medial lemniscus, which transmit sensory, touch, and vibrotactile information; thus, decreased dorsal activity in patients not taking opioids, and to some extent in patients who were taking opioids, indicates potential decreased transmission of sensory information in fibromyalgia. Ultimately, these differences in patient groups suggest a potential imbalance in ventral-dorsal transmission of noxious and innocuous information, respectively. When simultaneous noxious and innocuous stimuli are administered to the skin, they inhibit the transmission of each other in the central nervous system (47, 48). Future studies including sensory testing experiments, such as thermal and vibrotactile stimuli, could help identify potential correlations with spinal cord activity, and support the hypothesis of imbalanced transmission of pain vs. sensory information in fibromyalgia, and how these changes may be influenced by opioid use.

Opioids exert their analgesic effects primarily via inhibitory, e.g., GABAergic, mechanisms, and this may explain the reduced

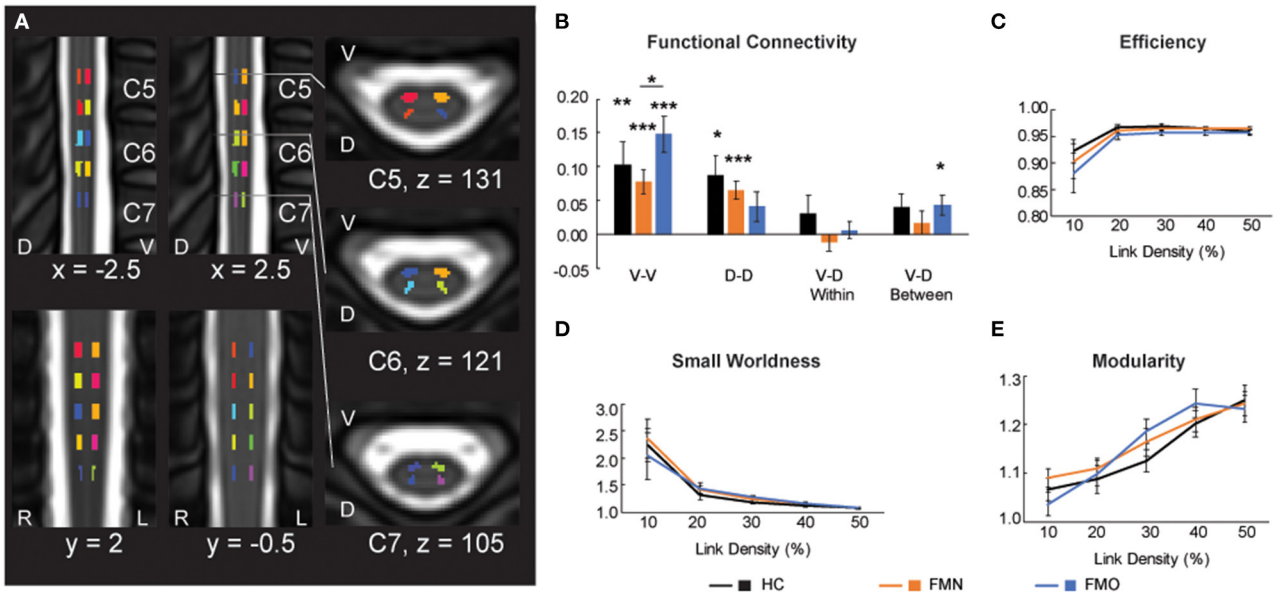


FIGURE 5 | Functional connectivity and graph metrics. **(A)** Colored regions indicate spinal cord regions of interest that were used for the functional connectivity and graph metric analyses. Reused and modified with permission from Martucci et al. (16). **(B)** Functional connectivity for ventral-ventral (V-V), dorsal-dorsal (D-D), ventral-dorsal within (V-D Within), and ventral-dorsal between (V-D Between). **(C–E)** Graph metrics of efficiency, small worldness and modularity across the three groups: healthy controls (HC), fibromyalgia patients not taking opioids (FMN), and fibromyalgia patients taking opioids (FMO). D, dorsal; L, left; R, right; V, ventral. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

observed differences in spinal cord activity in our patients taking opioids. Both patient groups (opioid and non-opioid) showed increased ventral spinal cord activity (i.e., Mean ALFF) vs. healthy controls, however, in the patients taking opioids the increased ventral spinal cord activity was much more limited. The limited increase in ventral spinal cord activity in patients taking opioids may represent opioid effects that would be expected to result in reduced transmission of pain-related information via the spinothalamic tract. The spinothalamic tract resides within the ventral spinal cord regions of observed activity differences in our results. Thus, our observation of less increased activity in the opioid patients is consistent with direct attenuation of responses of spinal nociceptive neurons (49), and indirect activation of descending supraspinal inhibition of noxious information by opioids (50). Further, opioids reduce brain response to noxious information, but not to vibrotactile information (51). Our findings similarly indicate that innocuous (e.g., vibrotactile) information transmission was not reduced by opioid use. Specifically, dorsal spinal cord activity (i.e., localized to dorsal column tracts that transmit innocuous/vibrotactile information) was minimally decreased in our opioid patients vs. healthy controls, but in contrast, dorsal spinal cord activity was markedly decreased in the non-opioid patients vs. healthy controls. Additionally, the minimally decreased dorsal spinal cord activity in the opioid group could be due to a secondary effect, whereby reduced pain transmission (as an effect of systemic opioid medication), in turn, enables increased transmission of sensory/vibrotactile information, via release of pain inhibition effects on sensory input (47, 52). More broadly, exogenous opioids inhibit primary nociceptive afferents, descending/ascending circuits, and downstream effects on supraspinal (brain and brainstem) targets (49). Indeed, differences in brain structure (7) and function (11) occur in chronic pain in the presence of opioids. Therefore, the group differences presently observed between opioid and non-opioid patients could be due to a wide-range of effects within the nervous system.

Across both patient groups, altered dorsal spinal cord ALFF positively correlated with self-reported fatigue, while ventral spinal cord ALFF negatively correlated with self-reported fatigue. These correlations between fatigue and spinal cord activity could relate to descending serotonergic drive or levels of metabolite concentrations in muscle tissue (e.g., protons, lactate, ATP), any of which could influence transmission of sensory and pain information within the spinal cord. For example, via descending spinal cord tracts, serotonin inhibits muscle afferents, which produces sensations of fatigue (53). Greater sensations of fatigue could also be produced by opioid-induced reductions in pain-related spinal cord activity, which thereby disinhibit transmission of sensory information, and increase serotonergic activity (54). Alternatively, increased metabolite concentrations in muscle tissue produce sensations of non-painful fatigue (55). Non-painful sensations of fatigue may be more prominent in the opioid patients due to reduced transmission of noxious information, allowing for disinhibited transmission of sensory information. Ultimately, the mechanisms underlying the relationships between fatigue and altered spinal cord activity in

opioid and non-opioid fibromyalgia patients are complex and require further investigation.

Limitations

There are several limitations to consider regarding our results. Overall, we found that patients taking opioids show less alterations in spinal cord activity vs. healthy controls (i.e., Mean ALFF) compared to patients not taking opioids (vs. the same healthy controls). Our findings are limited to fibromyalgia patients, within the observed ranges of pain severity, physical function, and psychological symptoms of the patients included in this study. Our patient groups reported similar levels of pain, depression, and anxiety, while a trend for greater fatigue was observed in the opioid patient group. Additionally, our groups sizes are modest in size and, due to the greater degree of noise inherent to spinal cord fMRI data, larger sample sizes ($N =$ 20 or greater) should be used in future studies to replicate our present findings. Future studies with larger sample sizes would be expected to identify more robust group differences at corrected thresholds (i.e., our uncorrected threshold findings are purely voxel-wise and not corrected for multiple comparisons; they were calculated for each voxel using its individual distribution). Our findings are limited to the cervical spinal cord and future studies should determine if differences in spinal cord activity also exist in the thoracic and lumbar spinal cord of individuals with fibromyalgia.

In the cervical spinal cord, our findings suggest imbalanced ventral vs. dorsal activity observed primarily within the non-opioid patient group, and to a lesser degree in the opioid patient group. This ventral-dorsal activity imbalance may relate to greater transmission of noxious information and reduced transmission of innocuous information in fibromyalgia patients. The imbalanced ventral-dorsal activity was minimally apparent in the opioid patients, suggesting a partial normalization of this imbalance in patients taking opioids. This observed partial normalization in opioid-taking patients, is not consistent with our hypothesis that opioid patients would show greater altered activity due to mechanisms associated with opioid-induced hyperalgesia. However, the observed partial normalization could be due to opioidergic effects inhibiting transmission of noxious information, which in turn could also result in disinhibited transmission of sensory information. Similarly, while patients taking opioids had slightly higher levels of fatigue compared to patients not taking opioids, higher fatigue correlated with less altered spinal cord activity in the opioid group, which could be due to opioidergic inhibition of noxious information, thereby enabling more normal transmission of sensory, non-painful fatigue, sensations. However, the correlations identified in the present study need to be replicated and these posited underlying mechanisms should be tested empirically in future investigations with larger sample sizes. It is also possible that the apparent normalized activity may be due to compensatory mechanisms and may differ under conditions of sensory and/or painful stimulation; such hypotheses remain to be prospectively tested.

Ultimately, from the present investigation conducted during the resting state, we are not able to conclusively determine how analgesic (or other) effects of opioids relate to these pilot findings. Additionally in this study, both groups of patients were taking a variety of medications (see **Supplementary Table 1**) and some of the opioid patients were taking tramadol, which is a multimodal analgesic with opioidergic, serotonergic, and noradrenergic effects; these factors may have influenced our present results. It is also important to note that we did not control for timing of opioid dose and this may additionally contribute to variability in our findings (**Supplementary Figure 1**). In summary, due to the preliminary nature of this study, and the present lack of replication, our findings should not be used to draw clinical conclusions as to the appropriateness of using opioids in the treatment of fibromyalgia.

CONCLUSION

In summary, our findings suggest that, compared to patients who do not take opioids, patients with fibromyalgia who take opioids show fewer alterations in spinal cord low frequency power and unique alterations in functional connectivity. These observed alterations in spinal cord activity may be related to opioid effects on spinal cord transmission of noxious vs. innocuous information and the experience of fatigue. It is hoped that future investigations building upon these preliminary and early findings may help us better understand the benefits vs. harms of long-term use of opioids in fibromyalgia, as well as help us understand the neurophysiologic effects of long-term opioid use for chronic pain.

DATA AVAILABILITY STATEMENT

The datasets generated for this study can be found in online repositories. The name of the repository and accession number can be found below: NeuroVault, https://identifiers.org/neurovault.collection:9624. The other raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Stanford University Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KM designed the study, collected the data, analyzed the data, wrote the manuscript, and edited and revised the manuscript. KW and SM provided assistance with study design, data analysis, and editing of the manuscript. All authors have read and approved the manuscript.

FUNDING

For this study the authors received funding from the National Institutes of Health via K99/R00 DA040154 (KM), T32 DA035165 (KW via SM), K23 NS104211 (KW), L30 NS108301

(KW), K24 DA029262 (SM), and from the Redlich Pain Research Endowment (SM).

ACKNOWLEDGMENTS

We thank Erin Perrine, Christina Cojocaru, and Elizabeth Cha for their assistance with recruitment, data collection, data organization, and analysis. We also thank the Stanford University Richard M. Lucas Center for Imaging and Dr. Gary Glover for expert assistance. Lastly, we thank all of the study participants for their time and contribution to advance clinical research and knowledge.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.694271/full#supplementary-material

REFERENCES

1. Fields HL. Understanding how opioids contribute to reward and analgesia. *Reg Anesth Pain Med.* (2007) 32:242–6. doi: 10.1016/j.rapm.2007.01.001
2. Crofford LJ. Adverse effects of chronic opioid therapy for chronic musculoskeletal pain. *Nat Rev Rheumatol.* (2010) 6:191–7. doi: 10.1038/nrrheum.2010.24
3. Fitzcharles M-A, Ste-Marie PA, Gamsa A, Ware MA, Shir Y. Opioid use, misuse, and abuse in patients labeled as fibromyalgia. *Am J Med.* (2011) 124:955–60. doi: 10.1016/j.amjmed.2011.05.031
4. Krebs EE, Gravely A, Nugent S, Jensen AC, DeRonne B, Goldsmith ES, et al. Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain: the SPACE randomized clinical trial. *JAMA.* (2018) 319:872–82. doi: 10.1001/jama.2018.0899
5. Peng X, Robinson RL, Mease P, Kroenke K, Williams DA, Chen Y, et al. Long-term evaluation of opioid treatment in fibromyalgia. *Clin J Pain.* (2015) 31:7–13. doi: 10.1097/AJP.0000000000000079
6. Younger JW, Chu LF, D'Arcy NT, Trott KE, Jastrzab LE, Mackey SC. Prescription opioid analgesics rapidly change the human brain. *Pain.* (2011) 152:1803–10. doi: 10.1016/j.pain.2011.03.028
7. Lin JC, Chu LF, Stringer EA, Baker KS, Sayyid ZN, Sun J, et al. One month of oral morphine decreases gray matter volume in the right amygdala of individuals with low back pain: confirmation of previously reported magnetic resonance imaging results. *Pain Med.* (2016) 17:1497–504. doi: 10.1093/pm/pnv047
8. Upadhyay J, Maleki N, Potter J, Elman I, Rudrauf D, Knudsen J, et al. Alterations in brain structure and functional connectivity in prescription opioid-dependent patients. *Brain.* (2010) 133:2098–114. doi: 10.1093/brain/awq138
9. McConnell PA, Garland EL, Zubieta J-K, Newman-Norlund R, Powers S, Froeliger B, et al. Impaired frontostriatal functional connectivity among chronic opioid using pain patients is associated with dysregulated affect. *Addict Biol.* (2020) 25:e12743. doi: 10.1111/adb.12743
10. Dowdle LT, Borckardt JJ, Back SE, Morgan K, Adams D, Madan A, et al. Sensitized brain response to acute pain in patients using prescription opiates for chronic pain: a pilot study. *Drug Alcohol Depend.* (2019) 200:6–13. doi: 10.1016/j.drugalcdep.2019.02.024
11. Martucci KT, MacNiven KH, Borg N, Knutson B, Mackey SC. Apparent effects of opioid use on neural responses to reward in chronic pain. *Sci Rep.* (2019) 9:9633. doi: 10.1038/s41598-019-45961-y
12. Powers JM, Ioachim G, Stroman PW. Ten key insights into the use of spinal cord fMRI. *Brain Sci.* (2018) 8. doi: 10.3390/brainsci8090173
13. Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthritis Rheum.* (2002) 46:1333–43. doi: 10.1002/art.10225
14. Oaklander AL, Herzog ZD, Downs HM, Klein MM. Objective evidence that small-fiber polyneuropathy underlies some illnesses currently labeled as fibromyalgia. *Pain.* (2013) 154:2310–6. doi: 10.1016/j.pain.2013.06.001
15. Clauw DJ. Fibromyalgia: a clinical review. *JAMA.* (2014) 311:1547–55. doi: 10.1001/jama.2014.3266
16. Martucci KT, Weber KAII, Mackey SC. Altered cervical spinal cord resting-state activity in fibromyalgia. *Arthritis Rheumatol.* (2019) 71:441–50. doi: 10.1002/art.40746
17. Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology.* (2006) 104:570–87. doi: 10.1097/00000542-200603000-00025
18. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain.* (2011) 152:S2–15. doi: 10.1016/j.pain.2010.09.030
19. Wolfe F, Clauw DJ, Fitzcharles M-A, Goldenberg DL, Häuser W, Katz RS, et al. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. *J Rheumatol.* (2011) 38:1113–22. doi: 10.3899/jrheum.100594
20. Dixon EA, Benham G, Sturgeon JA, Mackey S, Johnson KA, Younger J. Development of the Sensory Hypersensitivity Scale (SHS): a self-report tool for assessing sensitivity to sensory stimuli. *J Behav Med.* (2016) 39:537–50. doi: 10.1007/s10865-016-9720-3
21. Keller S, Bann CM, Dodd SL, Schein J, Mendoza TR, Cleeland CS. Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. *Clin J Pain.* (2004) 20:309–18. doi: 10.1097/00002508-200409000-00005
22. Broderick JE, DeWitt EM, Rothrock N, Crane PK, Forrest CB. Advances in patient-reported outcomes: the NIH PROMIS(®) measures. *EGEMS (Wash DC).* (2013) 1:1015. doi: 10.13063/2327-9214.1015
23. De Leener B, Fonov VS, Collins DL, Callot V, Stikov N, Cohen-Adad J. PAM50: unbiased multimodal template of the brainstem and spinal cord aligned with the ICBM152 space. *Neuroimage.* (2018) 165:170–9. doi: 10.1016/j.neuroimage.2017.10.041
24. Weber KA II, Chen Y, Wang X, Kahnt T, Parrish TB. Lateralization of cervical spinal cord activity during an isometric upper extremity motor task with functional magnetic resonance imaging. *Neuroimage.* (2016) 125:233–43. doi: 10.1016/j.neuroimage.2015.10.014
25. Weber KA II, Sentis AI, Bernadel-Huey ON, Chen Y, Wang X, Parrish TB, et al. Thermal stimulation alters cervical spinal cord functional connectivity in humans. *Neuroscience.* (2018) 369:40–50. doi: 10.1016/j.neuroscience.2017.10.035
26. Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, Smith SM. Fsl. *Neuroimage.* (2012) 62:782–90. doi: 10.1016/j.neuroimage.2011.09.015
27. De Leener B, Lévy S, Dupont SM, Fonov VS, Stikov N, Louis Collins D, et al. SCT: spinal Cord Toolbox, an open-source software for processing spinal cord MRI data. *Neuroimage.* (2017) 145:24–43. doi: 10.1016/j.neuroimage.2016.10.009
28. Jenkinson M, Bannister PR, Brady JM, Smith SM. Improved optimisation for the robust and accurate linear registration and motion correction of brain images. *Neuroimage.* (2002) 17:825–41. doi: 10.1006/nimg.2002.1132
29. Fonov VS, Le Troter A, Taso M, De Leener B, Lévêque G, Benhamou M, et al. Framework for integrated MRI average of the spinal cord white and gray matter: the MNI–Poly–AMU template. *Neuroimage.* (2014) 102:817–27. doi: 10.1016/j.neuroimage.2014.08.057
30. Giove F, Garreffa G, Giulietti G, Mangia S, Colonnese C, Maraviglia B. Issues about the fMRI of the human spinal cord. *Magn Reson Imaging.* (2004) 22:1505–16. doi: 10.1016/j.mri.2004.10.015
31. Brooks JCW, Beckmann CF, Miller KL, Wise RG, Porro CA, Tracey I, et al. Physiological noise modelling for spinal

functional magnetic resonance imaging studies. *Neuroimage.* (2008) 39:680–92. doi: 10.1016/j.neuroimage.2007.09.018
32. Kong Y, Jenkinson M, Andersson J, Tracey I, Brooks JC. Assessment of physiological noise modelling methods for functional imaging of the spinal cord. *Neuroimage.* (2012) 60:1538–49. doi: 10.1016/j.neuroimage.2011.11.077
33. Glover GH, Li TQ, Ress D. Image-based method for retrospective correction of physiological motion effects in fMRI: RETROICOR. *Magn Reson Med.* (2000) 44:162–7. doi: 10.1002/1522-2594(200007)44:1<162::aid-mrm23>3.0.co;2-e
34. Harita S, Stroman PW. Confirmation of resting-state BOLD fluctuations in the human brainstem and spinal cord after identification and removal of physiological noise. *Magn Reson Med.* (2017) 78:2149–56. doi: 10.1002/mrm.26606
35. Woolrich MW, Ripley BD, Brady M, Smith SM. Temporal autocorrelation in univariate linear modeling of FMRI data. *Neuroimage.* (2001) 14:1370–86. doi: 10.1006/nimg.2001.0931
36. Zuo X-N, Di Martino A, Kelly C, Shehzad ZE, Gee DG, Klein DF, et al. The oscillating brain: complex and reliable. *Neuroimage.* (2010) 49:1432–45. doi: 10.1016/j.neuroimage.2009.09.037
37. Chao-Gan Y, Yu-Feng Z. DPARSF: A MATLAB toolbox for "pipeline" data analysis of resting-state fMRI. *Front Syst Neurosci.* (2010) 4:13. doi: 10.3389/fnsys.2010.00013
38. Smith SM, Nichols TE. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. *Neuroimage.* (2009) 44:83–98. doi: 10.1016/j.neuroimage.2008.03.061
39. Barry RL, Smith SA, Dula AN, Gore JC. Resting state functional connectivity in the human spinal cord. *Elife.* (2014) 3:e02812. doi: 10.7554/eLife.02812
40. Barry RL, Rogers BP, Conrad BN, Smith SA, Gore JC. Reproducibility of resting state spinal cord networks in healthy volunteers at 7 Tesla. *Neuroimage.* (2016) 133:31–40. doi: 10.1016/j.neuroimage.2016.02.058
41. Eippert F, Kong Y, Winkler AM, Andersson JL, Finsterbusch J, Buchel C, et al. Investigating resting-state functional connectivity in the cervical spinal cord at 3T. *Neuroimage.* (2017) 147:589–601. doi: 10.1016/j.neuroimage.2016.12.072
42. Chen LM, Mishra A, Yang P-F, Wang F, Gore JC. Injury alters intrinsic functional connectivity within the primate spinal cord. *Proc Natl Acad Sci U S A.* (2015) 112:5991–6. doi: 10.1073/pnas.1424106112
43. Rubinov M, Sporns O. Complex network measures of brain connectivity: uses and interpretations. *Neuroimage.* (2010) 52:1059–69. doi: 10.1016/j.neuroimage.2009.10.003
44. Kruschwitz JD, List D, Waller L, Rubinov M, Walter H. GraphVar: a user-friendly toolbox for comprehensive graph analyses of functional brain connectivity. *J Neurosci Methods.* (2015) 245:107–15. doi: 10.1016/j.jneumeth.2015.02.021
45. Kong Y, Eippert F, Beckmann CF, Andersson J, Finsterbusch J, Büchel C, et al. Intrinsically organized resting state networks in the human spinal cord. *Proc Natl Acad Sci U S A.* (2014) 111:18067–72. doi: 10.1073/pnas.1414293111
46. Liu X, Zhou F, Li X, Qian W, Cui J, Zhou IY, et al. Organization of the intrinsic functional network in the cervical spinal cord: a resting state functional MRI study. *Neuroscience.* (2016) 336:30–8. doi: 10.1016/j.neuroscience.2016.08.042
47. Apkarian AV, Stea RA, Bolanowski SJ. Heat-induced pain diminishes vibrotactile perception: a touch gate. *Somatosens Mot Res.* (1994) 11:259–67. doi: 10.3109/08990229409051393
48. Tommerdahl M, Delemos KA, Vierck CJ Jr., Favorov OV, Whitsel BL. Anterior parietal cortical response to tactile and skin-heating stimuli applied to the same skin site. *J Neurophysiol.* (1996) 75:2662–70. doi: 10.1152/jn.1996.75.6.2662
49. Yaksh TL. Pharmacology and mechanisms of opioid analgesic activity. *Acta Anaesthesiol Scand.* (1997) 41:94–111. doi: 10.1111/j.1399-6576.1997.tb04623.x
50. Jensen TS. Opioids in the brain: supraspinal mechanisms in pain control. *Acta Anaesthesiol Scand.* (1997) 41:123–32. doi: 10.1111/j.1399-6576.1997.tb04626.x
51. Casey KL, Svensson P, Morrow TJ, Raz J, Jone C, Minoshima S. Selective opiate modulation of nociceptive processing in the human brain. *J Neurophysiol.* (2000) 84:525–33. doi: 10.1152/jn.2000.84.1.525
52. Apkarian AV, Stea RA, Manglos SH, Szeverenyi NM, King RB, Thomas FD. Persistent pain inhibits contralateral somatosensory cortical activity in humans. *Neurosci Lett.* (1992) 140:141–7. doi: 10.1016/0304-3940(92)90088-O
53. Taylor JL, Amann M, Duchateau J, Meeusen R, Rice CL. Neural contributions to muscle fatigue: from the brain to the muscle and back again. *Med Sci Sports Exerc.* (2016) 48:2294–306. doi: 10.1249/MSS.0000000000000923
54. Matos FF, Rollema H, Brown JL, Basbaum AI. Do opioids evoke the release of serotonin in the spinal cord? An *in vivo* microdialysis study of the regulation of extracellular serotonin in the rat. *Pain.* (1992) 48:439–47. doi: 10.1016/0304-3959(92)90097-U
55. Pollak KA, Swenson JD, Vanhaitsma TA, Hughen RW, Jo D, White AT, et al. Exogenously applied muscle metabolites synergistically evoke sensations of muscle fatigue and pain in human subjects. *Exp Physiol.* (2014) 99:368–80. doi: 10.1113/expphysiol.2013.075812

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2021 Martucci, Weber and Mackey. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Neurology

REVIEW
published: 31 August 2021
doi: 10.3389/fneur.2021.732034

Brain Circuits Involved in the Development of Chronic Musculoskeletal Pain: Evidence From Non-invasive Brain Stimulation

Mina Kandić [1], Vera Moliadze [2], Jamila Andoh [1,3], Herta Flor [1] and Frauke Nees [1,2]*

[1] Institute of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany, [2] Institute of Medical Psychology and Medical Sociology, University Hospital Schleswig-Holstein, Kiel University, Kiel, Germany, [3] Department of Psychiatry and Psychotherapy, Medical Faculty Mannheim, Central Institute of Mental Health, University of Heidelberg, Mannheim, Germany

It has been well-documented that the brain changes in states of chronic pain. Less is known about changes in the brain that predict the transition from acute to chronic pain. Evidence from neuroimaging studies suggests a shift from brain regions involved in nociceptive processing to corticostriatal brain regions that are instrumental in the processing of reward and emotional learning in the transition to the chronic state. In addition, dysfunction in descending pain modulatory circuits encompassing the periaqueductal gray and the rostral anterior cingulate cortex may also be a key risk factor for pain chronicity. Although longitudinal imaging studies have revealed potential predictors of pain chronicity, their causal role has not yet been determined. Here we review evidence from studies that involve non-invasive brain stimulation to elucidate to what extent they may help to elucidate the brain circuits involved in pain chronicity. Especially, we focus on studies using non-invasive brain stimulation techniques [e.g., transcranial magnetic stimulation (TMS), particularly its repetitive form (rTMS), transcranial alternating current stimulation (tACS), and transcranial direct current stimulation (tDCS)] in the context of musculoskeletal pain chronicity. We focus on the role of the motor cortex because of its known contribution to sensory components of pain via thalamic inhibition, and the role of the dorsolateral prefrontal cortex because of its role on cognitive and affective processing of pain. We will also discuss findings from studies using experimentally induced prolonged pain and studies implicating the DLPFC, which may shed light on the earliest transition phase to chronicity. We propose that combined brain stimulation and imaging studies might further advance mechanistic models of the chronicity process and involved brain circuits. Implications and challenges for translating the research on mechanistic models of the development of chronic pain to clinical practice will also be addressed.

Keywords: non-invasive brain stimulation, transcranial magnetic stimulation, transcranial alternating current stimulation, transcranial direct current stimulation, development of chronic musculoskeletal pain, brain mechanisms

OPEN ACCESS

Edited by:
Marie-Eve Hoeppli, Cincinnati Children's Hospital Medical Center, United States

Reviewed by:
Milind Deogaonkar, West Virginia University, United States
Joshua Cheng, Stony Brook Medicine, United States

****Correspondence:***
Mina Kandić
mina.kandic@zi-mannheim.de

Specialty section:
This article was submitted to Applied Neuroimaging, a section of the journal Frontiers in Neurology

Received: *28 June 2021*
Accepted: *06 August 2021*
Published: *31 August 2021*

Citation:
Kandić M, Moliadze V, Andoh J, Flor H and Nees F (2021) Brain Circuits Involved in the Development of Chronic Musculoskeletal Pain: Evidence From Non-invasive Brain Stimulation. Front. Neurol. 12:732034. doi: 10.3389/fneur.2021.732034

INTRODUCTION

Chronic musculoskeletal pain is defined as a persisting or reoccurring pain that originates in musculoskeletal structure (1). In the new ICD-11 classification it is listed under the chronic primary pain category where it is recognized as a "disease in its own right" that cannot be explained by another disease (2).

Living with chronic musculoskeletal pain is a great burden to an individual experiencing pain, along with large-scale implications for society including enormous medical annual costs worldwide, the occurrence of sick leave, and work disability (3). Despite these high individual and societal costs, efforts to effectively treat chronic pain have been met with moderate success and in many patients, chronic pain remains untreated or poorly treated (4). The prevention of the transition from acute to chronic pain is therefore an important goal. The mechanisms of this transition remain, however, poorly understood (4).

Research has revealed that the brain in chronic and acute pain stage differs (5). However, the relationship between changes in a certain brain circuit and pain is never one-dimensional, since these alterations in the brain can relate to other factors such as medication intake and affective comorbidity (6–8). Since it has been shown that circuits that subserve emotional, learning, reward, and memory processes are key factors in the development of chronicity, these mechanisms themselves could be driving forces or catalysts of the transition (9–11). Moreover, genetic, and epigenetic factors (12), physiological and psychosocial expressions of stress (13, 14), have also been implicated in the development of chronic musculoskeletal pain. This stresses the importance of considering these factors when modeling and investigating brain-pain relationship. A mechanistic model of pain therefore acknowledges several key elements and their interaction in chronic pain pathogenesis and maintenance (15).

Multiple emotional and cognitive factors impact on the experience of pain, thus brain circuits involved in the processing of emotion might play an important role in the development of chronic pain (16, 17). Evidence from longitudinal imaging studies suggests a shift from brain regions involved in nociceptive processes toward brain areas supporting emotion, motivation, and memory processes when acute musculoskeletal pain persists (5, 18). Such findings are an important step toward unraveling neural changes associated with chronic pain.

Although neuroimaging studies allowed to further advance our knowledge about plastic changes related to pain chronicity, they cannot provide causal relationships between them. In this context, non-invasive brain stimulation (NIBS) methods have been used to modulate cortical excitability in specific brain areas, in order to show a direct relationship between brain and behavior. NIBS allows a step further into the understanding on the mechanisms of pain, acute and chronic, and can be applied on both healthy participants and chronic pain patients (19).

In this review, we will present an overview of the available NIBS studies with respect to pain development and discuss these studies in the context of a mechanistic understanding of pain chronicity. We further review to what extent NIBS studies offer additional targets on brain circuits (see **Figure 1**) involved in transition from acute to chronic pain. Lastly, we suggest future directions for NIBS research and discuss implications for the clinical practice.

NEURAL CIRCUITS INVOLVED IN CHRONIC MUSCULOSKELETAL PAIN: NEUROIMAGING EVIDENCE

Neuroimaging studies in chronic pain patients have revealed altered structure and function of the brain in chronic pain. Studies in fibromyalgia, chronic tension-type headache, and chronic back pain patients have reported structural and functional changes in regions not typically involved in nociceptive processing, such as limbic and prefrontal cortices (16, 20, 21). Furthermore, the default mode network (DMN), which is active in the absence of any task to maintain resting brain activity and is deactivated during task-based fmri (functional magnetic resonance imaging), showed persistent increased activity rather than deactivation in chronic pain patients (22) and abnormal functional connectivity with other brain regions at rest (23, 24) that was associated with the duration of chronic pain (24, 25).

In addition, the brain of chronic pain patients might differentially process acute and chronic pain, with the prefrontal cortex being a key region for this dissociation (16). Moreover, the prefrontal cortex is also believed to constitute one of the key regions in descending inhibitory pathways (26), and this pathway has also been found to be impaired in many chronic pain conditions, including chronic musculoskeletal pain (27, 28). Neuroimaging evidence documented distinct neural patterns for tonic and chronic pain in comparison to experimental phasic pain, with somatomotor, frontoparietal, and dorsal attention networks emerging as key circuits (29).

From the few available longitudinal data, it seems that similar networks are involved in the acute to chronic transition process, and that particularly corticostriatal circuits play an important role in pain chronicity. In a sample of subacute back pain patients followed over 1 year, increased functional connectivity between the medial prefrontal cortex (mPFC) and the nucleus accumbens (NAc) (18), and decreased hippocampal-medial prefrontal cortex functional connectivity during spontaneous pain were found predictive for the transition to pain chronicity (30). In addition, volumes of amygdala, hippocampus (31), and NAc (32) could predict chronic pain development. In further support of these results, denser white matter corticolimbic connections, specifically between mPFC and NAc, predicted the shift to the chronic state after a 1 year period (33).

NON-INVASIVE BRAIN STIMULATION: BASIC PRINICIPLES AND FINDINGS IN CHRONIC MUSCULOSKELETAL PAIN

Two methods of non-invasive transcranial brain stimulation have dominated recent decades: transcranial magnetic stimulation (TMS), which activates axons through short-pulsed stimulation and leads thereby to new action potentials; and transcranial electric stimulation (tES), most used transcranial direct current

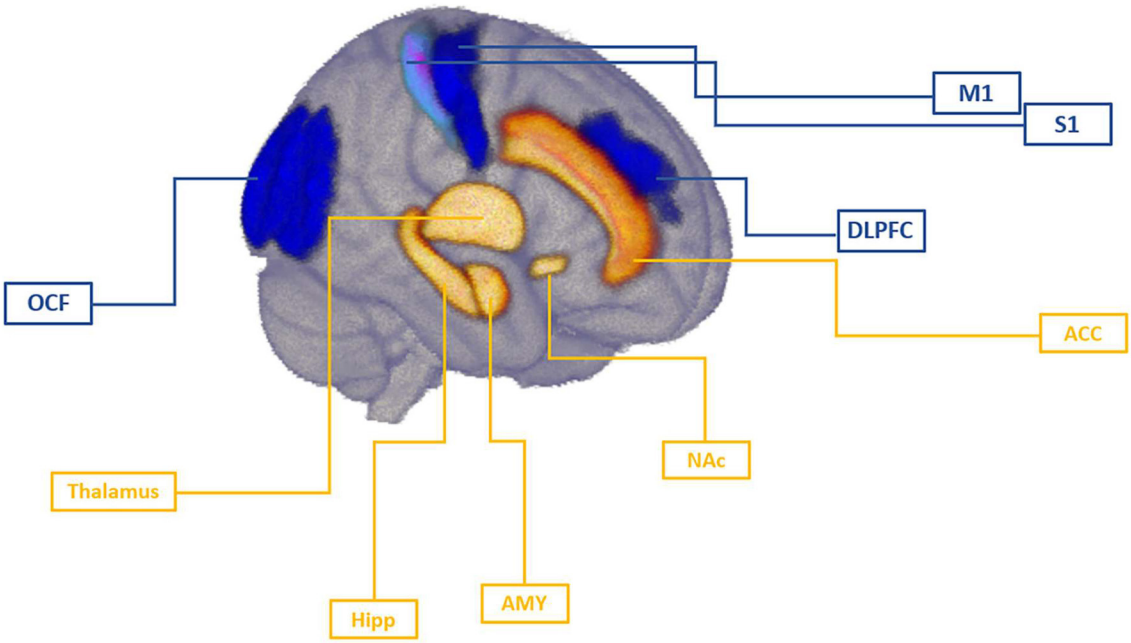


FIGURE 1 | Brain targets involved in the mechanism of pain chronicity. Cortical targets of NIBS studies were primary motor cortex (M1), primary somatosensory cortex (S1), dorsolateral prefrontal cortex (DLPFC), and occipital field (OCF). Imaging studies have identified thalamus, hippocampus (Hipp), amygdala (AMY), and nucleus accumbens (NAc) as key subcortical regions implicated in pain chronicity. Anterior cingulate cortex (ACC) has been identified as an important relay in the medial pain pathway integrating sensory, attentional, and motivational components of pain that can also been targeted via cortical stimulation due to its interconnections with these targets. In tonic, acute pain stage, motor cortex, as well as somatosensory regions may undergo rapid changes as response to peripheral insult, and the magnitude of this response might be shaped by pre-existing individual differences within these regions. As demonstrated in NIBS studies, DLPFC regulates top-down inhibition of pain independently of motor cortex activation, possibly modulating sensory component in an early stage of pain development. As pain develops to the chronic stage, cognitive aspects of pain become more important mechanism and prefrontal regions may regulate the affective component of pain via their influence on cingulate and limbic circuits.

stimulation (tDCS), which can be used to manipulate the membrane potential of neurons and modulate spontaneous firing rates, but which by itself is not sufficient to discharge resting neurons or axons (34).

Transcranial Magnetic Stimulation

TMS operates on the electromagnetic induction principle (35). The device unit typically encompasses a capacitor that accumulates and discharges a rapidly changing current of high voltage through the transducing coil placed to the subject's head. This sequentially creates a powerful (2–3 T) and brief (100–200 μs) magnetic field in the wires of the coil, inducing in turn an electrical field perpendicular to the coil surface in the neural tissue beneath the coil (36). The current induced at the neuronal layer is attenuated through the cranium and extracerebral tissues, yet it can exert enough strength to act in a suprathreshold manner and elicit an action potential (37). TMS primarily affects neurons in superficial areas directly below the coil, where the intensity of the current decays with the distance away from the coil (38). Different coils produce slightly different electrical field strengths and spreads, but all follow a depth-focality trade-off (39). Apart from local effects, stimulation can induce distant effects via propagation to interconnected regions belonging to the same neural network (40). Spread of the current is dependent on individual and tissue properties, which, however, cannot be controlled, and stimulation parameters that can be selected such as geometry of the coil, pulse waveform, intensity, frequency, and number of delivered pulses (41, 42).

A range of combinations of possible parameters constitutes the stimulation patterns that serve different purposes. For example, single pulses are applied in studies that investigate functioning of brain regions, while paired pulse regimes can be used to explore inhibitory or excitatory intracortical networks or connectivity of two cortical regions via conduction time that two successive pulses induce between them (43). When delivered in repetitive stimulation trains, the TMS regime is termed *repetitive transcranial magnetic stimulation* with low repetition rates under or at about 1 Hz decreasing excitation, whereas high frequencies of $\geq$5 Hz are generally believed to increase excitability of stimulated region (36). Due to the short interstimulus period, effects of rTMS sum up and can modulate neural activity beyond the stimulation period, thereby promoting neuronal plasticity (44). It is assumed that rTMS after-effects are based on long-term potentiation (LTP) and long-term depression-like (LTD)-like mechanisms of synaptic plasticity (36, 37). Recently, neurostimulation research has become interested in theta-burst stimulation (TBS), a modification of high-frequency rTMS. There is evidence that TBS produces even more robust changes

in cortical excitability than those observed in the conventional rTMS protocols. TBS typically consists of bursts of three pulses at 30 Hz or 50 Hz, repeated five times per second with 600 pulses in total (i.e., at theta frequency). There are two different paradigms: intermittent TBS (iTBS) and continuous TBS (cTBS). While iTBS facilitates CE, cTBS attenuates it (45–49). The advantage of TBS as compared to low and high frequency rTMS is that by using a similar number of pulses but considerably shorter duration and lower intensity of stimulation, experimental time is reduced without jeopardizing effect strength.

Using TMS, the brain can be briefly activated or briefly inhibited. Applications were first in the motor system and have now been used to map sensory processes and cognitive function. When TMS is delivered onto the primary motor cortex, it has the capacity to initiate descending volleys from pyramidal axons to spinal motor neurons, as demonstrated by epidural recordings in anesthetized humans (50). When the target of stimulation is a region subserving higher cortical function, TMS can interfere with neuronal firing and intercommunication within that region, which has been termed "virtual lesion" and reflects a momentary disruption of ongoing neuronal activity (51). Corresponding effects in the cognitive and/or behavioral domain can be measured through specific tasks, and enable to establish brain-behavior relationships. Such change in behavior can be observed online, i.e., being the product of concurrent stimulation, or offline, i.e., immediately after or up to an hour after the stimulation period, called after-effects. These effects emerge as a result of repeated depolarization events that temporally change neuronal firing (40).

Transcranial Direct and Alternating Current Stimulation

Transcranial current stimulation employs electric current through two or more surface electrodes attached directly to scalp and connected to the battery-driven stimulator (52). Unlike strong magnetically induced electric field in TMS, electrical current produced by TES (Transcranial electrical stimulation) is of weaker potential (53). This leaves the neural tissue excited below the necessary threshold to produce an action potential, but sufficient to modulate the firing of neurons in case of upcoming neural input (54). In general, direct current has been shown to influence a range of different neurotransmitters [for review, see (55)], while the long-lasting effects thought to induce plasticity have been attributed to the modulation of the N-Methyl-D-aspartate (NMDA) receptors and GABA modulation has a gating function on respective plasticity (56, 57).

The most common bipolar montage comprises of anode and cathode electrodes, producing polarity-specific modulation effects. Following the simplified assumption, in tDCS, a constant current flows between the electrodes, with anodal stimulation increasing cortical excitability and cathodal stimulation decreasing it (58). Similarly to TMS, the modulatory effects induced by tDCS depend on the choice of electric current intensity, waveform, and position and size of electrodes (59). Computational modeling studies suggested that current flow is mostly focused under the stimulated electrode (53), although human imaging studies showed that tDCS could even modulate spinal network excitability (60), which is in line with animal studies showing spread of tDCS-related effects to subcortical networks (61). Novel approaches emerged to improve spatial targeting, such as high definition transcranial current stimulation (HD-tCS) (62) or network-targeted multichannel stimulation (net-tCS) (63, 64) that make use of multiple electrodes improving focality.

Transcranial alternating current stimulation (tACS) occupies intermediate positions, in the physical sense, between pulsed rTMS and continuous tDCS. In tACS, the electrical current alternates between electrodes, usually in a sinusoidal form (65). The exact mechanisms by which tACS modulates brain activity are still not fully understood, five common explanations for direct, modulatory "online" effects include stochastic resonance and rhythm resonance, temporal biasing of spikes, network entrainment and imposed patterns (66). These mechanisms are assumed to affect activity in larger networks in the brain. Contrary to these suggested direct online mechanisms of electrical stimulation, the after-effects of tACS likely depend on the induction of neural plasticity (67). When brain activity is aimed to be modulated in a frequency-specific manner, tACS is an unprecedented method of choice, since it can target and interfere with the specific intrinsic oscillations of the brain region (68).

There is a substantial variability of responses to NIBS techniques across subjects on an individual level (69). Beside the methodological factors of stimulation, which generally affect both inter- and intra-subject variability, there is a number of other determinants which have to be taken into account including anatomical features of the head and brain (70), initial level of brain function (71, 72), genetics (73), development, and aging (74).

NIBS Studies on the Transition to Chronic Musculoskeletal Pain

The two most explored NIBS targets in pain are the primary motor cortex (M1) (19), which has been shown to undergo reorganization in chronic pain conditions (75), and the dorsolateral prefrontal cortex (DLPFC), due to its role in the affective and motivational components of pain (76). We discuss the contribution of NIBS studies targeting these two regions in the mechanistic understanding of chronic pain development. We then discuss additional NIBS targets that could potentially be beneficial to provide a mechanistic explanation of pain chronicity.

To uncover the mechanisms behind pain chronicity, the NIBS studies that are helpful are the ones that (1) focus on an experimental induction of prolonged pain in healthy individuals and follow the course of pain progression and pain resolution, thus providing a time course of pain development in relation to extended painful stimulation, or (2) focus on stimulation effects on clinical and induced pain in chronic pain patients to disentangle brain alterations from non-clinical compared to functionally and structurally altered clinical brain states, in relation to findings from (1).

Studies of Long-Term Pain Induced in Healthy Subjects

Through the experimental application and manipulation of pain in healthy individuals, we can monitor the time course when pain develops and gradually resolves and relate these changes with other clinical or neural measures. Prolonged pain in healthy humans can mimic symptoms seen in chronic conditions such as increased pain sensitivity (hyperalgesia), increased sensitivity to sensory stimuli (allodynia), or muscle soreness (77, 78).

Among the available NIBS studies of long-term pain induced in healthy subjects, NIBS has been used in the context of central sensitization, which has been proposed to underlie pain chronicity (79), and can manifest as secondary hyperalgesia or increased pain sensitivity at non-painful remote sites (80), and allodynia, painful sensation to usually non-noxious stimuli (81), shown in chronic back pain (82) and fibromyalgia (83). Available TMS studies applied both, stimulation protocols (rTMS) to modulate neural activity, and single pulse TMS as a measurement protocol to investigate cortical excitability changes and organization within the circuits of the motor cortex network.

Motor Cortex

Motor cortex was often targeted with NIBS due to analgesic effects that stimulation of this region has exhibited, most successfully when the target within M1 was the somatotopic representation of the painful body area (84).

Meeker et al. (85) delivered 1mA over the left M1 following the application of capsaicin on the right leg of 27 healthy subjects. They used capsaicin—heat pain model (C-HP model) where the thermode was attached to the participant's leg after the incubation of capsaicin applied into the bandage on the right leg. Warmth, heat, mechanical pain thresholds and suprathreshold mechanical pain ratings were obtained before the heat exposure, and the heat pain scores were assessed every minute throughout the heat exposure. Anodal tDCS started 12 min after the application of capsaicin and was delivered for 20 min. Additionally, extent and intensity of secondary mechanical hyperalgesia, and residual heat pain intensity were assessed at four time points, up to 65 min after removal of capsaicin and tDCS stimulation. In addition, 15 subjects from this study who have developed secondary mechanical hyperalgesia underwent three fMRI sessions before and after the application of the C-HP model receiving either anodal, cathodal, or sham tDCS in each session. Painful mechanical stimuli using weighted probes were assessed during and after the scanning sessions. Anodal tDCS renormalized the BOLD activation in several brain regions including mPFC, pregenual anterior cingulate cortex (pgACC), the periaqueductal gray (PAG), and brainstem, whose activity was prominent in response to mechanical pain, supporting the involvement of descending inhibitory circuits to supress prolonged influx of nociceptive stimuli (85). However, no effect of anodal stimulation was found on primary hyperalgesia (heat stimuli). This is consistent with a study that used repetitive heat stimuli in healthy individuals and found no effect of motor cortex tDCS stimulation on heat hyperalgesia (86). Meeker et al. (85) interpreted their findings as evidence that, due to its effects on secondary hyperalgesia, M1 likely influences supraspinal circuits that are altered due to central sensitization. The capsaicin injection was indeed shown to decrease regional cerebral blood flow (rCBF) in right the mPFC and increase rCBF in the caudal part of the right anterior cingulate cortex (ACC) after application of 1 Hz rTMS over right M1, as revealed by single-photon emission computed tomography (SPECT) (87). Moreover, the authors showed that pain decreased significantly after active rTMS compared to sham, and pain reduction significantly correlated with previously reported rCBF changes in mPFC and right ACC. This suggests that M1 is strongly related to mPFC and ACC regions during pain perception (87). In line with previous findings, Hughes et al. showed that compared to sham, active tDCS over M1 significantly reduced dynamical mechanical allodynia and mechanical pain sensitivity initiated by capsaicin-induced pain applied before tDCS in 12 healthy subjects. The authors concluded that M1 exhibits top-down modulation of inhibitory descending pathways to reduce the increased excitability in the dorsal horn, which has previously been associated with the development of allodynia (78).

In contrast to previous findings, (77) reported no significant effect of 10 Hz rTMS over the right M1 on motor excitability nor on the conditioned pain modulation (CPM), a reliable indicator of endogenous descending inhibitory pain control (88). Compared to a sham condition, active rTMS delivered over 5 successive days reduced the intensity of the pain induced by injection of neuronal growth factor (NGF) in the right forearm of 30 healthy participants. NGF induced pain spanning weeks, therefore more closely mimicking prolonged pain than capsaicin. Subjects in both groups developed multifocal, widespread pain, resembling the pattern seen in the chronic musculoskeletal pain conditions.

rTMS also reduced muscle soreness, narrowed the painful area, and increased pressure pain thresholds, and by day 14, the last experimental session, almost completely resolved muscle soreness and pain. Interestingly, rTMS did not exhibit significant effects on corticomotor excitability (activated cortical map volumes were increased over time in a similar fashion compared with the sham condition). Since the CPM task and motor excitability remained unaltered, the authors concluded that the observed effects are neither likely to be the result of M1 stimulation affecting descending pain inhibition networks, nor that they might emerge from local changes in M1. They rather discussed that the beneficial effects might have arose from changed activity of areas connected to M1 that are involved in pain processing or in affective processing of pain. Since these results were not confirmed by imaging, the mechanisms remained unclear. Nevertheless, it is plausible that M1 can indeed affect the activity of ACC, thalamus, insula, or DLPFC, as shown by imaging studies and by studies using electric field modeling to determine the current spread after M1 stimulation (89, 90).

Schabrun et al. (91) examined pain processing in an already sensitized system that resembles chronic conditions. They tracked M1 transient adaptation in response to saline injection in addition to NGF injection. The study involved 12 healthy subjects who were injected with NGF on day 0 and day 2, followed by an assessment of corticomotor excitability. Hypertonic saline was

also injected on day 4 to enhance pain in an already sensitized system and measures of motor function and organization were assessed during induced pain lasting about 10 min, and again after the pain had resolved. Interestingly, TMS measurement protocol showed that motor cortex reorganization assessed by motor maps and number of discrete peaks in M1 activity occurred as early as on day 4 in response to the onset of pain and muscle soreness. Corticomotor excitability, assessed by MEP amplitude, was unchanged directly after the NGF injection, but increased on day 2 following repeated NGF injection in an already sensitized system (91). In contrast to what is known in chronic pain conditions, where the extent of M1 reorganization was associated with pain severity (75), this study showed that M1 reorganization was not associated with the development of pain severity and disability. This suggests that changes in muscles, rather than pain, are predominately driving early plasticity (91). Additionally, the authors argue that M1 reorganization is probably driven by a release of intracortical networks, as the observed increased intracortical facilitation enables redistribution of muscle activity from the affected site to non-affected surrounding areas. Disturbed balance between inhibitory and facilitatory motor circuits has been observed in various chronic pain conditions (92), but the results were not always straightforward.

Given that rapidly occurring neuroplastic changes often relate to pain duration in chronic pain conditions, it has been suggested that these changes could be preceding the chronic stage and therefore represent a risk factor for chronicity (75, 93). Moreover, individual differences in motor plasticity could underlie vulnerability to pain development, with some individuals adopting maladaptive changes due to abnormalities in pre-existing brain circuits characteristics. For example, Seminowicz et al. (94) showed that differences in motor cortex changes in response to NGF injection were not apparent when analyzed on the group level but emerged when individuals were divided according to their excitability responses. In individuals who showed corticomotor facilitation, motor maps were increased, whereas participants who showed depressed responses of corticomotor excitability, had reduced map volumes, and displayed higher pain severity and worse cognitive performance (94).

DLPFC

Among the studies that have addressed the DLPFC, Fierro et al. (95) showed how stimulation applied over the DLPFC affects motor cortex excitability during 1 h of capsaicin-induced heat pain. The authors first assessed how induced pain affects corticospinal excitability and short intercortical inhibition (SICI). As pain developed, reduced corticospinal excitability assessed by MEP amplitudes was reported together with intracortical disinhibition on the contralateral motor cortex, evidenced by SICI using paired-pulse TMS over M1. Interestingly, 5Hz rTMS over the left DLPFC delivered 10 min after capsaicin application reversed effects observed within the motor cortex, at the same time lowering pain ratings. The control condition designed to explore the effects of DLPFC stimulation on motor cortex excitability in absence of pain showed no effect upon motor cortex excitability. This suggests that pain might mediate the relationship between activation of the DLPFC and motor cortex and that DLPFC influences on pain might induce changes in the motor cortex. Moreover, such findings also show that DLPFC stimulation might be able to reverse excitability changes induced by pain (95). Importantly, motor excitability changes were associated with concurrent high pain ratings, but as motor cortex inhibition started to diminish, pain ratings were still high. These findings suggest that perceived pain intensity was at least partially independent of the observed changes in excitability of the motor cortex. This is in accordance with research that used infusion of hypertonic saline in healthy adults, which supressed motor evoked potentials immediately as pain reached the pain threshold, supressed up to 25 min after the pain declined. This could imply that recovery from acute pain itself does not prompt the brain to change accordingly, since the brain is not only shaped by the presence or absence of acute, but also by previous pain-related learning processes (96). This is in line with imaging evidence of shifted pain processing from nociceptive circuits to circuits involved in emotion and learning (5). It is thus conceivable that changed motor function is driving changes in motor organization, but motor reorganization itself is not a (sole) generator of chronic pain.

Studies that applied brain stimulation shortly after induced pain onset showed how a specific region can foster recovery from pain, but since stimulation was usually initiated when pain already developed, these studies cannot tell if such a targeted stimulation would also prevent the development of pain. To investigate whether stimulation applied before pain onset can induce early recovery, Seminowicz et al. (97) applied rTMS over left DLPFC before injecting NGF to the right forearm of 30 healthy subjects. The study protocol involved rTMS stimulation on 5 consecutive days beginning before first NGF injection that was applied in the initial experimental session and 2 days afterwards. Compared with sham TMS, active TMS significantly reduced pain severity, muscle soreness and the size of the painful body area compared to sham over time, while depression, anxiety, Positive and Negative Affect Schedule scores, and pain catastrophizing scores remained unchanged. There was a trend toward better performance on an attention task post-stimulation. The authors concluded that the mechanism of action was possibly either through descending modulatory endogenous circuits or by affecting cognitive aspects of pain (97). Effects of TMS were tested on each of the 5 days of intervention, and up to 14 days and were stronger on the intervention day and were detectable up to 3 days after the intervention, which might be indicative of immediate effects rather than initiation of long-term plasticity-like effects.

NIBS studies underline the importance of the DLPFC in pain chronicity, since it seems that DLPFC affects not only the affective but also sensory component of the pain, independently of motor cortex activation. This is in accordance with a study in fibromyalgia patients where tDCS over DLPFC modulated heat pain thresholds (98). In further support of this finding, Lin et al. showed that pain reduction after DLPFC stimulation was not related to M1 activity, but rather through direct thalamic inhibition (99). A naloxone injection interfered with the analgesic effects of M1 stimulation, while it had no effect on DLPFC

stimulation, suggesting different mechanisms behind the effects on pain of these two cortical regions (100). In addition, anodal M1 tDCS and anodal DLPFC showed differential effects on other cortical and subcortical areas, as revealed by resting state fMRI pre and post tDCS stimulation (101).

Notably, structural and functional differences that may be "prewired" could make individuals more prone to the development of chronic pain. Lin et al. (99) found that immediate analgesic effects of anodal tDCS over left DLPFC are dependent on structural connectivity between left DLPFC and thalamus. Sham compared to tDCS over DLPFC stimulation revealed increased blood perfusion in posterior insula and thalamus on the left side and lower perfusion in M1, implying that these regions are involved in the processing of ongoing tonic pain, while anodal tDCS normalized this activity. Specifically, subjects who showed the strongest structural connectivity between left DPFC and thalamus, displayed the highest functional coupling between these two regions during anodal compared to sham tDCS (99). These findings are in line with previous research showing that resting state functional connectivity (102, 103), and individual morphology (104) predict pain sensitivity in healthy controls. Considering that pain sensitivity is a known risk factor for chronicity (105), these findings confirm the idea that structural and functional networks involving DLFPC relate to pain chronicity.

Brain Targets in Chronic Musculoskeletal Pain Patients

Motor Cortex

The processing of acute pain can be profoundly altered in chronic pain conditions, such that distinct patterns of alterations emerge across several brain regions including somatosensory cortex, thalamus, insula, motor and cingulate cortices (20, 106–108). The first study that explored how immediate effects of tDCS to M1 influence acute pain in chronic pain patients compared pain ratings to repetitive heat and electric stimuli in chronic low back patients before and after tDCS, with no significant outcome (109). In addition, although clinical pain was not the focus of this study, no effect on ongoing back pain emerged during or after tDCS compared to baseline or sham (109). Nevertheless, with improved tDCS parameters such as increased intensity and smaller, more focal electrodes, anodal tDCS over M1 was shown to decrease experimental pain scores in chronic low back patients (110). The peak value of current density was modeled to show that most of the current was delivered to M1, although one could not exclude that other regions such as DLPFC or primary somatosensory cortex (S1) may be affected. Interestingly, low back muscle activity did not show any differential response to stimulation (110). This is in line with the previous findings of prolonged pain in healthy subjects, where motor map volume remained unchanged after tDCS to M1, whereas pain decreased (111). These findings suggest that pain changes are not confined to motor cortex itself, but rather that M1 stimulation conveys its effect through other interconnected regions, or it acts in synergy with other regions.

To date, only one study employed non-invasive stimulation methods to study changes in the acute stage of clinical musculoskeletal pain. Chang et al. (112) recruited individuals experiencing acute low back pain lasting <4 weeks to elucidate which changes previously found in chronic stage of clinical back pain are present already early in acute clinical pain development. Employing electroencephalography (EEG), sensory evoked potentials (SEP) to non-painful electrical stimulation at the site of pain in area of the paraspinal muscles were recorded. Compared to healthy controls, corticospinal excitability assessed by TMS in M1 was lower in the 36 assessed patients. In addition, patients with low back pain had lower amplitudes of sensory evoked potentials related to secondary somatosensory cortex (S2) and ACC regions. Notably, the number of discrete motor map peaks did not show significant differences between subjects with and without pain, suggesting that the early phase of clinical pain development is not characterized by considerable motor cortex reorganization (112). However, this study was conducted in a cross-sectional manner. Further studies with follow-up measurements would be needed to examine whether the observed changes remained present up to the chronic stage.

Occipital Field

Occipital nerve field stimulation with subcutaneously implanted electrodes was shown to have positive effects in treating fibromyalgia (113). De Ridder and Vanneste (114) used source-localized resting-state EEG and tDCS over the occipital nerve field (OCF) to investigate mechanisms behind fibromyalgia pain. Using effective connectivity analyses, the authors showed that the connectivity changes between pgACC to the dorsal anterior cingulate cortex (dACC) were causally related to chronic pain. Specifically, active OCF tDCS compared to sham normalized disturbed effective connectivity from the pregenual anterior cingulate cortex to the dorsal anterior cingulate cortex, with a reduction of clinical pain. Considering the role of dACC in salience encoding and the role of pgACC in inhibitory pain control, the authors concluded that OCF tDCS exerted its modulatory effect via activation of the descending pain inhibitory pathway and de-activation of the salience network. Using directional functional connectivity measures to determine information transmission from one region to another it was revealed that pain increased with more information sent from dACC to pgACC, which led the authors to conclude that fibromyalgia is primarily driven by increased pain sensitization. Altered activity of pgACC, a part of the descending inhibitory system, is in accordance with imaging studies showing that smaller rostral ACC volume and cortical thickness in fibromyalgia patients were correlated with pain duration (106). The ACC is an important relay in the medial pain pathway and since it integrates sensory, attentional, and motivational components of pain, it could have a pivotal role in the development of chronic pain (115). Disrupted functional and structural connectivity between cingular areas and striatal regions have also been shown to be a predictor of the development of chronic pain (18).

Primary Somatosensory Cortex

rTMS and tDCS are the most prominent non-invasive techniques used in chronic pain studies. Oscillatory protocols such as tACS

are largely unexplored and underrepresented in pain research (116). To date, only one study has examined tACS-related effects in chronic pain patients. Ahn et al. (117) administered 10 Hz tACS bilaterally over the S1 and showed reduction in ongoing back pain and disability ratings in chronic low back pain patients. In addition, this reduction correlated with increased alpha oscillations in the regions under the electrodes, but also within frontal areas, as documented by electrophysiological recordings (117). These findings suggest a causal relationship between somatosensory alpha oscillations and ongoing chronic pain and is in line with previous research that found associations between manipulations of neural activity at the alpha frequency in somatosensory cortices and the processing of phasic heat pain (118). However, the latter study showed that reduction in pain is dictated by the context of the painful stimuli, namely that tACS has an influence only when the intensity of the painful stimuli was uncertain. Moreover, electrophysiological studies indicated that the intensity of ongoing pain in chronic back pain patients is encoded by prefrontal gamma activity (119). This points to a prefrontal involvement in the early and subsequent evolvement of pain. These findings are consistent to the ones of Ahn et al. (117) since they found significant associations of pain severity not only with the somatosensory cortex, but also alpha oscillations in frontal regions. However, the question of the specificity of a certain region and its endogenous frequencies that give rise to the pain experience as it temporally unfolds, prompts further research that would combine stimulation and electrophysiological methods and utilize different types of pain. In accordance with what we know so far from imaging studies (5, 120, 121), it is conceivable that acute phasic pain is predominately processed by somatosensory cortices and subserved by its intrinsic frequencies. But when pain develops, a shift toward prefrontal areas was shown, and hence the longer lasting and chronic pain may primarily be governed by rhythmic activity in prefrontal regions (116). This does not exclude that activity in somatosensory regions might also change in response to chronic pain, as well as a possible interplay between alpha and gamma frequencies, known to engage in cross-frequency coupling and modulating each other (122).

FUTURE DIRECTIONS

Medial Prefrontal Cortex as an Additional NIBS Target

With respect to the non-invasive stimulation targets, only very recently additional targets such as the medial prefrontal cortex were investigated in chronic pain patients. In a study that attempted to modulate clinical pain manifestations via affective and attentional manipulations, chronic low back patients underwent active and sham HD-tDCS over the medial prefrontal cortex (123). Conditioned pain modulation was not altered by attentional and affective manipulations, and in addition HD-tDCS compared with sham did not show effects on the magnitude of the effects of these manipulations. However, as the authors acknowledged, the small sample size and the inclusion of only mild clinical pain might be the main reasons for the absence of an effect. Further studies with larger sample size and including severe clinical pain are needed to further our understanding of the role the mPFC in chronic musculoskeletal pain. Noteworthy, connectivity patterns of the mPFC were shown to be altered in chronic back pain (102, 124) and have been suggested as a predictor for pain chronicity (18, 30). A two-fold role of mPFC as a site exhibiting opposing effects on pain has also been suggested: it is a relay between higher and downstream areas in modulating pain perception, and its dysfunction can lead to chronicity via projections to striatal reward pathway that could lead to overstimulation of the thalamus and possibly of the insula (125). Due to the substantial body of mPFC neurotransmitters that tune the prefrontal processing of affective components of pain, mPFC has also been proposed as a central hub subserving cognitive and affective comorbidities seen in chronic pain states (126).

NIBS Mechanistic Interference Framework

Studies that would be suited to mechanistically investigate the role of specific brain circuits in the development of chronic pain would have to consider several factors. Firstly, we could target neural activity previously found to be associated with and/or predictive for the development of musculoskeletal pain to investigate immediate effects of such a manipulation on pain regulation and demonstrate causal relation to chronicity. Studies thus far used either excitatory or inhibitory stimulation protocols depending on the method in question to potentiate analgesic effects, but rarely focused on up and downregulation with the aim to investigate a causal involvement of targeted area in pain processing. For instance, since it has been shown that activity in prefrontal brain regions in relation to spontaneous pain is increased in CBP patients (16), neuromodulation that inhibits prefrontal activity should decrease spontaneous clinical pain. In the same vein, if stimulated in an excitatory manner, prefrontal activity should amplify pre-existing overactivation and result in upregulation of pain intensity.

However, there are inherent challenges related to NIBS studies in chronic pain aiming to arrive to mechanistic explanations. A common non-invasive stimulation approach to investigate the causal role of a brain region in a specific behavioral or cognitive domain follows the "virtual lesion" principle. Hereby brief disruption of normal brain activity leads to immediate effects on the behavioral and/or cognitive level reflected by a changed response to the experimental task (51). Given that chronic pain is a subjective experience and thus is not experimentally induced, the task in this case is highly reliant on the subjects' perception and ability to transfer that perception into self-reported pain ratings. On the same grounds, chronic ongoing pain cannot be precisely time-locked to the stimulation as it can be for other experimental stimuli, such as, for example, visual stimuli delivered with millisecond precision concurrent with a stimulation pulse (127). In addition, stimulation procedures, particularly TMS, can themselves be painful depending on the site of the stimulation (128), hence they can interfere with the perception of ongoing clinical pain. Due to all these reasons, effects are investigated post-stimulation rather than in an online fashion, which, however, imposes time delay and make effects more indirect (129). If explored online, i.e., during the

stimulation, caution should be taken when interpreting the effects on chronic ongoing pain.

Next, careful consideration of the control conditions is a prerequisite toward more conclusive mechanistic interference. Sham procedures ensure the control of non-specific effects of TMS such as placebo effect, auditory noise, or sensory percepts of pulse discharge. To evaluate specificity of the brain region, TMS can be applied over another area presumably not involved in pain processing (129). To confirm behavioral specificity, effects of the targeted area should be confined to the task in question (130), in this case to the (pre)chronic ongoing pain. This could be examined by introducing a control task that requires neural processes that are not involved in pain perception, such as, for example, visuo-motor coordination (16). The power of mechanistic evidence increases with increasing control conditions (130), but also decreases statistical power. There is therefore a compromise to be found between the choice of control conditions and the conclusive mechanistic interference.

Importantly, our recent tACS studies emphasize the need for an active control condition to explicitly test frequency specificity, which is usually ignored in most NIBS studies to date (131, 132). NIBS studies should follow the general recommendations in terms of good scientific practice for planning a tACS experiment, which include the recommendation to choose an appropriate control frequency to demonstrate frequency specificity (54, 133). Following this rationale, the optimal control condition would be a frequency at which no modulatory effect would be expected. Therefore, it is important to avoid a synchronization between the frequency of interest and the control frequency.

Precise targeting is necessary to restrict stimulation effects to the desired region. Due to intrasubject variability, MRI-based TMS neuronavigation should be preferred instead of the traditional 10–20 EEG system positioning that is less accurate and has been found to induce different electrical field distributions compared to imaging-based localization (134, 135).

Next, to track which changes are pre-existing in the chronic stage and at the same time putative causes of chronicity, NIBS interventions might be introduced in the acute and then to and in the subacute stage. In this manner, any brain activity-pain relation found before the chronic stage would be marked as a potential risk factor for pain chronicity. In contrast to brain imaging studies which enable mainly correlational evidence between brain activity and pain, NIBS would provide controlled manipulation cause-effect relationships.

Combining NIBS With Imaging and Electrophysiological Methods

The mapping of NIBS-related effects could be performed by combining NIBS and imaging or NIBS and electrophysiological methods. Non-invasive stimulation is primarily confined to the superficial cortical layers (38), but via interconnected areas it can have an effect on subcortical regions. Therefore, the stimulation effect of the target could be fully prescribed to the activation of deeper layers (40). Due to these reasons, more conceivable and more precise mechanistic explanations would require imaging the effects of the induced stimulation immediately after the intervention to obtain a clearer picture of the affected circuits. Previous studies showed that tACS can induce BOLD changes even in the absence of behavioral modulations (136–138). Different stimulation frequencies can lead to both an increase and a decrease of brain activity. Moreover, the frequency range in which the change in brain activity occurs can coincide with the stimulation frequency, or lie in a different frequency range (131, 139).

Since it is conceivable that complex perception such as the pain experience depends on several key factors, the neuronal network on a whole, rather than an isolated brain region, is highly likely to be affected as pain progresses to the chronic state. One specific characteristic of the neural network is its oscillatory activity (140), thus its exploration could aid our understanding of the role of brain networks in the transition to chronic pain. From the pool of non-invasive stimulation methods, rTMS and tACS emerge as approaches able to influence intrinsic rhythmic activity via the proposed mechanism of entrainment (68). This concept refers to synchronization of the rhythmic activity of a physical system to an external periodic oscillator (141), and in case of neural endogenous oscillations reflects their coupling to the stimulator (67). rTMS and tACS can act in a frequency-specific manner (68), and thus a causal role of brain oscillations and regions that recruit them could be investigated in (pre)-chronic pain patients. Electrophysiological research showed an association between prefrontal gamma activity and ongoing back pain intensity, indicating therefore that the prefrontal areas are vital parts of long-lasting pain development, showing that medial prefrontal cortex encodes tonic pain at the gamma frequency in healthy controls (142), and changes in prefrontal gamma activity are associated with changes in ongoing back pain intensity (119). It remains however unknown if additional oscillation frequencies could be involved in pain chronicity, and this deserves further investigation.

To date, only one study in chronic musculoskeletal pain patients at our knowledge, combined tACS and EEG to successfully demonstrate an impact on chronic low back pain via an influence on somatosensory alpha frequencies (117). Network pathology in chronic musculoskeletal pain should be further investigated because for instance, cross-frequency coupling could subserve interactions between large-scale neural networks and local dynamics (122). If applied in a longitudinal framework, such research could, in addition, reveal whether the communication within constituents of brain networks is affected in the states preceding chronic pain development, or at which time point such alterations possibly emerge.

CONCLUDING REMARKS AND IMPLICATIONS FOR CLINICAL PRACTICE

Overall, there is a great need to employ the NIBS interference framework to elucidate changes in brain circuits as potential causal factors of the development of chronic musculoskeletal pain. This research should be built upon previously demonstrated significant predictors of chronicity in imaging studies that

provide potential targets of non-invasive stimulation. Non-invasive stimulation applied in models of prolonged pain or in chronic musculoskeletal pain patients thus far seems to confirm the importance of prefrontal regions in the transition to chronic pain. Importantly, NIBS showed that interventions applied preceding or in an early time windows of long-lasting pain can revert maladaptive responses. Moreover, NIBS findings point to the relevance of the connectivity patterns and deeper areas, justifying their targeting by methods such as neurofeedback (143). Additionally, it highlights fast plastic changes in the motor cortex in response to pain onset, alongside interindividual differences, which calls for more investigation. Here, studies in other pain conditions may also provide important information. The results for chronic musculoskeletal pain are mirrored in studies on neuropathic pain suggesting that there might be considerable overlap in the brain processes between the two types of pain. This has been demonstrated, for example, very recently in a study by Attal et al. (144), where it was shown that M1-rTMS, but not DLPFC-rTMS, induces significant effects on pain intensity changes compared to sham-rTMS.

Furthermore, an intact descending inhibitory pathway seems necessary to counteract early maladaptive changes associated with central sensitization, although this could be related to the predominance of central sensitization in the mechanism behind symptoms, since not all chronic pain patients exhibit CS symptoms (145). It has been demonstrated that chronic conditions with absence of any tissue injury exhibit less efficient descending pain modulatory system as assessed by the CPM paradigm (146). At the same time, symptoms of central sensitization are not necessarily alone good predictors of chronicity, but rather work jointly with other factors such as psychological determinants, as shown in an acute stage of low back pain using the CPM paradigm and pain thresholds (147). Nevertheless, pain management directed at restoring functionality of descending inhibitory pathways in an early manifestation of the central sensitization phenomena could have important implications for chronic pain patients that exhibit those symptoms. Previous studies indicate that state-triggered and closed loop stimulation boosts effects of non-invasive transcranial brain stimulation [for review, see (148)].

Employment of novel variants of non-invasive stimulation, such as theta burst stimulation that has a potential for more reliable excitatory and inhibitory effects on brain regions (149), should be encouraged in an interference driven approach. This method successfully ameliorated pain in several other chronic pain conditions such as chronic orofacial pain, complex regional pain syndrome, and central neuropathic pain (150–152) and thus incites therapeutic applications. Another recent NIBS approach, a form of tACS called transcranial random noise stimulation (tRNS), has proven efficient to consistently induce increased cortical excitability with effects lasting up to 1 h after the stimulation (153). tRNS uses the alternating electric current following a random white noise spectrum (54). In addition, stimulation in high frequency range (80–250 Hz) was shown to be a potent stimulation protocol to increase human cortical excitability during and after the end of stimulation (154), opening a possibility to explore such a protocol in pathological conditions. A multi-coil magnetic stimulation design shown to modulate anterior cingulate cortex in fibromyalgia patients could be one possibility to effectively target deeper areas (155).

Last, spinal cord stimulation (SCS), as another well-established therapeutic option for the treatment of chronic pain, has also been examined for patients with chronic back pain, specifically those with failed back syndrome (156). A functional imaging study in patients with chronic pain showed that SCS reduced pain sensation along with abnormal functional connectivity between somatosensory and limbic circuits and increased the connectivity between somatosensory areas and the default mode network (157). These data also point to a close interaction of sensory and emotional processing networks in chronic pain that could be targeted in treatment.

A mechanistic understanding of the transition from acute to chronic musculoskeletal pain is needed to permit targeted early intervention (158). However, our knowledge of chronic pain mechanisms is still limited and the evidence for mechanistically guided treatments is sparse.

AUTHOR CONTRIBUTIONS

MK, HF, and FN conceived the design. MK drafted the manuscript. MK, VM, JA, HF, and FN edited the manuscript, provided the content, and contributed to the organization. All authors approved the submitted version.

FUNDING

This work was supported by grants from the Deutsche Forschungsgemeinschaft (SFB1158/B03 to FN and HF and SFB1158/B07 to HF and JA).

REFERENCES

1. Treede R-D, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. A classification of chronic pain for ICD-11. *Pain.* (2015) 156:1003–7. doi: 10.1097/j.pain.0000000000000160
2. Nicholas M, Vlaeyen JW, Rief W, Barke A, Aziz Q, Benoliel R, et al. The IASP classification of chronic pain for ICD-11: chronic primary pain. *Pain.* (2019) 160:28–37. doi: 10.1097/j.pain.0000000000001390
3. McBeth J, Jones K. Epidemiology of chronic musculoskeletal pain. *Best Pract Res Clin Rheumatol.* (2007) 21:403–25. doi: 10.1016/j.berh.2007.03.003
4. Langevin HM. Reconnecting the brain with the rest of the body in musculoskeletal pain research. *J Pain.* (2021) 22:1–8. doi: 10.1016/j.jpain.2020.02.006
5. Hashmi JA, Baliki MN, Huang L, Baria AT, Torbey S, Hermann KM, et al. Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits. *Brain J Neurol.* (2013) 136:2751–68. doi: 10.1093/brain/awt211
6. Hsu MC, Harris RE, Sundgren PC, Welsh RC, Fernandes CR, Clauw DJ, et al. No consistent difference in gray matter volume between individuals with

fibromyalgia and age-matched healthy subjects when controlling for affective disorder. *Pain.* (2009) 143:262–7. doi: 10.1016/j.pain.2009.03.017
7. Younger JW, Chu LF, D'Arcy NT, Trott KE, Jastrzab LE, Mackey SC. Prescription opioid analgesics rapidly change the human brain. *Pain.* (2011) 152:1803–10. doi: 10.1016/j.pain.2011.03.028
8. Murray K, Lin Y, Makary MM, Whang PG, Geha P. Brain structure and function of chronic low back pain patients on long-term opioid analgesic treatment: a preliminary study. *Mol Pain.* (2021) 17:1744806921990938. doi: 10.1177/1744806921990938
9. Apkarian AV, Baliki MN, Geha PY. Towards a theory of chronic pain. *Progr Neurobiol.* (2009) 87:81–97. doi: 10.1016/j.pneurobio.2008.09.018
10. Nees F, Rüddel H, Mussgay L, Kuehl LK, Römer S, Schächinger H. Alteration of delay and trace eyeblink conditioning in fibromyalgia patients. *Psychosom Med.* (2010) 72:412–8. doi: 10.1097/PSY.0b013e3181d2bbef
11. Flor H. Pain has an element of blank-a biobehavioral approach to chronicity. *Pain.* (2017) 158 (Suppl. 1):S92–6. doi: 10.1097/j.pain.0000000000000850
12. Diatchenko L, Anderson AD, Slade GD, Fillingim RB, Shabalina SA, Higgins TJ, et al. Three major haplotypes of the beta2 adrenergic receptor define psychological profile, blood pressure, and the risk for development of a common musculoskeletal pain disorder. *Am J Med Genet B Neuropsychiatr Genet.* (2006) 141B:449–62. doi: 10.1002/ajmg.b.30324
13. Nees F, Löffler M, Usai K, Flor H. Hypothalamic-pituitary-adrenal axis feedback sensitivity in different states of back pain. *Psychoneuroendocrinology.* (2019) 101:60–6. doi: 10.1016/j.psyneuen.2018.10.026
14. Buscemi V, Chang W-J, Liston MB, McAuley JH, Schabrun SM. The role of perceived stress and life stressors in the development of chronic musculoskeletal pain disorders: a systematic review. *J Pain.* (2019) 20:1127–39. doi: 10.1016/j.jpain.2019.02.008
15. Nees F, Becker S. Psychological processes in chronic pain: influences of reward and fear learning as key mechanisms - behavioral evidence, neural circuits, and maladaptive changes. *Neuroscience.* (2018) 387:72–84. doi: 10.1016/j.neuroscience.2017.08.051
16. Baliki MN, Chialvo DR, Geha PY, Levy RM, Harden RN, Parrish TB, et al. Chronic pain and the emotional brain: specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. *J Neurosci Off J Soc Neurosci.* (2006) 26:12165–73. doi: 10.1523/JNEUROSCI.3576-06.2006
17. Flor H. New developments in the understanding and management of persistent pain. *Curr Opin Psychiatry.* (2012) 25:109–13. doi: 10.1097/YCO.0b013e3283503510
18. Baliki MN, Petre B, Torbey S, Herrmann KM, Huang L, Schnitzer TJ, et al. Corticostriatal functional connectivity predicts transition to chronic back pain. *Nat Neurosci.* (2012) 15:1117–9. doi: 10.1038/nn.3153
19. O'Connell NE, Marston L, Spencer S, DeSouza LH, Wand BM. Non-invasive brain stimulation techniques for chronic pain. *Cochrane Database Syst Rev.* (2018) 4:CD008208. doi: 10.1002/14651858.CD008208.pub4
20. Burgmer M, Gaubitz M, Konrad C, Wrenger M, Hilgart S, Heuft G, et al. Decreased gray matter volumes in the cingulo-frontal cortex and the amygdala in patients with fibromyalgia. *Psychosom Med.* (2009) 71:566–73. doi: 10.1097/PSY.0b013e3181a32da0
21. Benedittis G de, Lorenzetti A, Sina C, Bernasconi V. Magnetic resonance imaging in migraine and tension-type headache. *Headache.* (1995) 35:264–8. doi: 10.1111/j.1526-4610.1995.hed3505264.x
22. Baliki MN, Geha PY, Apkarian AV, Chialvo DR. Beyond feeling: chronic pain hurts the brain, disrupting the default-mode network dynamics. *J Neurosci.* (2008) 28:1398–403. doi: 10.1523/JNEUROSCI.4123-07.2008
23. Tagliazucchi E, Balenzuela P, Fraiman D, Chialvo DR. Brain resting state is disrupted in chronic back pain patients. *Neurosci Lett.* (2010) 485:26–31. doi: 10.1016/j.neulet.2010.08.053
24. Tu Y, Jung M, Gollub RL, Napadow V, Gerber J, Ortiz A, et al. Abnormal medial prefrontal cortex functional connectivity and its association with clinical symptoms in chronic low back pain. *Pain.* (2019) 160:1308–18. doi: 10.1097/j.pain.0000000000001507
25. Fallon N, Chiu Y, Nurmikko T, Stancak A. functional connectivity with the default mode network is altered in fibromyalgia patients. *PLoS ONE.* (2016) 11:e0159198. doi: 10.1371/journal.pone.0159198
26. Ossipov MH, Morimura K, Porreca F. Descending pain modulation and chronification of pain. *Curr Opin Support Palliat Care.* (2014) 8:143–51. doi: 10.1097/SPC.0000000000000055
27. Jensen KB, Loitoile R, Kosek E, Petzke F, Carville S, Fransson P, et al. Patients with fibromyalgia display less functional connectivity in the brain's pain inhibitory network. *Mol Pain.* (2012) 8:32. doi: 10.1186/1744-8069-8-32
28. Yu R, Gollub RL, Spaeth R, Napadow V, Wasan A, Kong J. Disrupted functional connectivity of the periaqueductal gray in chronic low back pain. *Neuroimage Clin.* (2014) 6:100–8. doi: 10.1016/j.nicl.2014.08.019
29. Lee J-J, Kim HJ, Ceko M, Park B-Y, Lee SA, Park H, et al. A neuroimaging biomarker for sustained experimental and clinical pain. *Nat Med.* (2021) 27:174–82. doi: 10.1038/s41591-020-1142-7
30. Mutso AA, Petre B, Huang L, Baliki MN, Torbey S, Herrmann KM, et al. Reorganization of hippocampal functional connectivity with transition to chronic back pain. *J Neurophysiol.* (2014) 111:1065–76. doi: 10.1152/jn.00611.2013
31. Vachon-Presseau E, Centeno MV, Ren W, Berger SE, Tétreault P, Ghantous M, et al. The emotional brain as a predictor and amplifier of chronic pain. *J Dent Res.* (2016) 95:605–12. doi: 10.1177/0022034516638027
32. Makary MM, Polosecki P, Cecchi GA, DeAraujo IE, Barron DS, Constable TR, et al. Loss of nucleus accumbens low-frequency fluctuations is a signature of chronic pain. *Proc Natl Acad Sci USA.* (2020) 117:10015–23. doi: 10.1073/pnas.1918682117
33. Mansour AR, Baliki MN, Huang L, Torbey S, Herrmann KM, Schnitzer TJ, et al. Brain white matter structural properties predict transition to chronic pain. *Pain.* (2013) 154:2160–8. doi: 10.1016/j.pain.2013.06.044
34. Paulus W. Transcranial electrical stimulation (tES - tDCS; tRNS, tACS) methods. *Neuropsychol Rehabil.* (2011) 21:602–17. doi: 10.1080/09602011.2011.557292
35. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. *Lancet.* (1985) 325:1106–7. doi: 10.1016/S0140-6736(85)92413-4
36. Hallett M. Transcranial magnetic stimulation: a primer. *Neuron.* (2007) 55:187–99. doi: 10.1016/j.neuron.2007.06.026
37. Lefaucheur J-P, André-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clin Neurophysiol Off J Int Federat Clin Neurophysiol.* (2014) 125:2150–206. doi: 10.1016/j.clinph.2014.05.021
38. Wagner T, Valero-Cabre A, Pascual-Leone A. Noninvasive human brain stimulation. *Annu Rev Biomed Eng.* (2007) 9:527–65. doi: 10.1146/annurev.bioeng.9.061206.133100
39. Deng Z-D, Lisanby SH, Peterchev AV. Electric field depth-focality tradeoff in transcranial magnetic stimulation: simulation comparison of 50 coil designs. *Brain Stimul.* (2013) 6:1–13. doi: 10.1016/j.brs.2012.02.005
40. Valero-Cabré A, Amengual JL, Stengel C, Pascual-Leone A, Coubard OA. Transcranial magnetic stimulation in basic and clinical neuroscience: A comprehensive review of fundamental principles and novel insights. *Neurosci Biobehav Rev.* (2017) 83:381–404. doi: 10.1016/j.neubiorev.2017.10.006
41. Thielscher A, Opitz A, Windhoff M. Impact of the gyral geometry on the electric field induced by transcranial magnetic stimulation. *Neuroimage.* (2011) 54:234–43. doi: 10.1016/j.neuroimage.2010.07.061
42. Wessel MJ, Draaisma LR, Morishita T, Hummel FC. The effects of stimulator, waveform, and current direction on intracortical inhibition and facilitation: a TMS comparison study. *Front Neurosci.* (2019) 13:703. doi: 10.3389/fnins.2019.00703
43. Klomjai W, Katz R, Lackmy-Vallée A. Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). *Ann Phys Rehabil Med.* (2015) 58:208–13. doi: 10.1016/j.rehab.2015.05.005
44. Ziemann U, Paulus W, Nitsche MA, Pascual-Leone A, Byblow WD, Berardelli A, et al. Consensus: motor cortex plasticity protocols. *Brain Stimul.* (2008) 1:164–82. doi: 10.1016/j.brs.2008.06.006
45. Wischnewski M, Schutter DJ. Efficacy and time course of theta burst stimulation in healthy humans. *Brain Stimul.* (2015) 8:685–92. doi: 10.1016/j.brs.2015.03.004
46. Di Lazzaro V, Pilato F, Saturno E, Oliviero A, Dileone M, Mazzone P, et al. Theta-burst repetitive transcranial magnetic stimulation suppresses

specific excitatory circuits in the human motor cortex. *J Physiol.* (2005) 565:945–50. doi: 10.1113/jphysiol.2005.087288
47. Huang Y-Z, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. *Neuron.* (2005) 45:201–6. doi: 10.1016/j.neuron.2004.12.033
48. Suppa A, Ortu E, Zafar N, Deriu F, Paulus W, Berardelli A, et al. Theta burst stimulation induces after-effects on contralateral primary motor cortex excitability in humans. *J Physiol.* (2008) 586:4489–500. doi: 10.1113/jphysiol.2008.156596
49. Goldsworthy MR, Pitcher JB, Ridding MC. Neuroplastic modulation of inhibitory motor cortical networks by spaced theta burst stimulation protocols. *Brain Stimul.* (2013) 6:340–5. doi: 10.1016/j.brs.2012.06.005
50. Di Lazzaro V, Oliviero A, Profice P, Meglio M, Cioni B, Tonali P, et al. Descending spinal cord volleys evoked by transcranial magnetic and electrical stimulation of the motor cortex leg area in conscious humans. *J Physiol.* (2001) 537:1047–58. doi: 10.1111/j.1469-7793.2001.01047.x
51. Pascual-Leone A. Transcranial magnetic stimulation in cognitive neuroscience – virtual lesion, chronometry, and functional connectivity. *Curr Opin Neurobiol.* (2000) 10:232–7. doi: 10.1016/S0959-4388(00)00081-7
52. Antal A, Alekseichuk I, Bikson M, Brockmöller J, Brunoni AR, Chen R, et al. Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines. *Clin Neurophysiol Off J Int Federat Clin Neurophysiol.* (2017) 128:1774–809. doi: 10.1016/j.clinph.2017.06.001
53. Miranda PC, Lomarev M, Hallett M. Modeling the current distribution during transcranial direct current stimulation. *Clin Neurophysiol Off J Int Federat Clin Neurophysiol.* (2006) 117:1623–9. doi: 10.1016/j.clinph.2006.04.009
54. Antal A, Herrmann CS. Transcranial alternating current and random noise stimulation: possible mechanisms. *Neural Plast.* (2016) 2016:3616807. doi: 10.1155/2016/3616807
55. Medeiros LF, Souza IC de, Vidor LP, Souza A de, Deitos A, Volz MS, et al. Neurobiological effects of transcranial direct current stimulation: a review. *Front Psychiatry.* (2012) 3:110. doi: 10.3389/fpsyt.2012.00110
56. Stagg CJ, Nitsche MA. Physiological basis of transcranial direct current stimulation. *Neuroscientist.* (2011) 17:37–53. doi: 10.1177/1073858410386614
57. Yavari F, Jamil A, Mosayebi Samani M, Vidor LP, Nitsche MA. Basic and functional effects of transcranial electrical stimulation (tES)-An introduction. *Neurosci Biobehav Rev.* (2018) 85:81–92. doi: 10.1016/j.neubiorev.2017.06.015
58. Nitsche MA, Fricke K, Henschke U, Schlitterlau A, Liebetanz D, Lang N, et al. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. *J Physiol.* (2003) 553:293–301. doi: 10.1113/jphysiol.2003.049916
59. Nitsche MA, Doemkes S, Karaköse T, Antal A, Liebetanz D, Lang N, et al. Shaping the effects of transcranial direct current stimulation of the human motor cortex. *J Neurophysiol.* (2007) 97:3109–17. doi: 10.1152/jn.01312.2006
60. Roche N, Lackmy A, Achache V, Bussel B, Katz R. Impact of transcranial direct current stimulation on spinal network excitability in humans. *J Physiol.* (2009) 587:5653–64. doi: 10.1113/jphysiol.2009.177550
61. Bolzoni F, Baczyk M, Jankowska E. Subcortical effects of transcranial direct current stimulation in the rat. *J Physiol.* (2013) 591:4027–42. doi: 10.1113/jphysiol.2013.257063
62. Edwards D, Cortes M, Datta A, Minhas P, Wassermann EM, Bikson M. Physiological and modeling evidence for focal transcranial electrical brain stimulation in humans: a basis for high-definition tDCS. *Neuroimage.* (2013) 74:266–75. doi: 10.1016/j.neuroimage.2013.01.042
63. Mencarelli L, Menardi A, Neri F, Monti L, Ruffini G, Salvador R, et al. Impact of network-targeted multichannel transcranial direct current stimulation on intrinsic and network-to-network functional connectivity. *J Neurosci Res.* (2020) 98:1843–56. doi: 10.1002/jnr.24690
64. Ruffini G, Wendling F, Sanchez-Todo R, Santarnecchi E. Targeting brain networks with multichannel transcranial current stimulation (tCS). *Curr Opin Biomed Eng.* (2018) 8:70–7. doi: 10.1016/j.cobme.2018.11.001
65. Herrmann CS, Rach S, Neuling T, Strüber D. Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes. *Front Hum Neurosci.* (2013) 7:279. doi: 10.3389/fnhum.2013.00279
66. Liu A, Vöröslakos M, Kronberg G, Henin S, Krause MR, Huang Y, et al. Immediate neurophysiological effects of transcranial electrical stimulation. *Nat Commun.* (2018) 9:5092. doi: 10.1038/s41467-018-07233-7
67. Vosskuhl J, Strüber D, Herrmann CS. Non-invasive brain stimulation: a paradigm shift in understanding brain oscillations. *Front Hum Neurosci.* (2018) 12:211. doi: 10.3389/fnhum.2018.00211
68. Herrmann CS, Strüber D, Helfrich RF, Engel AK. EEG oscillations: From correlation to causality. *Int J Psychophysiol Off J Int Organ Psychophysiol.* (2016) 103:12–21. doi: 10.1016/j.ijpsycho.2015.02.003
69. Ziemann U, Siebner HR. Inter-subject and inter-session variability of plasticity induction by non-invasive brain stimulation: boon or bane? *Brain Stimul.* (2015) 8:662–3. doi: 10.1016/j.brs.2015.01.409
70. Kim J-H, Kim D-W, Chang WH, Kim Y-H, Kim K, Im C-H. Inconsistent outcomes of transcranial direct current stimulation may originate from anatomical differences among individuals: electric field simulation using individual MRI data. *Neurosci Lett.* (2014) 564:6–10. doi: 10.1016/j.neulet.2014.01.054
71. Bergmann TO, Karabanov A, Hartwigsen G, Thielscher A, Siebner HR. Combining non-invasive transcranial brain stimulation with neuroimaging and electrophysiology: current approaches and future perspectives. *Neuroimage.* (2016) 140:4–19. doi: 10.1016/j.neuroimage.2016.02.012
72. Miniussi C, Harris JA, Ruzzoli M. Modelling non-invasive brain stimulation in cognitive neuroscience. *Neurosci Biobehav Rev.* (2013) 37:1702–12. doi: 10.1016/j.neubiorev.2013.06.014
73. Wiegand A, Nieratschker V, Plewnia C. Genetic modulation of transcranial direct current stimulation effects on cognition. *Front Hum Neurosci.* (2016) 10:651. doi: 10.3389/fnhum.2016.00651
74. Ghasemian-Shirvan E, Farnad L, Mosayebi-Samani M, Verstraelen S, Meesen RL, Kuo M-F, et al. Age-related differences of motor cortex plasticity in adults: a transcranial direct current stimulation study. *Brain Stimul.* (2020) 13:1588–99. doi: 10.1016/j.brs.2020.09.004
75. Moseley GL, Flor H. Targeting cortical representations in the treatment of chronic pain: a review. *Neurorehabil Neural Repair.* (2012) 26:646–52. doi: 10.1177/1545968311433209
76. Seminowicz DA, Moayedi M. The dorsolateral prefrontal cortex in acute and chronic pain. *J Pain.* (2017) 18:1027–35. doi: 10.1016/j.jpain.2017.03.008
77. Cavaleri R, Chipchase LS, Summers SJ, Schabrun SM. Repetitive transcranial magnetic stimulation of the primary motor cortex expedites recovery in the transition from acute to sustained experimental pain: a randomised, controlled study. *Pain.* (2019) 160:2624–33. doi: 10.1097/j.pain.0000000000001656
78. Hughes SW, Ward G, Strutton PH. Anodal transcranial direct current stimulation over the primary motor cortex attenuates capsaicin-induced dynamic mechanical allodynia and mechanical pain sensitivity in humans. *Euro J Pain.* (2020) 24:1130–7. doi: 10.1002/ejp.1557
79. Nijs J, van Houdenhove B, Oostendorp RA. Recognition of central sensitization in patients with musculoskeletal pain: application of pain neurophysiology in manual therapy practice. *Man Ther.* (2010) 15:135–41. doi: 10.1016/j.math.2009.12.001
80. Treede R-D, Meyer RA, Raja SN, Campbell JN. Peripheral and central mechanisms of cutaneous hyperalgesia. *Prog Neurobiol.* (1992) 38:397–421. doi: 10.1016/0301-0082(92)90027-C
81. Sandkühler J. Models and mechanisms of hyperalgesia and allodynia. *Physiol Rev.* (2009) 89:707–58. doi: 10.1152/physrev.00025.2008
82. Sanzarello I, Merlini L, Rosa MA, Perrone M, Frugiuele J, Borghi R, et al. Central sensitization in chronic low back pain: a narrative review. *J Back Musculoskelet Rehabil.* (2016) 29:625–33. doi: 10.3233/BMR-160685
83. Petzke F, Clauw DJ, Ambrose K, Khine A, Gracely RH. Increased pain sensitivity in fibromyalgia: effects of stimulus type and mode of presentation. *Pain.* (2003) 105:403–13. doi: 10.1016/S0304-3959(03)00204-5
84. DosSantos MF, Ferreira N, Toback RL, Carvalho AC, Dasilva AF. Potential mechanisms supporting the value of motor cortex stimulation to treat chronic pain syndromes. *Front Neurosci.* (2016) 10:18. doi: 10.3389/fnins.2016.00018

85. Meeker TJ, Keaser ML, Khan SA, Gullapalli RP, Seminowicz DA, Greenspan JD. Non-invasive motor cortex neuromodulation reduces secondary hyperalgesia and enhances activation of the descending pain modulatory network. *Front Neurosci.* (2019) 13:467. doi: 10.3389/fnins.2019.00467
86. Ihle K, Rodriguez-Raecke R, Luedtke K, May A. tDCS modulates cortical nociceptive processing but has little to no impact on pain perception. *Pain.* (2014) 155:2080–7. doi: 10.1016/j.pain.2014.07.018
87. Tamura Y, Okabe S, Ohnishi T, N Saito D, Arai N, Mochio S, et al. Effects of 1-Hz repetitive transcranial magnetic stimulation on acute pain induced by capsaicin. *Pain.* (2004) 107:107–15. doi: 10.1016/j.pain.2003.10.011
88. Kennedy DL, Kemp HI, Ridout D, Yarnitsky D, Rice AS. Reliability of conditioned pain modulation: a systematic review. *Pain.* (2016) 157:2410–9. doi: 10.1097/j.pain.0000000000000689
89. Dasilva AF, Mendonca ME, Zaghi S, Lopes M, Dossantos MF, Spierings EL, et al. tDCS-induced analgesia and electrical fields in pain-related neural networks in chronic migraine. *Headache.* (2012) 52:1283–95. doi: 10.1111/j.1526-4610.2012.02141.x
90. DosSantos MF, Martikainen IK, Nascimento TD, Love TM, DeBoer MD, Schambra HM, et al. Building up analgesia in humans via the endogenous μ-opioid system by combining placebo and active tDCS: a preliminary report. *PLoS ONE.* (2014) 9:e102350. doi: 10.1371/journal.pone.0102350
91. Schabrun SM, Christensen SW, Mrachacz-Kersting N, Graven-Nielsen T. Motor cortex reorganization and impaired function in the transition to sustained muscle pain. *Cereb Cortex.* (2016) 26:1878–90. doi: 10.1093/cercor/bhu319
92. Parker RS, Lewis GN, Rice DA, McNair PJ. Is motor cortical excitability altered in people with chronic pain? A systematic review and meta-analysis. *Brain Stimul.* (2016) 9:488–500. doi: 10.1016/j.brs.2016.03.020
93. Andoh J, Milde C, Tsao JW, Flor H. Cortical plasticity as a basis of phantom limb pain: fact or fiction? *Neuroscience.* (2018) 387:85–91. doi: 10.1016/j.neuroscience.2017.11.015
94. Seminowicz DA, Thapa T, Schabrun SM. Corticomotor depression is associated with higher pain severity in the transition to sustained pain: a longitudinal exploratory study of individual differences. *J Pain.* (2019) 20:1498–506. doi: 10.1016/j.jpain.2019.06.005
95. Fierro B, Tommaso M de, Giglia F, Giglia G, Palermo A, Brighina F. Repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex (DLPFC) during capsaicin-induced pain: modulatory effects on motor cortex excitability. *Exp Brain Res.* (2010) 203:31–8. doi: 10.1007/s00221-010-2206-6
96. Schabrun SM, Burns E, Hodges PW. New insight into the time-course of motor and sensory system changes in pain. *PLoS ONE.* (2015) 10:e0142857. doi: 10.1371/journal.pone.0142857
97. Seminowicz DA, Martino E de, Schabrun SM, Graven-Nielsen T. Left dorsolateral prefrontal cortex repetitive transcranial magnetic stimulation reduces the development of long-term muscle pain. *Pain.* (2018) 159:2486–92. doi: 10.1097/j.pain.0000000000001350
98. Silva AF, Zortea M, Carvalho S, Leite J, Da Torres IL, Fregni F, et al. Anodal transcranial direct current stimulation over the left dorsolateral prefrontal cortex modulates attention and pain in fibromyalgia: randomized clinical trial. *Sci Rep.* (2017) 7:135. doi: 10.1038/s41598-017-00185-w
99. Lin RL, Douaud G, Filippini N, Okell TW, Stagg CJ, Tracey I. Structural connectivity variances underlie functional and behavioral changes during pain relief induced by neuromodulation. *Sci Rep.* (2017) 7:41603. doi: 10.1038/srep41603
100. Andrade DC de, Mhalla A, Adam F, Texeira MJ, Bouhassira D. Neuropharmacological basis of rTMS-induced analgesia: the role of endogenous opioids. *Pain.* (2011) 152:320–6. doi: 10.1016/j.pain.2010.10.032
101. Sankarasubramanian V, Cunningham DA, Potter-Baker KA, Beall EB, Roelle SM, Varnerin NM, et al. Transcranial direct current stimulation targeting primary motor versus dorsolateral prefrontal cortices: proof-of-concept study investigating functional connectivity of thalamocortical networks specific to sensory-affective information processing. *Brain Connect.* (2017) 7:182–96. doi: 10.1089/brain.2016.0440
102. Tu Y, Ortiz A, Gollub RL, Cao J, Gerber J, Lang C, et al. Multivariate resting-state functional connectivity predicts responses to real and sham acupuncture treatment in chronic low back pain. *Neuroimage Clin.* (2019) 23:101885. doi: 10.1016/j.nicl.2019.101885
103. Spisak T, Kincses B, Schlitt F, Zunhammer M, Schmidt-Wilcke T, Kincses ZT, et al. Pain-free resting-state functional brain connectivity predicts individual pain sensitivity. *Nat Commun.* (2020) 11:187. doi: 10.1038/s41467-019-13785-z
104. Zou R, Li L, Zhang L, Huang G, Liang Z, Zhang Z. predicting individual pain thresholds from morphological connectivity using structural MRI: a multivariate analysis study. *Front Neurosci.* (2021) 15:615944. doi: 10.3389/fnins.2021.615944
105. Nielsen CS, Staud R, Price DD. Individual differences in pain sensitivity: measurement, causation, and consequences. *J Pain.* (2009) 10:231–7. doi: 10.1016/j.jpain.2008.09.010
106. Jensen KB, Srinivasan P, Spaeth R, Tan Y, Kosek E, Petzke F, et al. Overlapping structural and functional brain changes in patients with long-term exposure to fibromyalgia pain. *Arthritis Rheum.* (2013) 65:3293–303. doi: 10.1002/art.38170
107. Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthritis Rheum.* (2002) 46:1333–43. doi: 10.1002/art.10225
108. Giesecke T, Gracely RH, Grant MA, Nachemson A, Petzke F, Williams DA, et al. Evidence of augmented central pain processing in idiopathic chronic low back pain. *Arthritis Rheum.* (2004) 50:613–23. doi: 10.1002/art.20063
109. Luedtke K, May A, Jürgens TP. No effect of a single session of transcranial direct current stimulation on experimentally induced pain in patients with chronic low back pain–an exploratory study. *PLoS ONE.* (2012) 7:e48857. doi: 10.1371/journal.pone.0048857
110. Jiang N, Wei J, Li G, Wei B, Zhu FF, Hu Y. Effect of dry-electrode-based transcranial direct current stimulation on chronic low back pain and low back muscle activities: a double-blind sham-controlled study. *Restor Neurol Neurosci.* (2020) 38:41–54. doi: 10.3233/RNN-190922
111. Schabrun SM, Jones E, Elgueta Cancino EL, Hodges PW. Targeting chronic recurrent low back pain from the top-down and the bottom-up: a combined transcranial direct current stimulation and peripheral electrical stimulation intervention. *Brain Stimul.* (2014) 7:451–9. doi: 10.1016/j.brs.2014.01.058
112. Chang W-J, Buscemi V, Liston MB, McAuley JH, Hodges PW, Schabrun SM. Sensorimotor cortical activity in acute low back pain: a cross-sectional study. *J Pain.* (2019) 20:819–29. doi: 10.1016/j.jpain.2019.01.006
113. Plazier M, Vanneste S, Dekelver I, Thimineur M, Ridder D. Peripheral nerve stimulation for fibromyalgia. *Prog Neurol Surg.* (2011) 24:133–46. doi: 10.1159/000323046
114. Ridder D de, Vanneste S. Occipital nerve field transcranial direct current stimulation normalizes imbalance between pain detecting and pain inhibitory pathways in fibromyalgia. *Neurotherapeutics.* (2017) 14:484–501. doi: 10.1007/s13311-016-0493-8
115. Apkarian VA, Hashmi JA, Baliki MN. Pain and the brain: specificity and plasticity of the brain in clinical chronic pain. *Pain.* (2011) 152:S49–S64. doi: 10.1016/j.pain.2010.11.010
116. Hohn VD, May ES, Ploner M. From correlation towards causality: modulating brain rhythms of pain using transcranial alternating current stimulation. *Pain Rep.* (2019) 4:e723. doi: 10.1097/PR9.0000000000000723
117. Ahn S, Prim JH, Alexander ML, McCulloch KL, Fröhlich F. Identifying and engaging neuronal oscillations by transcranial alternating current stimulation in patients with chronic low back pain: a randomized, crossover, double-blind, sham-controlled pilot study. *J Pain.* (2019) 20:277.e1–11. doi: 10.1016/j.jpain.2018.09.004
118. Arendsen LJ, Hugh-Jones S, Lloyd DM. Transcranial alternating current stimulation at alpha frequency reduces pain when the intensity of pain is uncertain. *J Pain.* (2018) 19:807–18. doi: 10.1016/j.jpain.2018.02.014
119. May ES, Nickel MM, Ta Dinh S, Tiemann L, Heitmann H, Voth I, et al. Prefrontal gamma oscillations reflect ongoing pain intensity in chronic back pain patients. *Hum Brain Mapp.* (2019) 40:293–305. doi: 10.1002/hbm.24373

120. Geha PY, Baliki MN, Wang X, Harden RN, Paice JA, Apkarian AV. Brain dynamics for perception of tactile allodynia (touch-induced pain) in postherpetic neuralgia. *Pain.* (2008) 138:641–56. doi: 10.1016/j.pain.2008.02.021
121. Parks EL, Geha PY, Baliki MN, Katz J, Schnitzer TJ, Apkarian AV. Brain activity for chronic knee osteoarthritis: dissociating evoked pain from spontaneous pain. *Euro J Pain.* (2011) 15:843.e1-14. doi: 10.1016/j.ejpain.2010.12.007
122. Canolty RT, Knight RT. The functional role of cross-frequency coupling. *Trends Cogn Sci.* (2010) 14:506–15. doi: 10.1016/j.tics.2010.09.001
123. McPhee ME, Graven-Nielsen T. Medial prefrontal transcranial direct current stimulation aimed to improve affective and attentional modulation of pain in chronic low back pain patients. *J Clin Med.* (2021) 10:889. doi: 10.3390/jcm10040889
124. Yu S, Li W, Shen W, Edwards RR, Gollub RL, Wilson G, et al. Impaired mesocorticolimbic connectivity underlies increased pain sensitivity in chronic low back pain. *Neuroimage.* (2020) 218:116969. doi: 10.1016/j.neuroimage.2020.116969
125. Ong W-Y, Stohler CS, Herr DR. Role of the prefrontal cortex in pain processing. *Mol Neurobiol.* (2019) 56:1137–66. doi: 10.1007/s12035-018-1130-9
126. Kummer KK, Mitrić M, Kalpachidou T, Kress M. The medial prefrontal cortex as a central hub for mental comorbidities associated with chronic pain. *Int J Mol Sci.* (2020) 21:3440. doi: 10.3390/ijms21103440
127. Herring JD, Thut G, Jensen O, Bergmann TO. Attention modulates tms-locked alpha oscillations in the visual cortex. *J Neurosci.* (2015) 35:14435–47. doi: 10.1523/JNEUROSCI.1833-15.2015
128. Tani K, Hirata A, Tanaka S. Quantitative assessment of pain threshold induced by a single-pulse transcranial magnetic stimulation. *Front Neurosci.* (2020) 14:559. doi: 10.3389/fnins.2020.00559
129. Stewart L, Walsh V. Transcranial magnetic stimulation in human cognition. In: Senior C, Russell T, Gazzaniga SM, editors. *Methods in Mind*. Cambridge, MA and London: MIT Press (2006). p. 1–26. ISBN 0-262-19541-0. p. 1–26.
130. Polanía R, Nitsche MA, Ruff CC. Studying and modifying brain function with non-invasive brain stimulation. *Nat Neurosci.* (2018) 21:174–87. doi: 10.1038/s41593-017-0054-4
131. Moliadze V, Sierau L, Lyzhko E, Stenner T, Werchowski M, Siniatchkin M, et al. After-effects of 10 Hz tACS over the prefrontal cortex on phonological word decisions. *Brain Stimul.* (2019) 12:1464–74. doi: 10.1016/j.brs.2019.06.021
132. Moliadze V, Stenner T, Matern S, Siniatchkin M, Nees F, Hartwigsen G. Online effects of beta-tACS over the left prefrontal cortex on phonological decisions. *Neuroscience.* (2021) 463:264–71. doi: 10.1016/j.neuroscience.2021.03.002
133. Bergmann TO, Hartwigsen G. Inferring causality from noninvasive brain stimulation in cognitive neuroscience. *J Cogn Neurosci.* (2021) 33:195–225. doi: 10.1162/jocn_a_01591
134. Rusjan PM, Barr MS, Farzan F, Arenovich T, Maller JJ, Fitzgerald PB, et al. Optimal transcranial magnetic stimulation coil placement for targeting the dorsolateral prefrontal cortex using novel magnetic resonance image-guided neuronavigation. *Hum Brain Mapp.* (2010) 31:1643–52. doi: 10.1002/hbm.20964
135. Witte S de, Klooster D, Dedoncker J, Duprat R, Remue J, Baeken C. Left prefrontal neuronavigated electrode localization in tDCS: 10-20 EEG system versus MRI-guided neuronavigation. *Psychiatry Res Neuroimaging.* (2018) 274:1–6. doi: 10.1016/j.pscychresns.2018.02.001
136. Alekseichuk I, Diers K, Paulus W, Antal A. Transcranial electrical stimulation of the occipital cortex during visual perception modifies the magnitude of BOLD activity: a combined tES-fMRI approach. *Neuroimage.* (2016) 140:110–7. doi: 10.1016/j.neuroimage.2015.11.034
137. Cabral-Calderin Y, Anne Weinrich C, Schmidt-Samoa C, Poland E, Dechent P, Bähr M, et al. Transcranial alternating current stimulation affects the BOLD signal in a frequency and task-dependent manner. *Hum Brain Mapp.* (2016) 37:94–121. doi: 10.1002/hbm.23016
138. Vosskuhl J, Huster RJ, Herrmann CS. BOLD signal effects of transcranial alternating current stimulation (tACS) in the alpha range: a concurrent tACS-fMRI study. *Neuroimage.* (2016) 140:118–25. doi: 10.1016/j.neuroimage.2015.10.003
139. Veniero D, Vossen A, Gross J, Thut G. Lasting EEG/MEG aftereffects of rhythmic transcranial brain stimulation: level of control over oscillatory network activity. *Front Cell Neurosci.* (2015) 9:477. doi: 10.3389/fncel.2015.00477
140. Fries P. A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. *Trends Cogn Sci.* (2005) 9:474–80. doi: 10.1016/j.tics.2005.08.011
141. Pikovsky A, Rosenblum M, Kurths J, Hilborn RC. Synchronization: a universal concept in nonlinear science. *Am J Phys.* (2002) 70:655. doi: 10.1119/1.1475332
142. Schulz E, May ES, Postorino M, Tiemann L, Nickel MM, Witkovsky V, et al. Prefrontal gamma oscillations encode tonic pain in humans. *Cereb Cortex.* (2015) 25:4407–14. doi: 10.1093/cercor/bhv043
143. Patel K, Sutherland H, Henshaw J, Taylor JR, Brown CA, Casson AJ, et al. Effects of neurofeedback in the management of chronic pain: a systematic review and meta-analysis of clinical trials. *Euro J Pain.* (2020) 24:1440–57. doi: 10.1002/ejp.1612
144. Attal N, Poindessous-Jazat F, De Chauvigny E, Quesada C, Mhalla A, Ayache SS, et al. Repetitive transcranial magnetic stimulation for neuropathic pain: a randomized multicentre sham-controlled trial. *Brain.* (2021) 7:1046–66. doi: 10.1093/brain/awab208
145. Aoyagi K, He J, Nicol AL, Clauw DJ, Kluding PM, Jernigan S, et al. A subgroup of chronic low back pain patients with central sensitization. *Clin J Pain.* (2019) 35:869–79. doi: 10.1097/AJP.0000000000000755
146. Caumo W, Deitos A, Carvalho S, Leite J, Carvalho F, Dussán-Sarria JA, et al. Motor cortex excitability and BDNF levels in chronic musculoskeletal pain according to structural pathology. *Front Hum Neurosci.* (2016) 10:357. doi: 10.3389/fnhum.2016.00357
147. Klyne DM, Moseley GL, Sterling M, Barbe MF, Hodges PW. Are signs of central sensitization in acute low back pain a precursor to poor outcome? *J Pain.* (2019) 20:994–1009. doi: 10.1016/j.jpain.2019.03.001
148. Karabanov A, Thielscher A, Siebner HR. Transcranial brain stimulation: closing the loop between brain and stimulation. *Curr Opin Neurol.* (2016) 29:397–404. doi: 10.1097/WCO.0000000000000342
149. Suppa A, Huang Y-Z, Funke K, Ridding MC, Cheeran B, Di Lazzaro V, et al. Ten years of theta burst stimulation in humans: established knowledge, unknowns and prospects. *Brain Stimul.* (2016) 9:323–35. doi: 10.1016/j.brs.2016.01.006
150. Kohútová B, Fricová J, Klírová M, Novák T, Rokyta R. Theta burst stimulation in the treatment of chronic orofacial pain: a randomized controlled trial. *Physiol Res.* (2017) 66:1041–7. doi: 10.33549/physiolres.933474
151. Gaertner M, Kong J-T, Scherrer KH, Foote A, Mackey S, Johnson KA. Advancing transcranial magnetic stimulation methods for complex regional pain syndrome: an open-label study of paired theta burst and high-frequency stimulation. *Neuromodulation.* (2018) 21:409–16. doi: 10.1111/ner.12760
152. Kim JK, Park HS, Bae JS, Jeong YS, Jung KJ, Lim JY. Effects of multi-session intermittent theta burst stimulation on central neuropathic pain: a randomized controlled trial. *NeuroRehabilitation.* (2020) 46:127–34. doi: 10.3233/NRE-192958
153. Terney D, Chaieb L, Moliadze V, Antal A, Paulus W. Increasing human brain excitability by transcranial high-frequency random noise stimulation. *J Neurosci.* (2008) 28:14147–55. doi: 10.1523/JNEUROSCI.4248-08.2008
154. Moliadze V, Antal A, Paulus W. Boosting brain excitability by transcranial high frequency stimulation in the ripple range. *J Physiol.* (2010) 588:4891–904. doi: 10.1113/jphysiol.2010.196998
155. Tzabazis A, Aparici CM, Rowbotham MC, Schneider MB, Etkin A, Yeomans DC. Shaped magnetic field pulses by multi-coil repetitive transcranial magnetic stimulation (rTMS) differentially modulate anterior cingulate cortex responses and pain in volunteers and fibromyalgia patients. *Mol Pain.* (2013) 9:33. doi: 10.1186/1744-8069-9-33
156. Knotkova H, Hamani C, Sivanesan E, Le Beuffe MFE, Moon JY, Cohen SP, et al. Neuromodulation for chronic pain. *Lancet.* (2021) 397:2111–24. doi: 10.1016/S0140-6736(21)00794-7

157. Deogaonkar M, Sharma M, Oluigbo C, Nielson DM, Yang X, Vera-Portocarrero L, et al. Spinal cord stimulation (SCS) and functional magnetic resonance imaging (fMRI): modulation of cortical connectivity with therapeutic SCS. *Neuromodulation.* (2016) 19:142–53. doi: 10.1111/ner.12346
158. Shraim MA, Massé-Alarie H, Hall LM, Hodges PW. Systematic review and synthesis of mechanism-based classification systems for pain experienced in the musculoskeletal system. *Clin J Pain.* (2020) 36:793–812. doi: 10.1097/AJP.0000000000000860

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2021 Kandić, Moliadze, Andoh, Flor and Nees. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Neurology

PERSPECTIVE
published: 07 September 2021
doi: 10.3389/fneur.2021.700833

Recommendations for the Development of Socioeconomically-Situated and Clinically-Relevant Neuroimaging Models of Pain

*Marianne C. Reddan**

Department of Psychology, Stanford University, Stanford, CA, United States

Pain is a complex, multidimensional experience that emerges from interactions among sensory, affective, and cognitive processes in the brain. Neuroimaging allows us to identify these component processes and model how they combine to instantiate the pain experience. However, the clinical impact of pain neuroimaging models has been limited by inadequate population sampling – young healthy college students are not representative of chronic pain patients. The biopsychosocial approach to pain management situates a person's pain within the diverse socioeconomic environments they live in. To increase the clinical relevance of pain neuroimaging models, a three-fold biopsychosocial approach to neuroimaging biomarker development is recommended. The first level calls for the development of diagnostic biomarkers *via* the standard population-based (nomothetic) approach with an emphasis on diverse sampling. The second level calls for the development of treatment-relevant models *via* a constrained person-based (idiographic) approach tailored to unique individuals. The third level calls for the development of prevention-relevant models *via* a novel society-based (social epidemiologic) approach that combines survey and neuroimaging data to predict chronic pain risk based on one's socioeconomic conditions. The recommendations in this article address how we can leverage pain's complexity in service of the patient and society by modeling not just individuals and populations, but also the socioeconomic structures that shape any individual's expectations of threat, safety, and resource availability.

Keywords: chronic pain, neuroimaging biomarkers, translational ability, social epidemiology, social determinants of health, machine learning, biopsychosocial pain models

OPEN ACCESS

Edited by:
Flavia Di Pietro,
Curtin University, Australia

Reviewed by:
Florian Rimmele,
University Hospital Rostock, Germany
Yann Quidé,
University of New South Wales, Australia
Ivan V. Brak,
State Scientific Research Institute of Physiology and Basic Medicine, Russia

****Correspondence:***
Marianne C. Reddan
mcreddan@stanford.edu

Specialty section:
This article was submitted to Applied Neuroimaging, a section of the journal Frontiers in Neurology

Received: *26 April 2021*
Accepted: *06 August 2021*
Published: *07 September 2021*

Citation:
Reddan MC (2021) Recommendations for the Development of Socioeconomically-Situated and Clinically-Relevant Neuroimaging Models of Pain. Front. Neurol. 12:700833. doi: 10.3389/fneur.2021.700833

INTRODUCTION

Neuroimaging models have significantly expanded our understanding of the neural processes that instantiate a person's subjective pain experience [for reviews see (1–3)]. Through neuroimaging, we have learned that the brain representation of pain is highly distributed and multidimensional involving sensory, cognitive, and affective components (4–7). Neuroimaging models employing multivariate [i.e., multivoxel pattern analysis or MVPA; (8)], predictive (i.e., machine learning), and network analysis techniques can, respectively, delineate multiple component processes that contribute to both acute and chronic pain (7, 9–11), predict a person's self-reported

evoked pain intensity (12, 13), and localize sites of functional connectivity disruption across chronic pain phenotypes (14, 15).

Despite these important advances, neuroimaging research has yet to significantly impact the clinic. Anatomical and resting state markers lack specificity- it remains unknown whether changes are due to chronic pain or to co-morbidities like anxiety and depression [for reviews see (16, 17)]. Furthermore, most models are developed on experimental data of evoked phasic pain where participants experience a brief (under 12 s) noxious stimulus such as prick or a hot plate against the skin. This does not translate well to chronic pain which must persist 3 or more months. Acute or phasic pain is typically appraised as temporary and separate from the self, while chronic pain is typically appraised as unending and apart of one's life (18). Chronic pain is also highly personalized and embedded in spontaneous and tonic, rather than evoked and phasic, activity in the brain (19–22). Finally, population samples are not well-stratified across economic class, race, or ethnicity (23). In most cases, participant socioeconomic status (SES) is not reported nor well-measured [for a review see (24)]. Because chronic pain disproportionately affects the poor and working class across the globe (25–33), neuroimaging models of pain must take socioeconomic information into account.

The biopsychosocial approach to pain management attempts to encapsulate the broader societal issues which situate interactions among the biological, psychological, and social components of the pain experience (34). This conceptual framework states that understanding pain requires an understanding of the whole patient, their relationships, and society (35, 36). However, the biopsychosocial approach is largely theoretical and has yet to be well-integrated into pain neuroimaging research. To resolve this translational gap, this perspective formulizes the biopsychosocial approach into testable neuroimaging models intended for the diagnosis, treatment, and prevention of chronic pain. These models endeavor to predict and understand chronic pain from three levels, that of the individual, of the population, and of society.

First, recommendations are made to increase the diagnostic relevance of the population-based, or nomothetic, approach to the development of pain neuroimaging models. These recommendations include a shift in focus from evoked phasic pain to evoked tonic pain paradigms and the recruitment of larger and more diverse population samples. Second, a person-based or idiographic approach to the development of treatment-relevant models is discussed. Recommendations are made for the training and implementation of these models so that they can be used to track disease progress and treatment efficacy within individual patients. Finally, a novel society-based, or social epidemiological approach to the development of prevention-relevant models is proposed. This approach situates an individual's disease state within the socioeconomic conditions they live in. Lastly, implications for both the clinic and public policy are outlined.

NOMOTHETIC (POPULATION-BASED) APPROACH TO DIAGNOSTIC MODELS

Human subjects research is largely nomothetic, that is, the goal is to generate an explanation of brain activity that is "universal" and generalizable to entire populations (**Figure 1A**). Such models are trained on many different people sampled from the same population. Individual differences are treated as noise and intentionally minimized through careful inclusion/exclusion criteria, outlier removal, and the inclusion of confound regressors controlling for demographic variables such as age and gender identity [for a review see (37)]. The nomothetic approach is appropriate for the development of diagnostic biomarkers because inferences must be drawn from the wider population to identify pain pathologies in new patients presenting symptoms for the first time.

Nomothetic neuroimaging model weights are estimates of population-level associations between brain activity and pain outcomes (i.e., self-reported pain intensity). Models are cross-validated via an iterative "leave-*N*-subjects-out" procedure to assess performance on out-of-sample participants [for recommendations see (38)]. Next, they are validated on held out "validation sets"; though this external validation process is not common in single neuroimaging studies due to the demand on sample size. More often, this validation process occurs over a series of papers across unique data sets collected on different scanners in varied locations [for a review see (2)]. This a slower validation process, but it is a more thorough and robust one. Once validated, the model's predictions are deemed suitable for application to a new individual drawn from the same population.

A strength of this approach is its ability to identify separable component processes of pain (7). For example, the neurologic pain signature (NPS) is a well-validated model for acute pain evoked by noxious events (13). It captures a component process that contributes to the perceived intensity of an acute painful stimulus. It includes patterns of activity in the anterior cingulate, somatosensory cortex, and periaqueductal gray. Woo et al. (7) developed a separate multivariate predictive model of pain called the stimulus intensity independent pain signature-1 (SIIPS1). SIIPS1 captures fluctuations in pain independent of noxious stimulus intensity. It includes activity in the nucleus accumbens, lateral prefrontal cortex (PFC), and parahippocampal cortex. When combined with the NPS, the two explain more variance in brain activity than either model alone. However, the combined variance explained is 30%, indicating that there are more component processes relevant to evoked pain experiencing that have yet to be discovered (**Figure 1C**).

Though the NPS and SIIPS1 can predict different aspects of acute pain experiencing, they cannot distinguish between chronic pain patients and controls. It is unclear whether models trained on evoked phasic pain are informative for the diagnosis of chronic pain. To distinguish between fibromyalgia patients and healthy controls, the NPS was subdivided into its positive activations and then combined with a multisensory model similar to SIIPS1 and a separate model trained to predict evoked pain in fibromyalgia patients (9). The combinatorial model

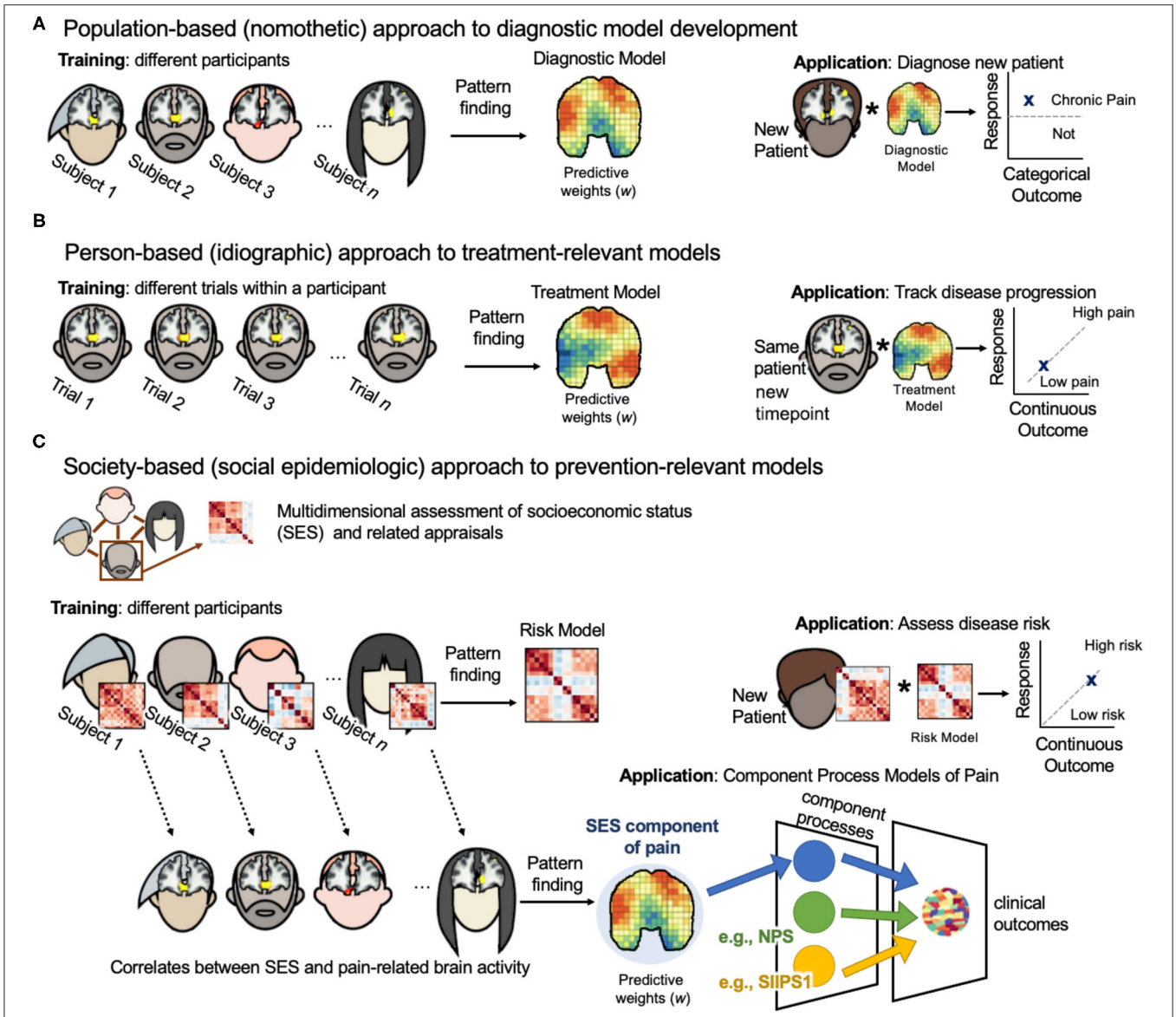


FIGURE 1 | Three-level biopsychosocial approach to neuroimaging biomarker development. **(A)** Population-based (nomothetic) approach to diagnostic model development. Neuroimaging model weights are estimates of population-level associations between brain activity and pain outcomes (i.e., diagnostic category vs. healthy control). Population samples should be large and diversely sampled across gender identity, race, and socioeconomic identities. Models should be validated on external clinical data sets. Models can then be applied to the brain activity of a new patient to diagnosis their pain condition. **(B)** Person-based (idiographic) approach to treatment-relevant models. Neuroimaging model weights are estimates of person-level associations between brain activity and pain outcomes (i.e., pain severity) for the same person through time. Models weights can be regulated by nomothetic models to lessen demands on data collection from one patient. Models can be applied in the same patient at later time points to assess their disease progression or to assess treatment efficacy. Such models can be used to tailor treatment selection on a case-by-case basis. **(C)** Society-based (social epidemiologic) approach to prevention-relevant models. This approach requires two steps. First, participants complete a multidimensional survey that assesses both their environment (i.e., socioeconomic status) and their personal internalization of these conditions (**Table 1**). Then, a risk model is trained on these survey data to predict pain severity. The weights of this risk model are estimates of population-level associations between a person's socioeconomic conditions and pain outcomes. This model can be applied to the survey data of a new patient to assess their risk of pain chronification. Person-level survey data can be related to person-level pain-related brain activity, and then a neuroimaging model of the SES component of pain processing can be developed. Neuroimaging model weights are estimates of group-level associations between the socioeconomic conditions a person lives in and their pain-related brain activity. Such a model could be combined with other neuroimaging component process models of pain, such as the NPS and SIIPS1, to predict clinical outcomes in new patients.

performed with high accuracy within the study it was developed, however, it is unknown how it performs in external data sets. Combining models like this may be prone to overfitting, so the preregistration of model combinations is recommended.

The translational limitations of evoked phasic pain models may be due to the phasic, rather than the evoked, nature of the noxious stimuli. Recently, a tonic pain neuroimaging biomarker with clinical relevance was developed. This biomarker, called TOPS, was trained on evoked *tonic* pain trails in healthy controls (39). In this experiment, capsaicin was placed on the tongue to evoke pain for 1-2 min. TOPS can predict clinical pain severity and distinguish between patients and controls in two independent studies of chronic low back pain. It is possible that tonic stimulations hold greater clinical utility than phasic because longer stimulations allow for rumination and the activation of resting state networks that may play a role in the chronification of pain (22, 40, 41).

TOPS was able to track within-individual variations in pain avoidance ratings with an average correlation of $r = 0.51$. Though this holds promise for the clinic, there is still much variance left to be explained. Pain is an idiosyncratic experience with many dimensions; therefore, the nomothetic approach may never be able to explain the entirely of an individual's pain experience, however, a "good enough" approximation might be achieved through the development of a suite of component process models that can be combined on a person-by-person basis. As we build more models of pain components, such as social context, interoception, affect, and expectations for pain relief, we may begin to chip away at this complex neural representation.

To this end, I make the following recommendations: First, a concerted effort must be made to recruit larger, more representative samples of the population. Nomothetic models are only suitable for application on new individuals drawn from the same population in which they were trained. The NPS was trained on only 20 participants, eight of which are women and 79% are White. Sampling procedures which primarily recruit from the student pool of the universities where the research is conducted unintentionally select for young high income and high education level White participants not of Hispanic origin (23). This is not representative of the world at large, nor is it representative of populations suffering from chronic pain. In the United States, most chronic pain patients are low-education and low-income women of color over the age of 45 (26, 42, 43).

Funding agencies must provide sufficient support so that researchers can expand their recruitment, possibly by employing companies that specialize in representative sampling to stratify samples across age, gender identity, race, ethnicity, wealth and income, education level, and personality traits. Second, pain models and pain data sets should be made open and shareable to increase collective clinical impact. Patient data sets, especially those involving spontaneous pain paradigms, are difficult to collect, but are the most clinically-relevant. With increased data sharing, new pain components developed in easier to collect (i.e., evoked pain in healthy controls) diverse populations can be validated in clinically-relevant samples to improve translation and impact.

IDIOGRAPHIC (PERSON-BASED) APPROACH TO TREATMENT-RELEVANT MODELS

Pain is heterogeneous. The nomothetic assumption that "one-size-fits-all" ignores diversity in economic class, cultural background, gender identity, ethnicity, and personality, and limits applicability in real-world pain treatment. For example, emotional pain is positively correlated with physical pain at the group level, but this relationship is inconsistent across time within unique individuals (44). Indeed, neither SIIPS1 nor TOPS positively predicts pain in each individual the model was trained on; approximately 2-3% of the training data show effects in the opposite direction. It is possible that one's unique experiences with pain can influence the magnitude or direction of the relationship a pain component process has on their individual pain response. The idiographic approach accounts for variance across individuals by allowing for *personalized* predictions. Individual differences in pain expression have made it difficult for biomarkers to be developed on lower dimensional data like facial expressions, skin conductance responses, and heart rate, however, recent idiographic approaches to modeling these types of data have significantly improved their predictive power (45–47). In the clinic, such models may provide objective assessments of disease progression and treatment progress.

In the person-based approach, models are trained on many different samples from the same individual (**Figure 1B**). This commonly involves estimating pain-related brain activity from single trials within one experimental session. Predictive brain maps developed on one participant should be internally cross-validated to test the model's ability to predict pain outcomes on out-of-sample trials from the same participant. While it might be useful to validate the model on later timepoints, current evidence suggests that there is stability in a single individual's network-level representation of the same stimulus through time (48).

Advantages of these models include improved accuracy and the ability to capture representations at finer spatial scales [e.g., (49–53)]. Because idiographic models require hours of data acquisition from a single participant, it can be difficult to collect from patients. One way to reduce the demands on scan time is to constrain the idiographic model with nomothetic priors. For example, Lindquist et al. (52) regularized an idiographic model of acute pain in healthy controls with the NPS. The regularized model performed better than both the NPS and a purely idiographic model trained on that subject's data alone. This method of regularization is known as group-regularized individual prediction (GRIP). It combines population-based and idiographic models in proportion to their variances. It does this by applying a shrinkage factor to the model weights. The shrinkage factor penalizes idiographic activity that appears unlikely (i.e., noise) relative to group activity.

Non-regularized idiographic models are still likely to be useful if sufficient data are collected from the patient. The

recommendation here is to compare the performance of regularized and non-regularized idiographic models within patients and select the best model on a patient-by-patient basis. This patient-tailored model can later be applied to their own brain activity in longitudinal follow-ups and intervention paradigms to track disease progress and treatment efficacy. It could also be deployed in real-time neurofeedback paradigms where participants can test multiple interventions and empirically validate which works best for them [see (54)]. Within this framework, a diversity of treatments (e.g., drugs, expectancy manipulations, placebo interventions, self-regulation, or mindfulness) can be tested with reduced bias.

SOCIAL EPIDEMIOLOGIC (SOCIETY-BASED) APPROACH TO PREVENTION-RELEVANT MODELS

Studies of global chronic pain prevalence suggest that societal stressors may contribute to the chronification of pain (32, 55–58). This is not surprising–the relationship between one's economic class and chronic illness has been observed as early as 1848, when Rudolph Virchow determined that treating the Typhus epidemic in Upper Silesia would require more than medicine. Virchow prescribed changes to the material conditions of the people whom the epidemic most severely impacted—the poor and working class (59). He concluded that though all illness has a biological origin, where it spreads and who is most susceptible is determined by structural factors such as housing, working conditions, diet, and sanitation (60). Similar observations have been made about chronic pain today. When controlling for age, race, and education level, a study conducted in an urban trauma center found that homelessness and low income were strongly associated with chronic pain (27).

Relationships between low economic class and chronic pain prevalence have been found across the United States (26, 61, 62) as well as across different cultures and countries including South Africa (63), Brazil (31), Iran (64), Germany (65), Austria (56), Sweden (66), Finland (67), the United Kingdom (25, 68), Japan (28), Nepal (33), and South Korea (69). Despite the long history and geographic spread of these associations, SES has largely been ignored by pain neuroimaging research. There are several reasons for this: First, there is little communication between epidemiologists and neuroimagers [an effort to correct this has begun, see (70)]. Second, the lack of socioeconomic diversity in research samples obfuscates this connection. Finally, it is difficult to mathematically relate complex social structures to functional brain activity. To the author's knowledge, only one neuroimaging study has done this to date (10). Here I propose to resolve this gap with a social epidemiologic approach to neuroimaging models of chronic pain.

Social epidemiologists study how socioeconomic structures, institutions (i.e., law, education), and social relationships influence health outcomes. A social epidemiologic approach to neuroimaging models of pain relates the structure of society to brain health and function. The primary goal of this approach is chronic pain prevention. The first step is to collect survey data assessing an individual's socioeconomic conditions and subjective experience of social status. This multidimensional assay can then be applied to pain-related brain activity to develop a neuroimaging model of socioeconomic contributions to chronic pain (**Figure 1C**). The resulting SES neuroimaging model may be a component process of pain useful for combinatorial models described earlier. This approach may allow us to identify patients most at risk for pain chronification because one's internalization of their socioeconomic conditions may play a role in the onset and maintenance of chronic pain (58, 61, 71).

The transition from acute to chronic pain is marked by a shift in processing from nociceptive components to socioemotional components of pain—specifically, PFC-limbic circuitry, including the NAc/striatum, amygdala, and hippocampus (72, 73), and the default mode network [DMN; (41)]. Changes to PFC-limbic circuitry may indicate a change in the valuation of pain (11, 74). Changes to DMN connectivity may change how the pain experience is construed in relation to the self (75, 76). Both of these networks are altered by poverty and socioeconomic stress (77). Activity in the PFC (78, 79) and ventral striatum (80) differs as a function of SES during both valuation and the processing of self-related information (81–83). Childhood poverty is correlated with aberrant functional connectivity within the DMN (84, 85). Interestingly, these aberrations can be reversed in people who have high income later in life (86). Relatedly, (10) found a threshold in annual income (>$25,000) that delineated vulnerability from protection in chronic pain patients. In the United States, the poverty line for a family of four is $26,200; meaning families that make less than this cannot afford food, rent, and other basic needs (87). It is unknown whether changes in income can reverse chronic pain status, however, chronic pain patients of high SES tend to have better clinical outcomes (88).

The impact of socioeconomic stress on chronic pain may not be reducible to income alone. The experience of social strain or subordination itself may contribute to chronic illness above and beyond income-level (89, 90). In non-human primates low social status is associated with immune system deficits that increase risk of infection and slow wound healing (91, 92). Chronic social stress may underlie immunosuppression in humans and animals [for a review see (93)]. People in lower social classes have a lower sense of personal control which is associated with higher levels of stress and pain (94). However, a high sense of self-efficacy is protective against chronic pain and pain severity (95). The protective effect of self-efficacy may be independent of class. For example, a large study in South Korea ($N = 28{,}532$) demonstrated that when controlling for monthly income, the presence of labor unions reduced low back pain prevalence (69). Another study in the United States found that unionized workers experience less severe pain for work-related musculoskeletal disorders (96). One interpretation of these effects is that labor unions change perceptions of self-efficacy, pain controllability, and expectations for care and safety by giving worker's the ability to advocate for themselves through collective bargaining (97).

A major barrier to the study of socioeconomic factors in chronic pain is the lack of a standardized assessment of

TABLE 1 | Socioeconomic Pain-Predispositions Profile Survey.

Level of assessment	Profile dimension	Examples
External conditions	Objective SES	Annual income, debt, amount of money in savings or investments, property ownership, housing status, number of people in a household, marital status, education level, parental education level, employment status, type of occupation, health insurance status, union membership
	Demographic Information	Age, race, gender identity, location of residence (urban vs. rural), location of birth, ethnicity, immigration status
	Sociopolitical Environment	Type of government in the country of residence, the gross domestic product (GDP) of country of residence, level of income inequality in country and city of residence, type of economic system in country of residence
Internalization of external conditions	Perceived SES	"I have a very high standing in my workplace or community." "If I got sick I would be able to access quality care." from The MacArthur Network on SES and Health and The MacArthur Scale of Subjective Social Status (98, 99)
	Perceived Social Support	"There is a person in my life who is around when I am in need." from the Multidimensional Scale of Perceived Social Support (100)
	Job satisfaction	"Over the past 12 months, have you ever experienced workplace discrimination based on your race, gender, education, etc?" from Perceived Workplace Discrimination (69) "I can get positive feed-back and respect in my work." from Work Satisfaction Index (101)
Beliefs about external conditions	System Justification	"Society is set up so that people usually get what they deserve." from General and Economic System Justification (102)
	Social Trust	"I feel that people generally earn the rewards and punishments that they get in this world." from Just World Scale (103) see also 'Kind of Person' Implicit Theory Scale (104)
	Perceptions of Self-efficacy	"Relief from pain is chiefly controlled by doctors" from Beliefs about Controlling Pain (105) see also, Locus of Control Scale (106)
Personality	Personality Type	"I am moody, tense, and lack self-confidence." from the Big 5 Personality Inventory (107)
	Emotional reactivity	"I often have concerned feelings for people less fortunate than me." "I sometimes feel helpless when I am in the middle of a very emotional situation." from the Interpersonal Reactivity Index (108)
	Attachment Style	"I find it difficult to allow myself to depend on others." from the Attachment Style Questionnaire (109)
	Pain catastrophizing	"When I am in pain I feel I can't go on." "I keep thinking of other painful events" from The Pain Catastrophizing Scale (110)
	Trait anxiety and depression	"I worry too much over something that really doesn't matter" from the State Trait Anxiety Inventory (111) see also Beck Depression Inventory (112)

A multidimensional assay of socioeconomic conditions, their internalization, and pain-related appraisals and personality traits.

SES. Here I propose the creation of a "Pain-Predispositions Profile Survey" (**Table 1**), a multidimensional assay of debt, income, property ownership, investments/savings, family wealth, education, perceived social status, environment (urban or rural), housing situation, childhood attachment, SES-related personality/evaluative traits (i.e., pain catastrophizing, controllability perceptions), as well as measures of income inequality within the city and country the patient resides in. A predisposition model of chronic pain can then be developed on these survey data that predicts patient pain status or severity. A cross-validated procedure similar to that employed by Vachon-Presseau et al. (10) can then be used to relate the survey data to functional networks in chronic pain patients (or healthy participants in evoked pain paradigms) to uncover a socioeconomic-related component process contributing to the pain experience (**Figure 1C**). Neuroimaging may not always be an available tool for the diagnosis and treatment of chronic pain—the survey-based model, however, is scalable and can be leveraged for treatment selection by matching people on survey similarity. Treatment programs that are validated on patients in neuroimaging studies can then be recommended to new patients with greater confidence.

DISCUSSION

An individual's valuation of a painful event (113–115), their expectations for support and health care (116–118), their beliefs about pain permanence (119, 120), personality traits (10, 121), and the socioeconomic conditions they exist in (10, 122) influence their brains' representation of pain. Pain, therefore, is a personal experience instantiated by biological processes and situated within one's socioeconomic conditions. Neuroimaging models situated within the socioeconomic structures of the population being studied are necessary for the development of a more complete understanding of the complexities of human pain. In this perspective, I discuss how three approaches to the development of pain neuroimaging models—nomothetic (population-based), idiographic (person-based), and social epidemiologic (society-based)—can be applied to the diagnosis, treatment, and prevention of chronic pain. These three approaches taken together serve to operationalize the biopsychosocial model of pain within a neuroimaging context.

It is estimated that 1% of the world's population controlled 44.8% of the world's wealth in 2018 (123). Economists from varied and opposing points on the political spectrum agree

that an increasingly globalized and automated economy will heighten existing barriers to economic mobility and make income inequality more stark, widespread, and permanent (124). Therefore, it is my final recommendation that scientists and clinicians advocate for chronic pain patients at the level of public policy. In the words of Virchow, "Disease is only a manifestation of life under pathological conditions… Medicine is a social science and politics is nothing else but medicine on a large scale."

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

FUNDING

NIMH (R01 MH112560), Computational and brain predictors of emotion cue integration (PI: Zaki).

ACKNOWLEDGMENTS

Special thanks to Bogdan Petre, Marta Ceko, Dean Baltiansky, and Jamil Zaki for providing comments on the ideas expanded in this paper.

REFERENCES

1. Apkarian AV, Baliki MN, Farmer MA. Predicting transition to chronic pain. *Curr Opin Neurol.* (2013) 26:360–7. doi: 10.1097/WCO.0b013e32836336ad
2. Reddan MC, Wager TD. Modeling pain using fMRI: from regions to biomarkers. *Neurosci Bull.* (2018) 34:208-15. doi: 10.1007/s12264-017-0150-1
3. Woo CW, Chang LJ, Lindquist MA, Wager TD. Building better biomarkers: brain models in translational neuroimaging. *Nat Neurosci.* (2017) 20:365–77. doi: 10.1038/nn.4478
4. Coghill RC, Sang CN, Maisog JM, Iadarola MJ. Pain intensity processing within the human brain: a bilateral, distributed mechanism. *J Neurophysiol.* (1999) 82:1934–43. doi: 10.1152/jn.1999.82.4.1934
5. Melzack R. Pain and the neuromatrix in the brain. *J Dent Educ.* (2001) 65:1378–82. doi: 10.1002/j.0022-0337.2001.65.12.tb03497.x
6. Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC. Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science.* (1997) 277:968–71. doi: 10.1126/science.277.5328.968
7. Woo C-W, Schmidt L, Krishnan A, Jepma M, Roy M, Lindquist MA, et al. Quantifying cerebral contributions to pain beyond nociception. *Nat Commun.* (2017) 8:14211. doi: 10.1038/ncomms14211
8. Haxby JV. Multivariate pattern analysis of fMRI: the early beginnings. *NeuroImage.* (2012) 62:852–855. doi: 10.1016/j.neuroimage.2012.03.016
9. López-Solà M, Woo CW, Pujol J, Deus J, Harrison BJ, Monfort J, et al. Towards a neurophysiological signature for fibromyalgia. *Pain.* (2017) 158:34-47. doi: 10.1097/j.pain.0000000000000707
10. Vachon-Presseau E, Berger SE, Abdullah TB, Griffith JW, Schnitzer TJ, Apkarian AV. Identification of traits and functional connectivity-based neurotraits of chronic pain. *PLoS Biol.* (2019) 17:e3000349. doi: 10.1371/journal.pbio.3000349
11. Woo CW, Roy M, Buhle JT, Wager TD. Distinct brain systems mediate the effects of nociceptive input and self-regulation on pain. *PLoS Biol.* (2015) 13:e1002036. doi: 10.1371/journal.pbio.1002036
12. Van Oudenhove L, Kragel PA, Dupont P, Ly HG, Pazmany E, Enzlin P, et al. Common and distinct neural representations of aversive somatic and visceral stimulation in healthy individuals. *Nat Commun.* (2020) 11:5939. doi: 10.1038/s41467-020-19688-8
13. Wager TD, Atlas LY, Lindquist MA, Roy M, Woo CW, Kross E. An fMRI-based neurologic signature of physical pain. *N Engl J Med.* (2013) 368:1388-97. doi: 10.1056/NEJMoa1204471
14. Kucyi A, Davis KD. The dynamic pain connectome. *Trends Neurosci.* (2015) 38:86–95. doi: 10.1016/j.tins.2014.11.006
15. Mansour A, Baria AT, Tetreault P, Vachon-Presseau E, Chang PC, Huang L, et al. Global disruption of degree rank order: a hallmark of chronic pain. *Sci Rep.* (2016) 6:1–17. doi: 10.1038/srep34853
16. Pfannmöller J, Lotze M. Review on biomarkers in the resting-state networks of chronic pain patients. *Brain Cogn.* (2019) 131:4–9. doi: 10.1016/j.bandc.2018.06.005
17. Tracey I, Woolf CJ, Andrews NA. Composite pain biomarker signatures for objective assessment and effective treatment. *Neuron.* (2019) 101:783–800. doi: 10.1016/j.neuron.2019.02.019
18. Grichnik KP, Ferrante FM. The difference between acute and chronic pain. *Mt Sinai J Med.* (1991) 58:217–20.
19. Baliki MN, Baria AT, Apkarian AV. The cortical rhythms of chronic back pain. *J Neurosci.* (2011) 31:13981–90. doi: 10.1523/JNEUROSCI.1984-11.2011
20. Baliki MN, Chialvo DR, Geha PY, Levy RM, Harden RN, Parrish TB, et al. Chronic pain and the emotional brain: specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. *J Neurosci.* (2006) 26:12165–73. doi: 10.1523/JNEUROSCI.3576-06.2006
21. Huang T, Zhao Z, Yan C, Lu J, Li X, Tang C, et al. Altered spontaneous activity in patients with persistent somatoform pain disorder revealed by regional homogeneity. *PLoS ONE.* (2016) 11:1–17. doi: 10.1371/journal.pone.0151360
22. Spisak T, Kincses B, Schlitt F, Zunhammer M, Schmidt-Wilcke T, Kincses ZT, et al. Pain-free resting-state functional brain connectivity predicts individual pain sensitivity. *Nat Commun.* (2020) 11: 187. doi: 10.1038/s41467-019-13785-z
23. Lewinn KZ, Sheridan MA, Keyes KM, Hamilton A, McLaughlin KA. Sample composition alters associations between age and brain structure. *Nat Commun.* (2017) 8:874. doi: 10.1038/s41467-017-00908-7
24. Farah MJ. The neuroscience of socioeconomic status: correlates, causes, and consequences. *Neuron.* (2017) 96:56–71. doi: 10.1016/j.neuron.2017.08.034
25. Aggarwal VR, Macfarlane TV, Macfarlane GJ. Why is pain more common amongst people living in areas of low socio-economic status? A population-based cross-sectional study. *Br Dent J.* (2003) 194:383–7. doi: 10.1038/sj.bdj.4810004
26. Grol-Prokopczyk H. Sociodemographic disparities in chronic pain, based on 12-year longitudinal data. *Pain.* (2017) 158:313–22. doi: 10.1097/j.pain.0000000000000762
27. Hanley O, Miner J, Rockswold E, Biros M. The relationship between chronic illness, chronic pain, and socioeconomic factors in the ED. *Am J Emerg Med.* (2011) 29:286–92. doi: 10.1016/j.ajem.2009.10.002
28. Ikeda T, Sugiyama K, Aida J, Tsuboya T, Watabiki N, Kondo K, et al. Socioeconomic inequalities in low back pain among older people: the JAGES cross-sectional study. *Int J Equity Health.* (2019) 18:1–11. doi: 10.1186/s12939-019-0918-1
29. Jackson T, Thomas S, Stabile V, Han X, Shotwell M, McQueen KA, et al. Chronic pain without clear etiology in low- and middle-income countries. *Anesth Analg.* (2016) 122:2028–39. doi: 10.1213/ANE.0000000000001287
30. Qiu Y, Li H, Yang Z, Liu Q, Wang K, Li R, et al. The prevalence and economic burden of pain on middle-aged and elderly Chinese people: results from the

China health and retirement longitudinal study. *BMC Health Serv Res.* (2020) 20:600. doi: 10.1186/s12913-020-05461-6
31. Rodrigues-De-Souza DP, Palacios-Ceña D, Moro-Gutiérrez L, Camargo PR, Salvini TF, Alburquerque-Sendín F. Socio-cultural factors and experience of chronic low back pain: a Spanish and Brazilian patients' perspective. A qualitative study. *PLoS ONE.* (2016) 11:1–15. doi: 10.1371/journal.pone.0159554
32. Sá KN, Moreira L, Baptista AF, Yeng LT, Teixeira MJ, Galhardoni R, et al. Prevalence of chronic pain in developing countries: systematic review and meta-analysis. *Pain Rep.* (2019) 4:e779. doi: 10.1097/PR9.0000000000000779
33. Sharma S, Pathak A, Jha J, Jensen MP. Socioeconomic factors, psychological factors, and function in adults with chronic musculoskeletal pain from rural Nepal. *J Pain Res.* (2018) 11:2385–96. doi: 10.2147/JPR.S173851
34. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. *Psychol Bull.* (2007) 133:581-624. doi: 10.1037/0033-2909.133.4.581
35. Darnall B. To treat pain, study people in all their complexity. *Nature.* (2018) 557:7–7. doi: 10.1038/d41586-018-04994-5
36. Hayes C, Hodson FJ. A whole-person model of care for persistent pain: from conceptual framework to practical application. *Pain Med.* (2011) 12:1738–49. doi: 10.1111/j.1526-4637.2011.01267.x
37. Salvatore S, Valsiner J. Between the general and the unique. *Theory Psychol.* (2010) 20:817–33. doi: 10.1177/0959354310381156
38. Varoquaux G, Raamana PR, Engemann DA, Hoyos-Idrobo A, Schwartz Y, Thirion B. Assessing and tuning brain decoders: Cross-validation, caveats, and guidelines. *NeuroImage.* (2017) 145:166–79. doi: 10.1016/j.neuroimage.2016.10.038
39. Lee JJ, Kim HJ, Ceko M, Park BY, Lee SA, Park H, et al. A neuroimaging biomarker for sustained experimental and clinical pain. *Nat Med.* (2021) 27:174–82. doi: 10.1038/s41591-020-1142-7
40. Ceko M, Frangos E, Gracely J, Richards E, Wang B, Schweinhardt P, et al. Default mode network changes in fibromyalgia patients are largely dependent on current clinical pain. *NeuroImage.* (2020) 216:116877. doi: 10.1016/j.neuroimage.2020.116877
41. Hemington KS, Wu Q, Kucyi A, Inman RD, Davis KD. Abnormal cross-network functional connectivity in chronic pain and its association with clinical symptoms. *Brain Struct Funct.* (2016) 221:4203–19. doi: 10.1007/s00429-015-1161-1
42. Walitt B, Nahin RL, Katz RS, Bergman MJ, Wolfe F. The prevalence and characteristics of fibromyalgia in the 2012 national health interview survey. *PLoS ONE.* (2015) 10:e0138024. doi: 10.1371/journal.pone.0138024
43. Zelaya C, Dahlhamer J, Lucas J, Connor E. Chronic pain and high-impact chronic pain among adults US 2019. In: *NCHS Data Brief.* vol. 390. Hyattsville, MD: The United States Centers for Disease Control and Prevention (CDC) National Center for Health Statistics (2020).
44. Frumkin MR, Haroutounian S, Rodebaugh TL. Examining emotional pain among individuals with chronic physical pain: nomothetic and idiographic approaches. *J Psychosom Res.* (2020) 136:110172. doi: 10.1016/j.jpsychores.2020.110172
45. Liu D, Peng F, Shea A, Rudovic O, Picard R. DeepFaceLIFT: interpretable personalized models for automatic estimation of self-reported pain. *ArXiv.* (2017) 66:1–16. Available online at: https://arxiv.org/abs/1708.04670
46. Lopez-Martinez D, Picard R. Multi-task neural networks for personalized pain recognition from physiological signals. *ArXiv.* (2017) 181–4. Available online at: https://arxiv.org/abs/1708.08755
47. Martinez DL, Rudovic O, Picard R. Personalized automatic estimation of self-reported pain intensity from facial expressions. *IEEE Comput Soc Confer Comput Vis Pattern Recogn Workshops.* (2017) 2017:2318–27. doi: 10.1109/CVPRW.2017.286
48. Gratton C, Laumann TO, Nielsen AN, Greene DJ, Gordon EM, Gilmore AW, et al. Functional brain networks are dominated by stable group and individual factors, not cognitive or daily variation. *Neuron.* (2018) 98:439–52.e5. doi: 10.1016/j.neuron.2018.03.035
49. Finn ES, Shen X, Scheinost D, Rosenberg MD, Huang J, Chun MM, et al. Functional connectome fingerprinting: Identifying individuals using patterns of brain connectivity. *Nat Neurosci.* (2015) 18:1664–71. doi: 10.1038/nn.4135
50. Haxby JV, Guntupalli JS, Connolly AC, Halchenko YO, Conroy BR, Gobbini MI, et al. A common, high-dimensional model of the representational space in human ventral temporal cortex. *Neuron.* (2011) 72:404–16. doi: 10.1016/j.neuron.2011.08.026
51. Lin Q, Li L, Liu J, Liu W, Huang G, Zhang Z. Influence of individual differences in fMRI-based pain prediction models on between-individual prediction performance. *Front Neurosci.* (2018) 12:1–12. doi: 10.3389/fnins.2018.00569
52. Lindquist MA, Krishnan A, López-Solà M, Jepma M, Woo C-W, Koban L, et al. Group-regularized individual prediction: theory and application to pain. *NeuroImage.* (2017) 145:274–87. doi: 10.1016/j.neuroimage.2015.10.074
53. Shinkareva SV, Mason RA, Malave VL, Wang W, Mitchell TM, Just MA. Using fMRI brain activation to identify cognitive states associated with perception of tools and dwellings. *PLoS ONE.* (2008) 3:e1394. doi: 10.1371/journal.pone.0001394
54. Reddan MC, Wager TD. Brain systems at the intersection of chronic pain and self-regulation. *Neurosci Lett.* (2019) 702:24-33. doi: 10.1016/j.neulet.2018.11.047
55. Chou EY, Parmar BL, Galinsky AD. Economic insecurity increases physical pain. *Psychol Sci.* (2016) 27:443–54. doi: 10.1177/0956797615625640
56. Dorner TE, Muckenhuber J, Stronegger WJ, Rsky É, Gustorff B, Freidl W. The impact of socio-economic status on pain and the perception of disability due to pain. *Eur J Pain.* (2011) 15:103–9. doi: 10.1016/j.ejpain.2010.05.013
57. Poleshuck EL, Green CR. Socioeconomic disadvantage and pain. *Pain.* (2008) 136:235–8. doi: 10.1016/j.pain.2008.04.003
58. Rios R, Zautra AJ. Socioeconomic disparities in pain: the role of economic hardship and daily financial worry. *Health Psychol.* (2011) 30:58–66. doi: 10.1037/a0022025
59. Taylor R, Rieger A. Medicine as social science: Rudolf Virchow on the typhus epidemic in upper Silesia. *Int J Health Serv.* (1985) 15:547–59. doi: 10.2190/XX9V-ACD4-KUXD-C0E5
60. Bhugra D. All medicine is social. *J Royal Soc Med.* (2014) 107:183–6. doi: 10.1177/0141076814525069
61. Goosby BJ. Early life course pathways of adult depression and chronic pain. *J Health Soc Behav.* (2013) 54:75–91. doi: 10.1177/0022146512475089
62. Vargas CM, MacEk MD, Marcus SE. Sociodemographic correlates of tooth pain among adults: United States, 1989. *Pain.* (2000) 85:87–92. doi: 10.1016/S0304-3959(99)00250-X
63. Igumbor E, Puoane T, Gansky SA. Prevalence and risk indicators of chronic pain in a rural community in South Africa. *J Rural Trop Public Health.* (2011) 10:61–9. Available online at: http://hdl.handle.net/10566/430
64. Zarei S, Bigizadeh S, Pourahmadi M, Ghobadifar MA. Chronic pain and its determinants: a population-based study in southern Iran. *Korean J Pain.* (2012) 25:245–53. doi: 10.3344/kjp.2012.25.4.245
65. Näher AF, Rummel-Kluge C, Hegerl U. Associations of suicide rates with socioeconomic status and social isolation: findings from longitudinal register and census data. *Front Psychiatry.* (2020) 10:1–9. doi: 10.3389/fpsyt.2019.00898
66. Kiadaliri A, Merlo J, Englund M. Complex sociodemographic inequalities in consultations for low back pain: lessons from multilevel intersectional analysis. *Pain.* (2021) 162:1135–43. doi: 10.1097/j.pain.0000000000002081
67. Saastamoinen P, Leino-Arjas P, Laaksonen M, Lahelma E. Socio-economic differences in the prevalence of acute, chronic and disabling chronic pain among ageing employees. *Pain.* (2005) 114:364–71. doi: 10.1016/j.pain.2004.12.033
68. Papageorgiou A, Croft P, Thomas E, Silman A, Macfarlane G. Psychosocial risks for low back pain: Are these related to work? *Ann Rheum Dis.* (1998) 59:319–20. doi: 10.1136/ard.59.4.319
69. Lee N, Sung H, Kim JH, Punnett L, Kim SS. Perceived discrimination and low back pain among 28,532 workers in South Korea: effect modification by labor union status. *Soc Sci Med.* (2017) 177:198–204. doi: 10.1016/j.socscimed.2017.01.057
70. LeWinn KZ, Shih EW. Social experience and the developing brain: opportunities for social epidemiologists in the era of population-based neuroimaging. *Curr Epidemiol Rep.* (2019) 6:466–75. doi: 10.1007/s40471-019-00222-4

71. Edwards RR. The association of perceived discrimination with low back pain. *J Behav Med.* (2008) 31:379–89. doi: 10.1007/s10865-008-9160-9
72. Baliki MN, Geha PY, Fields HL, Apkarian AV. Predicting value of pain and analgesia: nucleus accumbens response to noxious stimuli changes in the presence of chronic pain. *Neuron.* (2010) 66:149-60. doi: 10.1016/j.neuron.2010.03.002
73. Vachon-Presseau E, Tétreault P, Petre B, Huang L, Berger SE, Torbey S, et al. Corticolimbic anatomical characteristics predetermine risk for chronic pain. *Brain.* (2016) 139:1958–70. doi: 10.1093/brain/aww100
74. Borsook D, Upadhyay J, Chudler EH, Becerra L. A key role of the basal ganglia in pain and analgesia - insights gained through human functional imaging. *Mol Pain.* (2010) 6:27. doi: 10.1186/1744-8069-6-27
75. Kucyi A, Salomons TV, Davis KD. Mind wandering away from pain dynamically engages antinociceptive and default mode brain networks. *Proc Natl Acad Sci.* (2013) 110:18692–7. doi: 10.1073/pnas.1312902110
76. Kucyi A, Moayedi M, Weissman-Fogel I, Goldberg MB, Freeman BV, Tenenbaum HC, et al. Enhanced medial prefrontal-default mode network functional connectivity in chronic pain and its association with pain rumination. *J Neurosci.* (2014) 34:3969–75. doi: 10.1523/JNEUROSCI.5055-13.2014
77. Mcewen BS, Gianaros PJ. Central role of the brain in stress and adaptation: links to socioeconomic status, health, and disease. *Ann N Y Acad Sci.* (2010) 1186:190–222. doi: 10.1111/j.1749-6632.2009.05331.xStress
78. Muscatell KA, Dedovic K, Slavich GM, Jarcho MR, Breen EC, Bower JE, et al. Neural mechanisms linking social status and inflammatory responses to social stress. *Soc Cogn Affect Neurosci.* (2016) 11:915–22. doi: 10.1093/scan/nsw025
79. Muscatell KA, Morelli SA, Falk EB, Way BM, Pfeifer JH, Galinsky AD, et al. Social status modulates neural activity in the mentalizing network. *NeuroImage.* (2012) 60:1771–7. doi: 10.1016/j.neuroimage.2012.01.080
80. Ly M, Haynes MR, Barter JW, Weinberger DR, Zink CF. Subjective socioeconomic status predicts human ventral striatal responses to social status information. *Curr Biol.* (2011) 21:794–7. doi: 10.1016/j.cub.2011.03.050
81. Cascio CN, O'Donnell MB, Simons-Morton BG, Bingham CR, Falk EB. Cultural context moderates neural pathways to social influence. *Cult Brain.* (2017) 5:50–70. doi: 10.1007/s40167-016-0046-3
82. Gonzalez MZ, Puglia MH, Morris JP, Connelly JJ. Oxytocin receptor genotype and low economic privilege reverses ventral striatum-social anxiety association. *Soc Neurosci.* (2019) 14:67–79. doi: 10.1080/17470919.2017.1403954
83. Silverman ME, Muennig P, Liu X, Rosen Z, Goldstein MA. The impact of socioeconomic status on the neural substrates associated with pleasure. *Open Neuroimaging J.* (2009) 3:58–63. doi: 10.2174/1874440000903010058
84. Gao W, Alcauter S, Elton A, Hernandez-Castillo CR, Smith JK, Ramirez J, et al. Functional network development during the first year: Relative sequence and socioeconomic correlations. *Cereb Cortex.* (2015) 25:2919–28. doi: 10.1093/cercor/bhu088
85. Sripada RK, Swain JE, Evans GW, Welsh RC, Liberzon I. Childhood poverty and stress reactivity are associated with aberrant functional connectivity in default mode network. *Neuropsychopharmacology.* (2014) 39:2244–51. doi: 10.1038/npp.2014.75
86. Weissman DG, Conger RD, Robins RW, Hastings PD, Guyer AE. Income change alters default mode network connectivity for adolescents in poverty. *Dev Cogn Neurosci.* (2018) 30:93–9. doi: 10.1016/j.dcn.2018.01.008
87. Federal Register Notice. *The Poverty Guidelines Updated Periodically in the Federal Register by the U.S. Department of Health and Human Services Under the Authority of 42 U.S.C. 9902(2).* Washington, DC: The Federal Register (2020).
88. Fuentes M, Hart-Johnson T, Green CR. The association among neighborhood socioeconomic status, race and chronic pain in black and white older adults. *J Natl Med Assoc.* (2007) 99:1160–9.
89. Friedman EM, Karlamangla AS, Almeida DM, Seeman TE. Social strain and cortisol regulation in midlife in the US. *Soc Sci Med.* (2012) 74:607–15. doi: 10.1016/j.socscimed.2011.11.003
90. Marmot M, Wilkinson RG. Psychosocial and material pathways in the relation between income and health: a response to Lynch et al. *Br Med J.* (2001) 322:1233–6. doi: 10.1136/bmj.322.7296.1233
91. Archie EA, Altmann J, Alberts SC. Social status predicts wound healing in wild baboons. *Proc Natl Acad Sci U.S.A.* (2012) 109:9017–22. doi: 10.1073/pnas.1206391109
92. Cohen S, Line S, Manuck SB, Rabin BS, Heise ER, Kaplan JR. Chronic social stress, social status, and susceptibility to upper respiratory infections in nonhuman primates. *Psychosom Med.* (1997) 59:213–23. doi: 10.1097/00006842-199705000-00001
93. Takahashi A, Flanigan ME, McEwen BS, Russo SJ. Aggression, social stress, and the immune system in humans and animal models. *Front Behav Neurosci.* (2018) 12:56. doi: 10.3389/fnbeh.2018.00056
94. Kraus MW, Piff PK, Mendoza-Denton R, Rheinschmidt ML, Keltner D. Social class, solipsism, and contextualism: how the rich are different from the poor. *Psychol Rev.* (2012) 119:546–72. doi: 10.1037/a0028756
95. Jackson T, Wang Y, Wang Y, Fan H. Self-efficacy and chronic pain outcomes: a meta-analytic review. *J Pain.* (2014) 15:800–14. doi: 10.1016/j.jpain.2014.05.002
96. Morse T, Punnett L, Warren N, Dillon C, Warren A. The relationship of unions to prevalence and claim filing for work-related upper-extremity musculoskeletal disorders. *Am J Ind Med.* (2003) 44:83–93. doi: 10.1002/ajim.10234
97. Malinowski B, Minkler M, Stock L. Labor unions: a public health institution. *Am J Public Health.* (2015) 105:261–71. doi: 10.2105/AJPH.2014.302309
98. Adler NE, Stewart J. *The MacArthur Scale of Subjective Social Status.* (2007). Available online at: http://www.macses.ucsf.edu/research/psychosocial/subjective.php (accessed January 20, 2021).
99. Operario D, Adler NE, Williams DR. Subjective social status: reliability and predictive utility for global health. *Psychol Health.* (2004) 19:237–46. doi: 10.1080/08870440310001638098
100. Zimet GD, Dahlem NW, Zimet SG, Farley GK. The multidimensional scale of perceived social support. *J Pers Assess.* (1988) 52:30–41. doi: 10.1207/s15327752jpa5201_2
101. Tuomi K, Wagar K, Eskelinen L. Terveys, tyokyky ja tyoolot kunnallisissa ammattiryhmissa. *Tyoterveyslaitoksen Tutkimuksia.* (1985) 3:95–132.
102. Jost JT, Thompson EP. Group-based dominance and opposition to equality as independent predictors of self-esteem, ethnocentrism, and social policy attitudes among African Americans and European Americans. *J Exp Soc Psychol.* (2000) 36:209–32. doi: 10.1006/jesp.1999.1403
103. Lucas T, Zhdanova L, Alexander S. Procedural and distributive justice beliefs for self and others: Assessment of a four-factor individual differences model. *J Indvid Dif.* (2011) 32:14–25. doi: 10.1027/1614-0001/a000032
104. Dweck CS. *Self-Theories: Their Role in Motivation, Personality, and Development.* Philadelphia, PA: Psychology Press (1999).
105. Skevington SM. A standardised scale to measure beliefs about controlling pain (B.P.C.Q.): a preliminary study. *Psychol Health.* (1990) 4:221–32. doi: 10.1080/08870449008400392
106. Rotter JB. Generalized expectancies for internal versus external control of reinforcement. *Psychol Monogr.* (1966) 80:1. doi: 10.1037/h0092976
107. Costa PT, McCrae RR. *Revised NEO Personality Inventory (NEO-PI–R) and the NEO Five-Factor Inventory (NEO-FFI) professional manual.* Odessa, FL: Psychological Assessment Resources (1992).
108. Davis MH. Measuring individual differences in empathy: Evidence for a multidimensional approach. *J Pers Soc Psychol.* (1983) 44:113-26. doi: 10.1037/0022-3514.44.1.113
109. Feeney JA, Noller P, Hanrahan M. Attachment style questionnaire (ASQ). *APA PsycTests.* (1994). doi: 10.1037/t29439-000
110. Sullivan MJ, Bishop SR, Pivik J. The pain catastrophizing scale: development and validation. *Psychol Assess.* (1995) 7:524. doi: 10.1037//1040-3590.7.4.524
111. Spielberger CD. *State-Trait Anxiety Inventory: Bibliography.* 2nd ed. Palo Alto, CA: Consulting Psychologists Press (1989).

112. Beck AT, Steer RA, Brown G. Beck depression inventory–II. *APA PsycTests*. (1996). doi: 10.1037/t00742-000
113. Koban L, Jepma M, López-Solà M, Wager TD. Different brain networks mediate the effects of social and conditioned expectations on pain. *Nat Commun.* (2019) 10:1–13. doi: 10.1038/s41467-019-11934-y
114. Scott DJ, Stohler CS, Egnatuk CM, Wang H, Koeppe RA, Zubieta JK. Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. *Arch Gen Psychiatry*. (2008) 65:220-31. doi: 10.1001/archgenpsychiatry.2007.34
115. Zunhammer M, Bingel U, Wager TD. Placebo effects on the neurologic pain signature: a meta-analysis of individual participant functional magnetic resonance imaging data. *JAMA Neurol.* (2018) 75:1321–30. doi: 10.1001/jamaneurol.2018.2017
116. Coan JA, Beckes L, Gonzalez MZ, Maresh EL, Brown CL, Hasselmo K. Relationship status and perceived support in the social regulation of neural responses to threat. *Soc Cogn Affect Neurosci*. (2017) 12:1574-83. doi: 10.1093/scan/nsx091
117. López-Solà M, Geuter S, Koban L, Coan JA, Wager TD. *Brain mechanisms of social touch-induced analgesia*. *Pain.* (2019) 160:2072-85. doi: 10.1097/j.pain.0000000000001599
118. Reddan MC, Young H, Falkner J, López-Solà M, Wager TD. Touch and social support influence interpersonal synchrony and pain. *Soc Cogn Affect Neurosci.* (2020) 15:1064–75. doi: 10.1093/scan/nsaa048
119. Aytur SA, Ray KL, Meier SK, Campbell J, Gendron B, Waller N, et al. Neural mechanisms of acceptance and commitment therapy for chronic pain: a network-based fMRI approach. *Front Hum Neurosci.* (2021) 15:587018. doi: 10.3389/fnhum.2021.587018
120. Meier ML, Stämpfli P, Vrana A, Humphreys BK, Seifritz E, Hotz-Boendermaker S. Fear avoidance beliefs in back pain-free subjects are reflected by amygdala-cingulate responses. *Front Hum Neurosci.* (2015) 9:424. doi: 10.3389/fnhum.2015.00424
121. Shi Y, Huang S, Zhan H, Wang Y, Zeng Y, Cai G, et al. Personality differences of brain networks in placebo analgesia and nocebo hyperalgesia: a psychophysiological interaction (PPI) approach in fMRI. *Neural Plast.* (2020) 2020:1–13. doi: 10.1155/2020/8820443
122. Mechlin B. Lower socioeconomic status is associated with rating experimental pain as more intense. *J Pain.* (2012) 13:S52. doi: 10.1016/j.jpain.2012.01.218
123. Davies JB, Shorrocks AF. *Comparing Global Inequality of Income and Wealth.* WIDER Working Paper 2018/160. Helsinki: UNU-WIDER (2018). doi: 10.35188/UNU-WIDER/2018/602-9
124. Lynch J, Smith G, Kaplan G, House J. Income inequality and mortality: importance to health of individual income, psychosocial environment, or material conditions. *BMJ.* (2000) 321:1200–4. doi: 10.1136/bmj.320.7243.1200

Conflict of Interest: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2021 Reddan. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Neurology

ORIGINAL RESEARCH
published: 22 September 2021
doi: 10.3389/fneur.2021.722334

Complex Regional Pain Syndrome: Thalamic GMV Atrophy and Associations of Lower GMV With Clinical and Sensorimotor Performance Data

Martin Domin[1†], Sebastian Strauss[1,2†], James H. McAuley[3] and Martin Lotze[1]*

[1] fMRI Unit, Diagnostic Radiology and Neuroradiology, University Medicine Greifswald, Greifswald, Germany, [2] Neurology, University Medicine Greifswald, Greifswald, Germany, [3] NeuRA and the School of Health Sciences, University of New South Wales, Sydney, NSW, Australia

OPEN ACCESS

Edited by:
Marie-Eve Hoeppli,
Cincinnati Children's Hospital Medical Center, United States

Reviewed by:
Paul Geha,
University of Rochester, United States
Eduard Kraft,
Ludwig Maximilian University of Munich, Germany

***Correspondence:**
Martin Lotze
martin.lotze@uni-greifswald.de

[†] These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to Applied Neuroimaging, a section of the journal Frontiers in Neurology

Received: 08 June 2021
Accepted: 26 August 2021
Published: 22 September 2021

Citation:
Domin M, Strauss S, McAuley JH and Lotze M (2021) Complex Regional Pain Syndrome: Thalamic GMV Atrophy and Associations of Lower GMV With Clinical and Sensorimotor Performance Data. Front. Neurol. 12:722334. doi: 10.3389/fneur.2021.722334

Results on gray matter alterations in complex regional pain syndrome (CRPS) showed heterogeneous findings. Since CRPS is a rare disease, most studies included only small and heterogeneous samples resulting in a low reliability of findings between studies. We investigated 24 CRPS patients with right upper limb affection in the chronic stage of disease using structural MRI and clinical testing. We focused on gray matter volume (GMV) alterations of the brain in comparison to 33 age matched healthy controls, their association to clinical characteristics (duration of pain syndrome and pain intensity ratings) and sensorimotor performance (finger dexterity and spatiotactile resolution). When applying an explorative whole brain analysis CRPS patients showed lower GMV in the bilateral medial thalamus. No other areas showed a relevant GMV difference for the group comparisons. When applying a region of interest driven approach using anatomical masks of the thalamus, ACC/mPFC, putamen, and insula we found relevant associations of clinical and behavioral data in ACC and insula. Whereas, the GMV in ACC showed negative associations with pain intensity and CRPS duration, the GMV of the left posterior insula was negatively associated with sensorimotor performance of the affected hand side. Overall, our results are in accordance to results of others describing a thalamic reduction of GMV in patients with neuropathic pain and are also in accordance with associations of pain intensity and duration with reduced ACC in general in patients with chronic pain syndromes. Sensorimotor performance seems to be related to posterior insula GMV reduction, which has not been described yet for other patient groups.

Keywords: CRPS, chronic pain, neuropathic pain, gray matter volume, thalamus, ACC, insula

INTRODUCTION

GMV-Alterations in Chronic Pain

Chronic pain has a substantial impact on quality of life of patients and their families. With a prevalence of 20% (1) it also represents a major socio-economic challenge. By definition, chronic pain lasts for more than 12 weeks and importantly does not depend on sustained physical damage, i.e., may be maintained by alterations in the central nervous

system (2). For structural alterations in patients suffering from various chronic pain conditions several meta-analyses [e.g., (3, 4)] have consistently described decreased gray matter volume in the medial prefrontal cortex (mPFC) and the anterior cingulate cortex (ACC) of the brain. For chronic low back pain (CLBP), as the most frequently occuring chronic pain syndrome, loss of gray matter volume (GMV) has been described for the medial prefrontal cortex, the anterior (ACC) and midcingulate (MCC) cortex and anterior insula [e.g., (5, 6)], but also for the thalamus [e.g., (7)].

Besides CLBP, neuropathic facial pain such as trigeminal neuralgia showed robust effects of GMV decrease in bilateral ACC (8, 10), insula (8) but also a reduction in thalamic GMV especially for those areas which are involved in sensorimotor processing (medial parts of the thalamus) (8, 9). Furthermore, since less pronounced pain intensity such as temporomandibular disorder (TMD) showed only marginal effects in ACC/mPFC GMV an association of GMV loss and pain severity has been assumed (11).

When using large samples, especially general population-based cohorts, the inter-individual random noise in the variance is significantly reduced, resulting in reliable and robust statistical testing, including correction, for e.g., multiple comparisons (12).

CRPS Epidemiology and Characteristics

Chronic pain can be differentiated into various syndromes. One of these syndromes, which has been categorized as a subtype of neuropathic pain [for an overview see (13)], is complex regional pain syndrome (CRPS) which affects 4–7% of patients after limb injury (14, 15). After several weeks, patients develop chronic neuropathic pain in the affected limb that often includes somatosensory, motor and autonomic dysfunctions (16). Perceptual symptoms have been described which most frequently comprise impaired somatosensory discrimination (17), allodynia (18), neglect like symptoms (19), and a feeling of swelling of the affected limb [for a latest systematic observation (20)]. Motor dysfunction may involve dystonic movements (21), tremor, a reduced motion range and coordination deficits (22).

GMV-Alterations in CRPS

Contradictory findings have been reported for GMV alterations in CRPS (23–27). Geha et al. (23) included 22 CRPS patients with upper and lower limb but also trunk affection and 22 healthy controls (HC) in a VBM analysis. Group differences were based on cluster thresholding after using permutation-based interference and was performed with FSL-scripts. ROI-analyses for linear regression were based on group differences. Overall, the slope of GMV-decrease with age was stronger in CRPS patients. Circumscribed GMV decrease for patients had been detected for the ventromedial PFC, anterior insula and the nucleus accumbens and this decrease was associated with years of persistence of CRPS (very heterogeneous patient group with 3 months to 13.5 years CRPS persistence) but also for the vmPFC with pain intensity [VAS (0–10); varied between 1.5 and 9.7].

Pleger et al. (24) applied VBM in 20 CRPS patients with unilateral upper limb affection and 1–63 months of CRPS duration (current pain intensity on a NRS from 1.5 to 8) and 20 age and gender matched controls. Group comparisons were based on cluster thresholding (FWE) after peak thresholding with $p = 0.001$. In addition, the authors applied a ROI-analysis for the pre- and postcentral gyrus. The results of this study were surprising since they found higher GMV for CRPS patients compared to HCs in dmPFC and M1 contralateral to the affected hand side. However, it is unknown how generalizable these findings are since some of the methods used in this study were older (1.5 T MRI, SPM/VBM8 used for GMV quantification, no total intracranial volume included as covariate for statistical analysis) and most patients (with 2 exclusions) were in the subacute stage of the disease.

Barad et al. (25) applied VBM in 15 right upper limb CRPS female patients and 15 matched HCs. Pain duration ranged from 2 months to 17 years and pain intensity was 7.5 of 10 (VAS) on average. The study used a 3 T MRI and non-isometric voxel size with unusual poor spatial resolution (28 slices; 4 mm slice thickness; 1 mm gap; in plane resolution 1.5 mm). The authors applied a FDR corrected threshold with $p < 0.005$; resulting in $t = 3.71$ threshold but only reported clusters with at least 30 voxels (both for group comparisons and linear regression with clinical data). The study found decreased GMV in the posterior insula, left OFC and CC (posterior ACC, posterior medial CC). However, an increase in GMV in bilateral putamen and right hypothalamus was also found. Higher pain intensity resulted in lower GMV in the dlPFC.

van Velzen et al. (26) did not observe any significant differences when comparing GMV in 19 upper limb patients (with right and left hand affection) and 19 matched HCs. The latest VBM-investigations on CRPS-patients (27) investigated 20 CRPS patients with affected right upper limbs. They performed elaborate sensorimotor testing with a focus on rigidity and dystonic symptoms, but also performed somatosensory testing, testing of autonomic function, and psychological testing. They applied state of the art MRI and VBM methods (3T imaging, SPM12 and CAT12, DARTEL based normalization, 5 mm smoothing) but performed a ROI-analysis restricted on basal ganglia, thalamus, insula, and postcentral gyrus. When compared to HCs only bilateral putamen showed relevant decrease in GMV. GMV reduction in the basal ganglia were associated with dystonic symptoms.

These divergent results of the aforementioned studies might well be caused by small sample sizes, inhomogeneous patient groups (lateralization/localization of the affected area, severity and/or duration of disease, type of CRPS), and differing or non-optimized evaluation strategies focusing on structural gray matter alterations. Overall, small sample sizes and large variances often prevent exploratory whole brain volume analyses and the necessary correction for multiple comparisons over said volume, favoring less conservative statistical approaches which are one cause of the reproducibility crisis in psychology [for the field of brain imaging see (28)]. By using a region of interest (ROI) driven approach any statistical effects detected are dependent on the ROIs defined. However, this definition is statistically only justified if based on previous investigations utilizing an exploratory

whole brain approach, corrected for multiple comparisons over all measurements.

Hypothesis and Methodological Approach

We here investigated common and specific GMV alterations in patients with CRPS from two study samples in an explorative (multiple comparison correction for the whole brain volume) and a hypothesis-driven approach (multiple comparison correction for regions of interest comprising mPFC/ACC, thalamus, and insula). The following hypotheses were tested:

(A) Explorative approach with correction over the whole brain volume and a ROI approach for those areas which already showed effects in previous investigations surviving a correction for multiple comparisons over the measurement volume: Are there GMV alterations in CRPS patients compared to healthy controls?

(B) ROI-approach for those areas which already showed effects in previous investigations surviving a correction for multiple comparisons over the measurement volume: Are there associations between GMV decrease in CRPS patients and pain severity, chronicity, and relevant performance impairment alterations in GMV?

METHODS

Participants

Participants were recruited *via* support groups in Northern Germany and *via* the hand surgery and Anesthesiology of the University of Greifswald. Twenty-four right hand affected CRPS-patients have been included which have been characterized in detail in **Table 1**.

Twenty-four patients had been diagnosed based on the Budapest criteria (31) were on average 50.75 ± 14 years old, with 4 male, 17 right handed (assessed using the Edinburgh Handedness score) (32), CRPS-severity with CSS (CRPS severity score) (33) was 11.78 ± 3.23 on average, duration of symptoms on average for 48.12 ± 37 months, average rest pain was 4.80 ± 2.82 (VAS 0–100). Thirty-three healthy controls (25 right handed) were recruited by advertising from the University Medicine faculty with 54.42 ± 13.49 years old on average (sex not matched since these were 14 male participants). All participants were free from other neurological and psychiatric problems as assessed by a neurologist (ML). All participants gave their written informed consent. The two study samples have been approved by the local ethics committee of the University Medicine Greifswald (BB 45/09, BB 055/18).

Sample Size Estimation

Sample size calculation was based on the first study published on GMV changes in CRPS patients (23). They included 22 CRPS patients and 22 HCs and described a cluster volume $p < 0.05$ effect for GMV decrease in the medial prefrontal cortex (mPFC). The mPFC appeared to be a robust finding in a number of different studies on associations of GMV decrease with pain chronicity; see also Kang et al. (34). Since the methods of determining GMV differences between samples were performed with other software packages we increased group size for both samples and included more homogeneous patients with respect to pain locations (upper limb, only dominant side). In a ROI-based approach for thalamus, ACC, mPFC, putamen, and insula we had to correct for false positive results within 39 resels (smoothed spatial units as the basis for the GLM). Therefore, we can expect a significant GMV-effect, based on results in other chronic pain groups, with a t-value of $\geq$4.1. Therefore, group sizes of our samples should be sufficient to test the aims as defined above.

Assessments and Scores

Behavioral testing for the CRPS patients was performed in the same way as described before in previous investigations from our group [in healthy (35) in CRPS-patients (36)]. Two-point-discrimination (TPD) was tested using a wheel-discriminator (Sensidisk, Hannover, Germany) on fingertip of D1 in a pseudorandomized order of space intervals from 15 to 1 mm. Finger dexterity of the affected hand was assessed using the Roeder Manipulative Aptitude Test (Lafayette Instrument Company, Lafayette, IN, USA). In this test, the time needed to screw small rods into a row with ten holes was measured. Patients were asked for their current medication at the day when the imaging was performed (see **Table 1**).

MRI-Measurements

MRI was performed with a 3 T Magnetom Verio (Siemens, Erlangen, Germany) using a 32-channel head coil. T1-weighted structural scans were acquired using the following characteristics: MP-RAGE, TR 1,690, TE 2.52 ms, flip angle 9°, matrix size 256 × 256, voxel size 1 × 1 × 1 mm^3.

MRI Evaluations

GMV alterations between all patients and controls were compared using CAT12/SPM12 packages. Statistical thresholding had been obtained in a generalized procedure for all comparisons: We will apply $p < 0.05$ (voxel height) using a family wise error (FWE) correction over (1) the whole brain, and (2) in an additional ROI-correction (FWE voxel height) comprising mPFC (one medial region), ACC (one medial region), and bilateral ROIs (anterior insula, thalamus, putamen). ROIs for GMV analyses were tested on the basis of prior investigations (23–27) and reports on GMV alterations in patients with neuropathic pain [e.g., (37)].

We aimed to identify differences in GMV between CRPS patients and age matched HCs. Furthermore, we investigated whether clinical symptoms (pain intensity and duration of CRPS) or sensorimotor performance (Roeder and TPD) were associated with GMV.

RESULTS

CRPS patients showed decreased motor performance with their affected right hand than HCs (Roeder test; $t = 3.24$; $p = 0.001$). In addition, CRPS patients showed a decrease in spatiotactile discrimination as tested with the two-point discrimination (TPD; $t = 2.91$; $p = 0.012$; see **Figure 1**).

TABLE 1 | Characteristics of CRPS patients.

Participants	Age	CSS[a]	BDI[b]	Pain rest (VAS)	Duration (months)	Roeder_aff[c]	Two point discrimination (TPD)	Medication[d]
Subject 1	56	17	7	2.5	14	250	8.0	A, B, D
Subject 2	48	15	35	5.0	14	117	3.0	A, B, C, D
Subject 3	65	–	3	8.0	104	250	3.0	–
Subject 4	60	9	14	5.5	72	80	3.2	D
Subject 5	24	11	22	4.5	84	48	3.7	A, B, D
Subject 6	47	10	11	4.5	22	51	1.7	B, D
Subject 7	19	13	6	0.0	12	76	1.9	B, C, D
Subject 8	53	14	14	7.0	26	250	10.0	B, D
Subject 9	58	13	3	4.5	61	104	1.5	B, C, D
Subject 10	64	8	20	2.5	13	65	1.8	B, C, D
Subject 11	44	9	6	9.5	77	81	3.5	B
Subject 12	79	5	17	10.0	50	106	3.3	–
Subject 13	57	12	7	3.0	84	95	3.7	A, B, D
Subject 14	19	13	32	2.0	48	74	2.7	B, C, D
Subject 15	33	11	13	5.0	51	109	3.00	A, B, C
Subject 16	56	13	22	10.0	106	50	3.3	A, B, D
Subject 17	59	16	16	3.0	95	84	3.7	B, C, D
Subject 18	64	13	10	2.0	74	48	2.7	A, B, C, D
Subject 19	54	13	10	5.0	109	51	3.0	A
Subject 20	61	13	–	1.5	4	38	4.4	A
Subject 21	40	16	–	2.4	8	84	7.0	A, C
Subject 22	58	7	–	8.1	5	63	4.0	A
Subject 23	45	14	–	7.9	15	250	10.0	A
Subject 24	55	6	–	2.7	7	51	4.6	–
Average ± SD	50.8 ± 14	11.8 ± 3.2	14.0 ± 8.9	4.8 ± 2.9	48 ± 37	103 ± 70	4.0 ± 2.4	

[a]*CSS, CRPS severity score (29).*
[b]*BDI, Beck-Depression-Inventory (30).*
[c]*Roeder_aff, Roeder test for the affected hand side.*
[d]*A: NSAID, non-steroidal anti-inflammatory drugs; B: opioid; C: amitriptyline; D: pregabalin.*

Pain intensity at rest, duration of CRPS symptoms, and performance were not relevantly associated with GMV alterations (for rest pain associations: duration: $r = 0.32$; n.s.; Roeder: $r = 0.28$; n.s.; TPD: $r = 0.15$; n.s.).

For the exploratory GMV analyses (corrected for the whole brain volume) CRPS patients showed lower GMV in the bilateral thalamus (cluster level whole brain correction: $t = 4.42$; 1,227 voxels; $p_{FWE} = 0.015$) than HCs (**Figure 2**). In particular, the strongest effects were detected in the thalamus proper (Neuromorphometrics brain atlas) for both hemispheres (left: $t = 4.42$; coordinates: −2, −10, 17; right: $t = 4.03$; coordinates: 9, −4, 11). For the ANATOMY/Oxford atlas differentiation (based on connectivity information) the temporal (right: $t = 4.32$; coordinates: 3, −10, 14) and the prefrontal (left: $t = 3.67$; coordinates: −6, −9, 6) parts of the thalamus showed highest effects. Effects remained largely unchanged when only including patents with more than 12 months of disease persistence for the group comparisons (CRPS: $n = 20$; left thalamus (coordinates: −5, −7, 8); $t = 4.26$; cluster level $p = 0.008$).

When using ROI-analysis (bilateral thalamus mask) we again only observed bilateral anterior-medial thalamus GMV decrease for CRPS (ri: coordinates: 3, −11, 16; $t = 4.26$; $p_{FWE} = 0.008$; le: coordinates: −3, −14, 14; $t = 4.14$; $p_{FWE} = 0.011$) but not for the other ROIs selected.

Linear regression analyses for duration of CRPS revealed a decrease in GMV for the ACC (coordinates: −6, 31, 18; $t = 4.07$, $p_{FWE} = 0.033$; one sided). Pain intensity was negatively associated with GMV in the same Area (ACC; coordinates: 3, 34, 15; $t = 4.23$, $p_{FWE} = 0.026$; one sided; see **Figure 3**).

When testing possible associations between decrease in GMV with sensorimotor performance we used those parameters which were impaired in our patients compared to healthy controls. For the motor testing with the Roeder test we found a negative association with GMV in the left posterior insula [MNI coordinates: −42, −12, 9; $t = 4.49$; p_{FWE} (insula ROI) = 0.038]. For the somatosensory testing with TPD we observed a negative association with GMV in the left posterior insula [MNI coordinates: −44, −13, 6; $t = 4.40$; p_{FWE} (insula ROI) = 0.047].

DISCUSSION

By using voxel-based morphometry to compare gray matter volume of a highly homogeneous CRPS patient sample with those of healthy age matched controls we found a decrease

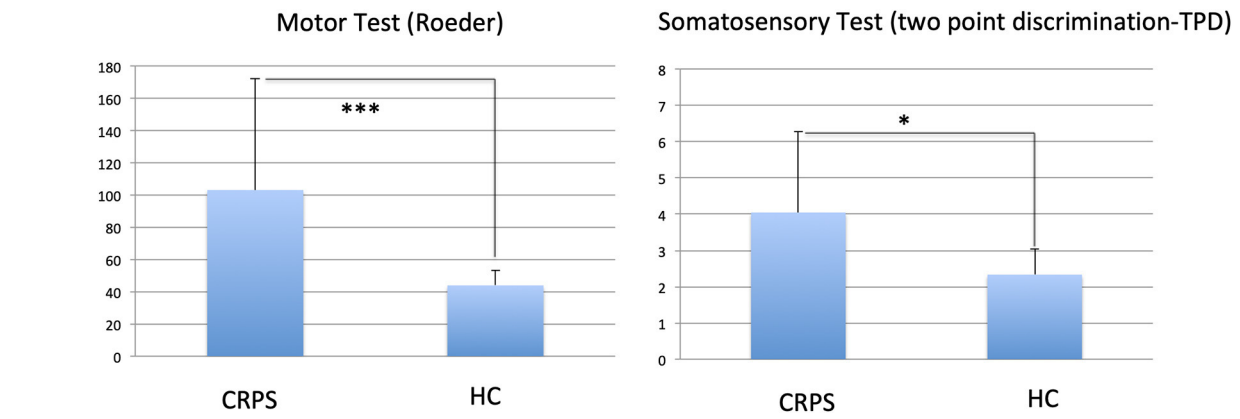


FIGURE 1 | Comparison of motor (Roeder Test) and somatosensory (two point discrimination TPD) tests between CRPS patients and healthy controls (HC); stars indicate p-value of differences; ***0.001; *0.05. Larger values indicate lower performance.

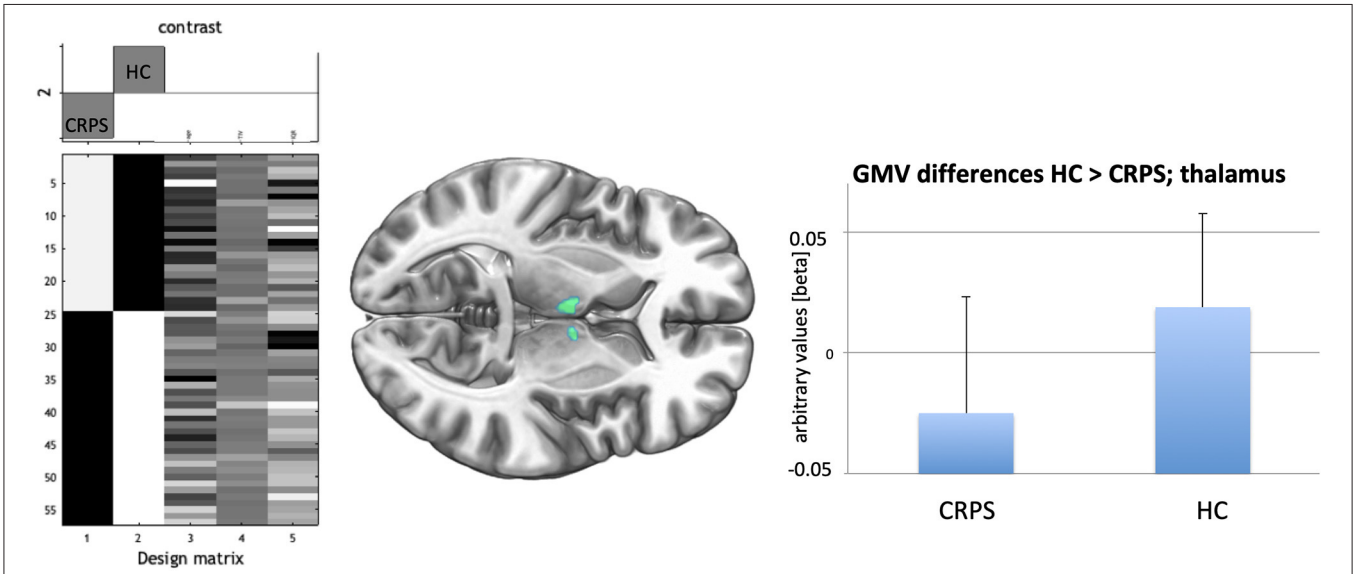


FIGURE 2 | (Left) Design matrix of the t-test comparison CRPS (−1) against HC (+1) with the three covariates age, total intracranial volume, and a quality score/IQR derived from CAT12 preprocessing. **(Middle)** Bilateral decreased GMV ($p_{FWE} < 0.05$; cluster level) in the medio-anterior thalamus for the CRPS patients indicated in green. **(Right)** bars indicate averages together with SDs (lines) for the GMV-effect in the highest significant voxel of the medio-anterior thalamus for CRPS patients and HCs.

for the patients GMV in the medial parts of the thalamus. This finding is analogous to other studies comparing GMV in neuropathic pain patients with those of healthy volunteers (9). It also matches well to reports on altered functional thalamo-cortical interaction in patients with neuropathic pain (38) and to models describing interactions of thalamic GMV decrease, a decrease of thalamic inhibitory neurotransmitters, and increased cortical excitability (37). Furthermore, anterior cingulate cortex GMV was negatively associated with duration of CRPS and pain intensity. This finding supports the results of others who showed associations of persistence of CRPS and GMV (23), and showed a decrease in ACC GMV in patients with other neuropathic pain syndromes [trigeminal neuralgia (8, 10)], or patients with milder non-neuropathic pain syndromes (11, 12). In addition, somatosensory performance impairment in CRPS patients was associated with lower GMV in the posterior left insula cortex. Although many studies already observed insula GMV decrease in patients with chronic neuropathic pain [trigeminal neuralgia (8, 10); herpes zoster (39); burning mouth syndrome (40)] and non-neuropathic pain [e.g., CBP (12)] no such associations with sensorimotor performance have yet been described.

Thalamus Effect

In the present VBM investigation in a group of carefully selected patients with upper limb affection of the dominant right hand we found decreased GMV in comparison to matched healthy

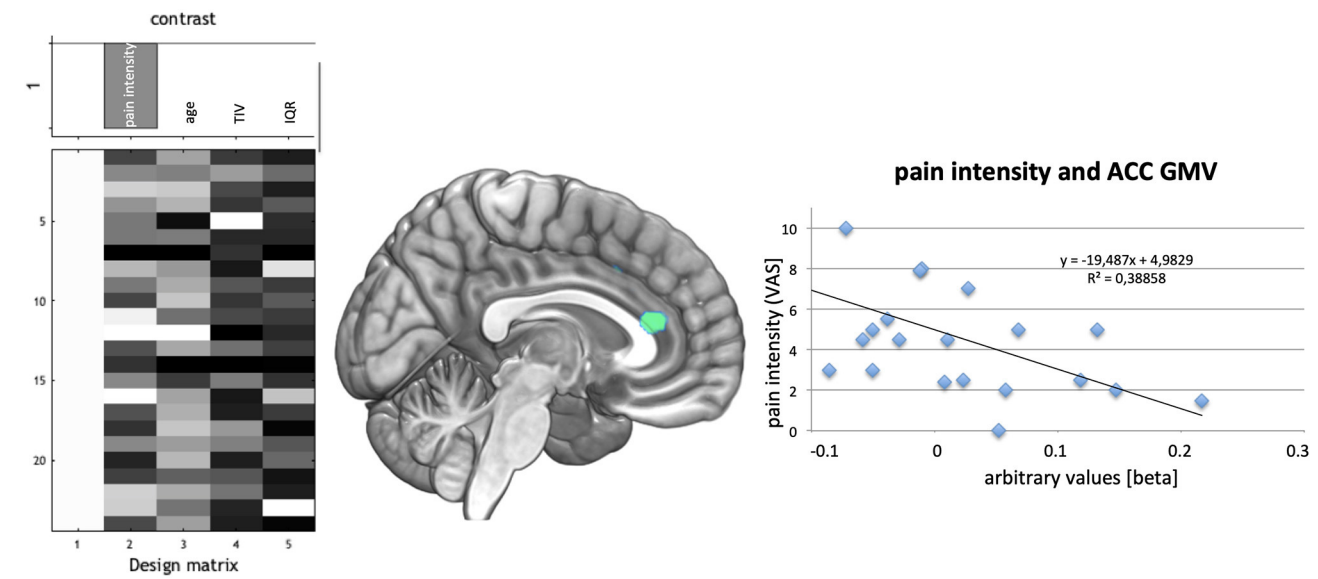


FIGURE 3 | (Left) Design of regression analysis in the CRPS patient group for the factor pain intensity during rest using age, total intracranial volume (TIV), and quality of T1-images for segmentation (IQR) as covariates. **(Middle)** Association of pain during rest with GMV decrease in the cingulate cortex- indicated green. **(Right)** Plot of the association of decreased GMV in the highest significant voxel with pain intensity showed an r^2 of 0.388.

controls in the bilateral thalamus proper. This effect remained largely unchanged after excluding all patients with <1 year of disease persistence, underlining the observation that GMV decrease is related to persistence of chronic pain [e.g., (23)]. Compared to a connectivity-based atlas this resembles the areas connected to the prefrontal and temporal cortex. Especially for the prefrontal interactions these parts of the thalamus might be related to both pain modulation [discussion see (41)] or effects of the ACC [e.g., (11)] which had been described to be vulnerable to both chronic pain but also stressors in animal research before (42, 43). Especially the thalamo-prefrontal axis is an important hub which shows changes in cholinergic neurotransmitters in chronic pain patients (41) and specifically a decrease connectivity for CRPS patients (38). At least with respect to the ACC GMV decrease it seems to be highly associated with the duration of CRPS. For the temporal areas this might well be related also to parts of the limbic system known to be involved in the modulation of pain intensity [for animal literature (44)].

An overlapping area in the ventroposterior thalamus has been described to be reduced in GMV before, showing reduced connectivity and reduced GABA for patients with neuropathic pain [for trigeminal neuralgia (9, 37)].

Interestingly, Fukumato et al. used radioactive labeled iodoamphetamine in a SPECT study in 10 patients with CRPS to investigate perfusion differences between the hemispheres contra- and ipsilateral to the affected upper limb. When compared to ipsilateral, contralateral thalamus showed a reduction in perfusion and this reduction index was related to time of onset of the disease (6–36 months). In contrast, healthy controls showed symmetric thalamic perfusion. They discussed their results with the finding that chronic neuropathic pain results in a long-term thalamic inhibition whereas acute pain increases its activity. In contrast to Fukumoto, we observed a bilateral reduction in thalamic GMV. However, the effect for the contralateral hemisphere to the affected hand was stronger—especially when investigating only patients who had more than 12 months duration of CRPS.

ACC Effect

Here, the anterior cingulate cortex GMV was negatively associated with the duration of CRPS and pain intensity. This finding supports finding of others who showed associations of persistence of CRPS and GMV (23), showed a decrease in ACC GMV in patients with other neuropathic pain syndromes [trigeminal neuralgia (8, 10)], or patients with milder non-neuropathic pain syndromes (11, 12). In a monkey model the anterior cingulate cortex and the medial PFC showed that reduced GMV was associated with stress (42). In addition, cognitive deficit, e.g., for attention, was associated with a decrease in ACC/mPFC GMV in fibromyalgia (45). Neuropathic pain, increased stress, sleeplessness, attention deficits, and decrease in prefrontal pain suppression might well contribute to the maladaptive chronification circle into sustained pain.

Insula Effect

In the rodent neuropathic pain model using nerve compression induced by surgical intervention S1, ACC, and insula GMV loss was associated with somatosensory impairment (43). The insula serves as an internal monitor adjusting all incoming input into a current body state. The anterior insula is densely interconnected with the prefrontal cortex and the limbic system (46), it is therefore part of the emotional/anticipation pain system. In contrast, the posterior insula is highly interconnected with the thalamus and the somatosensory cortices (S1 and S2)

and is therefore part of the somatosensory discriminative pain processing system. Hence, it is not surprising that a reduction in gray matter volume in this area is associated with somatosensory performance such as spatiotactile resolution (as tested with the TPD) but also with pinch grip performance (as tested with the Roeder test). Prior studies have demonstrated associations between pinch grip, motor and TPD testing in CRPS patients (17). Several studies already observed insula GMV decrease in patients with chronic neuropathic pain [trigeminal neuralgia (8, 10); herpes zoster (39); burning mouth syndrome (40)] and non-neuropathic pain [e.g., CBP (12)]. In contrast to Geha et al., who found an association of GMV-decrease with duration of CRPS for the anterior insula, we here observed effects for the posterior insula. Overall, the anterior insula activity had been identified to be associated with catastrophizing pain and trait anxiety in other groups of chronic pain patients (TMD) (47), and its increased activation in chronic pain patients decreases following interventions successfully reducing pain intensity (48). When considering its connections to the prefrontal lobe an association of persistence of the pain syndrome in the Geha et al. (23) study and our finding of an association of posterior insula GMV with a somatosensory performance is in a good concordance with anatomical connectivity of this area.

What Else Could Be the Basis of GMV-Alterations in Chronic Pain?

There is an ongoing debate concerning the fundamental neural substrates of GMV alterations. Underlying mechanisms for GMV decrease in patients with chronic pain have been discussed recently on the basis of ACC/mPFC GMV (34). One of the rare longitudinal studies examined patients who underwent hip surgery suffering chronic pain due to hip osteoarthritis. After the intervention the patients were pain free and the study authors suggested that VBM changes are a consequence but not the cause of pain (49). Research in chronic pain models in animals have provided insight into the underlying mechanisms of GMV decrease in the presence of chronic pain [e.g., (42)]. Neuropathic pain, using nerve compression models in rodents, revealed a loss of GMV after surgery in the primary somatosensory cortex (S1), ACC and insula that was associated with a decrease in somatosensory performance (43). Taken together, animal studies showed that (1) prefrontal GMV loss is causally related to surgical intervention resulting in chronic neuropathic pain in rodents, and (2) S1, ACC, and insula GMV loss is associated with somatosensory impairment induced by neuropathic pain as a result of a surgical intervention.

Methodological Considerations

When reviewing the literature on GMV alterations in CRPS it is very difficult to summarize common findings. One important reason might be the inhomogeneous patient cohorts investigated before. Geha et al. (23) included upper limb, lower limb and trunk localization of CRPS. Inhomogeneity in CRPS-affection and symptoms increase noise and more recent studies (27) focused on patients with right upper limb affection. In addition, the stage of CRPS is crucial since persistence of the pain syndrome has been associated with GMV loss [for non-neuropathic pain see for instance (11)]. Pleger et al. (24) predominantly included CRPS patients in the subacute stage and tested them against healthy controls. Their surprising finding of an increase in GMV in areas which show a clear GMV decrease in most other studies might well be related to that inclusion criteria. Furthermore, most samples were clearly underpowered when considering effect sizes resulting from larger samples of chronic pain patients [e.g., (11, 12)]. On the measurement side, a high resolution isotropic spatial resolution (at least 1 mm^3) should be standard nowadays. Resampling 4 mm slice thickness with 1 mm spacing between slices (gap) into a voxel-based morphometry is not even justifiable when considering technical deficits of past decades (25). It is also essential on the measurement side, that only data derived from the same MRI should be included in the group analysis or advanced harmonization approaches are used prior to analysis. In addition, the latest data processing tools for GMV-analysis provide state-of-the art approaches regarding preparation, artifact reduction, segmentation, advanced normalization procedures and quality assessment (e.g., CAT—A computational anatomy toolbox for the analysis of structural MRI data; C Gaser, R Dahnke; OHBM 2016, 4057) which is extremely important for accuracy of the VBM method. Last, but not least, a reliable statistical approach is essential: a severe problem in the field is the restriction of analysis on regions of interest, especially if these have not stood the proof of an exploratory whole brain corrected analysis before as performed by Azqueta-Gavaldon et al. (27). It has also to be mentioned that for the highly important longitudinal studies on chronic pain and GMV alterations the current software packages do not offer reliable and comparable solutions leaving some necessary methodological work on standardized procedures for trustworthily detecting longitudinal changes in GMV.

Limitations

Studies on diseases with fortunately rare occurrence always lack from low statistical power. However, this study currently is based on the largest and most homogeneous sample of CRPS patients and healthy controls. However, we did not equally balance control participants for gender but controlled for TIV as a nuisance variable in our statistical design. However, we did not lodge and lock our protocol and statistical analysis plan prior to commencing data collection. It was not commonplace to do so when we started this study, but now it is recommended (50). Failure to do this clearly represents a shortcoming in transparency and reporting. We here decided to follow a voxel-wise GMV estimation to detect local changes within the brain between groups which also enabled a whole-brain statistical analyses approach. We admit that ROI-based comparisons between groups for the whole thalamus might show different effects since they are not testing local changes within the structure. Although we carefully documented the current medication at the time point of MRI-investigation (see **Table 1**) patients had a long-lasting history of all kind of interventions and these might well have an impact on our findings. In addition, we did not score mood disorders over all patients and therefore cannot exclude that depression might have had

an impact on our findings. However, in a new ALE meta-analysis comprising 46 VBM studies on mood disorders the anterior insula predominantly showed a reduction in GMV (51). Therefore, GMV reduction of the bilateral thalamus induced by mood disorder, which is more frequent for patients with chronic pain syndromes than in healthy subjects, might be improbable.

CONCLUSION

In conclusion, we here present a VBM analysis on a considerable sample of CRPS patients in the chronic stage of the disease. In contrast to studies of non-neuropathic chronic pain, which primarily report a loss of GMV in ACC and the insula, our patients predominantly showed medial thalamic GMV loss. Additionally, regression analyses with pain intensity and duration identified a negative association with ACC GMV. Furthermore, somatosensory impairment was associated with GMV loss in the insula, until now a finding in rodent neuropathic pain models, here for the first time shown in a human sample of patients with chronic neuropathic pain.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the local ethics committee of the University Medicine Greifswald (BB 45/09, BB 055/18). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SS organized patient recruitment and corrected the manuscript. MD helped with data evaluation and corrected the manuscript. JM corrected the manuscript and added ideas in data evaluation. ML managed the study, evaluated data, wrote the manuscript, and corrected and submitted the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

ML and JM were supported by the Australian National Health and Medical Research Council (NHMRC) grant #1163149. SS was awarded a Gerhard-Domagk fellowship for undertaking this study; he also received a grant by the Else Kröner Fresenius-Stiftung 2019-A24. In addition, the investigations of GMV in chronic pain are subject to a funding of the DFG for ML (LO 795/37-1).

ACKNOWLEDGMENTS

We would like to thank S. Barby, J. Härtlein, and M. Kohler for data assessments and I. Langner and T. Usichenko for help with patient recruitment.

REFERENCES

1. van Hecke O, Torrance N, Smith BH. Chronic pain epidemiology and its clinical relevance. *Br J Anaesth.* (2013) 111:13–8. doi: 10.1093/bja/aet123
2. Phillips K, Clauw DJ. Central pain mechanisms in chronic pain states–maybe it is all in their head. *Best Pract Res Clin Rheumatol.* (2011) 25:141–54. doi: 10.1016/j.berh.2011.02.005
3. Cauda F, Palermo S, Costa T, Torta R, Duca S, Vercelli U, et al. Gray matter alterations in chronic pain: a network-oriented meta-analytic approach. *Neuroimage Clin.* (2014) 4:676–86. doi: 10.1016/j.nicl.2014.04.007
4. Lin C, Lee SH, Weng HH. Gray matter atrophy within the default mode network of fibromyalgia: a meta-analysis of voxel-based morphometry studies. *Biomed Res Int.* (2016) 2016:7296125. doi: 10.1155/2016/7296125
5. Baliki MN, Geha PY, Apkarian AV, Chialvo DR. Beyond feeling: chronic pain hurts the brain, disrupting the default-mode network dynamics. *J Neurosci.* (2008) 28:1398–403. doi: 10.1523/JNEUROSCI.4123-07.2008
6. Schmidt-Wilcke T, Leinisch E, Gänssbauer S, Draganski B, Bogdahn U, Altmeppen J, et al. Affective components and intensity of pain correlate with structural differences in gray matter in chronic back pain patients. *Pain.* (2006) 125:89–97. doi: 10.1016/j.pain.2006.05.004
7. Apkarian AV, Sosa Y, Sonty S, Levy RM, Harden RN, Parrish TB, et al. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. *J Neurosci.* (2004) 24:10410–5. doi: 10.1523/JNEUROSCI.2541-04.2004
8. Obermann M, Rodriguez-Raecke R, Naegel S, Holle D, Mueller D, Yoon MS, et al. Gray matter volume reduction reflects chronic pain in trigeminal neuralgia. *Neuroimage.* (2013) 74:352–8. doi: 10.1016/j.neuroimage.2013.02.029
9. Gustin SM, Peck CC, Wilcox SL, Nash PG, Murray GM, Henderson LA. Different pain, different brain: thalamic anatomy in neuropathic and non-neuropathic chronic pain syndromes. *J Neurosci.* (2011) 31:5956–64. doi: 10.1523/JNEUROSCI.5980-10.2011
10. Wang Y, Cao DY, Remeniuk B, Krimmel S, Seminowicz DA, Zhang M. Altered brain structure and function associated with sensory and affective components of classic trigeminal neuralgia. *Pain.* (2017) 158:1561–70. doi: 10.1097/j.pain.0000000000000951
11. Domin M, Grimm NK, Klepzig K, Schmidt CO, Kordass B, Lotze M. Gray matter brain alterations in temporomandibular disorder tested in a population cohort and three clinical samples. *J Pain.* (2021) 22:739–47. doi: 10.1016/j.jpain.2021.01.003
12. Fritz HC, McAuley JH, Wittfeld K, Hegenscheid K, Schmidt CO, Langner S, et al. Chronic back pain is associated with decreased prefrontal and anterior insular gray matter: results from a Population-Based Cohort Study. *J Pain.* (2016) 17:111–8. doi: 10.1016/j.jpain.2015.10.003
13. Dworkin SF, Sherman J, Mancl L, Ohrbach R, LeResche L, Truelove E. Reliability, validity, and clinical utility of the research diagnostic criteria for temporomandibular disorders axis II scales: Depression, non-specific physical symptoms, and graded chronic pain. *J Orofac Pain.* (2002) 16:207–20.
14. Beerthuizen A, Stronks DL, Van't Spijker A, Yaksh A, Hanraets BM, Klein J, et al. Demographic and medical parameters in the development of complex regional pain syndrome type 1 (CRPS1): prospective study on 596 patients with a fracture. *Pain.* (2012) 153:1187–92. doi: 10.1016/j.pain.2012.01.026
15. Birklein F, Handwerker HO. Complex regional pain syndrome: how to resolve the complexity? *Pain.* (2001) 94:1–6. doi: 10.1016/S0304-3959(01)00393-1
16. Veldman PH, Reynen HM, Arntz IE, Goris RJ. Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. *Lancet.* (1993) 342:1012–6. doi: 10.1016/0140-6736(93)92877-V
17. Pleger B, Ragert P, Schwenkreis P, Förster AF, Wilimzig C, Dinse H, et al. Patterns of cortical reorganization parallel impaired tactile discrimination

and pain intensity in complex regional pain syndrome. *Neuroimage.* (2006) 32:503–10. doi: 10.1016/j.neuroimage.2006.03.045
18. Maihöfner C, Handwerker HO, Birklein F. Functional imaging of allodynia in complex regional pain syndrome. *Neurology.* (2006) 66:711–7. doi: 10.1212/01.wnl.0000200961.49114.39
19. Galer BS, Jensen M, Butler S. Neglect-like signs and symptoms in CRPS. *Pain.* (2013) 154:961–2. doi: 10.1016/j.pain.2013.02.024
20. Reinersmann A, Skinner IW, Lücke T, Massy-Westropp N, Rudolf H, Moseley GL, et al. Intact tactile anisotropy despite altered hand perception in complex regional pain syndrome: rethinking the role of the primary sensory cortex in tactile and perceptual dysfunction. *PeerJ.* (2021) 9:e11156. doi: 10.7717/peerj.11156
21. Birklein F, Rowbotham MC. Does pain change the brain? *Neurology.* (2005) 65:666–7. doi: 10.1212/01.wnl.0000179148.80687.f3
22. Maihöfner C, Baron R, DeCol R, Binder A, Birklein F, Deuschl G, et al. The motor system shows adaptive changes in complex regional pain syndrome. *Brain.* (2007) 130(Pt 10):2671–87. doi: 10.1093/brain/awm131
23. Geha PY, Baliki MN, Harden RN, Bauer WR, Parrish TB, Apkarian AV. The brain in chronic CRPS pain: abnormal gray-white matter interactions in emotional and autonomic regions. *Neuron.* (2008) 60:570–81. doi: 10.1016/j.neuron.2008.08.022
24. Pleger B, Draganski B, Schwenkreis P, Lenz M, Nicolas V, Maier C, et al. Complex regional pain syndrome type I affects brain structure in prefrontal and motor cortex. *PLoS One.* (2014) 9:e85372. doi: 10.1371/journal.pone.0085372
25. Barad MJ, Ueno T, Younger J, Chatterjee N, Mackey S. Complex regional pain syndrome is associated with structural abnormalities in pain-related regions of the human brain. *J Pain.* (2014) 15:197–203. doi: 10.1016/j.jpain.2013.10.011
26. van Velzen GA, Rombout SA, van Buchem MA, Marinus J, van Hilten JJ. Is the brain of complex regional pain syndrome patients truly different? *Eur J Pain.* (2016) 20:1622–33. doi: 10.1002/ejp.882
27. Azqueta-Gavaldon M, Youssef AM, Storz C, Lemme J, Schulte-Göcking H, Becerra L, et al. Implications of the putamen in pain and motor deficits in complex regional pain syndrome. *Pain.* (2020) 161:595–608. doi: 10.1097/j.pain.0000000000001745
28. Poldrack RA, Baker CI, Durnez J, Gorgolewski KJ, Matthews PM, Munafò MR, et al. Scanning the horizon: towards transparent and reproducible neuroimaging research. *Nat Rev Neurosci.* (2017) 18:115–26. doi: 10.1038/nrn.2016.167
29. Harden RN, Maihofner C, Abousaad E, Vatine JJ, Kirsling A, Perez RSGM, et al. A prospective, multisite, international validation of the complex regional pain syndrome severity score. *Pain.* (2017) 158:1430–6. doi: 10.1097/j.pain.0000000000000927
30. Beck AT, Steer RA, Brown GK. *Manual for the Beck Depression Inventory-II.* San Antonio, TX: Psychol Corporation (1996).
31. Harden RN, Bruehl S, Stanton-Hicks M, Wilson PR. Proposed new diagnostic criteria for complex regional pain syndrome. *Pain Med.* (2007) 8:326–31. doi: 10.1111/j.1526-4637.2006.00169.x
32. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia.* (1971) 9:97–113. doi: 10.1016/0028-3932(71)90067-4
33. Harden NR, Bruehl S, Perez RSGM, Birklein F, Marinus J, Maihofner C, et al. Development of a severity score for CRPS. *Pain.* (2010) 151:870–6. doi: 10.1016/j.pain.2010.09.031
34. Kang D, McAuley JH, Kassem MS, Gatt JM, Gustin SM. What does the grey matter decrease in the medial prefrontal cortex reflect in people with chronic pain? *Eur J Pain.* (2019) 23:203–19. doi: 10.1002/ejp.1304
35. Härtner J, Strauss S, Pfannmöller J, Lotze M. Tactile acuity of fingertips and hand representation size in human Area 3b and Area 1 of the primary somatosensory cortex. *Neuroimage.* (2021) 232:117912. doi: 10.1016/j.neuroimage.2021.117912
36. Strauss S, Grothe M, Usichenko T, Neumann N, Byblow WD, Lotze M. Inhibition of the primary sensorimotor cortex by topical anesthesia of the forearm in patients with complex regional pain syndrome. *Pain.* (2015) 156:2556–61. doi: 10.1097/j.pain.0000000000000324
37. Henderson LA, Peck CC, Petersen ET, Rae CD, Youssef AM, Reeves JM, et al. Chronic pain: lost inhibition? *J Neurosci.* (2013) 33:7574–82. doi: 10.1523/JNEUROSCI.0174-13.2013
38. Di Pietro F, Lee B, Henderson LA. Altered resting activity patterns and connectivity in individuals with complex regional pain syndrome. *Hum Brain Mapp.* (2020) 41:3781–93. doi: 10.1002/hbm.25087
39. Liu J, Gu L, Huang Q, Hong S, Zeng X, Zhang D, et al. Altered gray matter volume in patients with herpes zoster and postherpetic neuralgia. *J Pain Res.* (2019) 12:605–16. doi: 10.2147/JPR.S183561
40. Lee YC, Jahng GH, Ryu CW, Byun JY. Change in gray matter volume and cerebral blood flow in patients with burning mouth syndrome. *J Oral Pathol Med.* (2019) 48:335–42. doi: 10.1111/jop.12838
41. Kummer KK, Mitrić M, Kalpachidou T, Kress M. The medial prefrontal cortex as a central hub for mental comorbidities associated with chronic pain. *Int J Mol Sci.* (2020) 21:3440. doi: 10.3390/ijms21103440
42. Magariños AM, McEwen BS, Flügge G, Fuchs E. Chronic psychosocial stress causes apical dendritic atrophy of hippocampal CA3 pyramidal neurons in subordinate tree shrews. *J Neurosci.* (1996) 16:3534–40. doi: 10.1523/JNEUROSCI.16-10-03534.1996
43. Seminowicz DA, Laferriere AL, Millecamps M, Yu JS, Coderre TJ, Bushnell MC. MRI structural brain changes associated with sensory and emotional function in a rat model of long-term neuropathic pain. *Neuroimage.* (2009) 47:1007–14. doi: 10.1016/j.neuroimage.2009.05.068
44. McIlwrath SL, Montera MA, Gott KM, Yang Y, Wilson CM, Selwyn R, et al. Manganese-enhanced MRI reveals changes within brain anxiety and aversion circuitry in rats with chronic neuropathic pain- and anxiety-like behaviors. *Neuroimage.* (2020) 223:117343. doi: 10.1016/j.neuroimage.2020.117343
45. Luerding R, Weigand T, Bogdahn U, Schmidt-Wilcke T. Working memory performance is correlated with local brain morphology in the medial frontal and anterior cingulate cortex in fibromyalgia patients: structural correlates of pain-cognition interaction. *Brain.* (2008) 131(Pt 12):3222–31. doi: 10.1093/brain/awn229
46. Dupont S, Bouilleret V, Hasboun D, Semah F, Baulac M. Functional anatomy of the insula: new insights from imaging. *Surg Radiol Anat.* (2003) 25:113–9. doi: 10.1007/s00276-003-0103-4
47. Dammann J, Klepzig K, Schenkenberger E, Kordass B, Lotze M. Association of decrease in insula fMRI activation with changes in trait anxiety in patients with craniomandibular disorder (CMD). *Behav Brain Res.* (2020) 379:112327. doi: 10.1016/j.bbr.2019.112327
48. Lickteig R, Lotze M, Kordass B. Successful therapy for temporomandibular pain alters anterior insula and cerebellar representations of occlusion. *Cephalgia.* (2013) 33:1248–57. doi: 10.1177/0333102413491028
49. Rodriguez-Raecke R, Niemeier A, Ihle K, Ruether W, May A. Brain gray matter decrease in chronic pain is the consequence and not the cause of pain. *J Neurosci.* (2009) 29:13746–50. doi: 10.1523/JNEUROSCI.3687-09.2009
50. Lee H, Lamb SE, Bagg MK, Toomey E, Cashin AG, Moseley GL. Reproducible and replicable pain research: a critical review. *Pain.* (2018) 159:1683–9. doi: 10.1097/j.pain.0000000000001254
51. Jabbi M, Arasappan D, Eickhoff SB, Strakowski SM, Nemeroff CB, Hofmann HA. Neuro-transcriptomic signatures for mood disorder morbidity and suicide mortality. *J Psychiatr Res.* (2020) 127:62–74. doi: 10.1016/j.jpsychires.2020.05.013

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2021 Domin, Strauss, McAuley and Lotze. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Neurology

ORIGINAL RESEARCH
published: 04 October 2021
doi: 10.3389/fneur.2021.716500

Pre-operative Limbic System Functional Connectivity Distinguishes Responders From Non-responders to Surgical Treatment for Trigeminal Neuralgia

Hayden Danyluk[1,2], *Stefan Lang*[3,4], *Oury Monchi*[3,4] *and Tejas Sankar*[2]*

[1] Division of Surgical Research, University of Alberta, Edmonton, AB, Canada, [2] Division of Neurosurgery, Department of Surgery, University of Alberta, Edmonton, AB, Canada, [3] Department of Clinical Neurosciences, University of Calgary, Calgary, AB, Canada, [4] Health Research Innovation Centre, Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada

OPEN ACCESS

Edited by:
Flavia Di Pietro,
Curtin University, Australia

Reviewed by:
Prasad Shirvalkar,
University of California, San Francisco,
United States
Ajmal Zemmar,
University of Toronto, Canada

***Correspondence:**
Tejas Sankar
tsankar@ualberta.ca

Specialty section:
This article was submitted to
Applied Neuroimaging,
a section of the journal
Frontiers in Neurology

Received: 28 May 2021
Accepted: 31 August 2021
Published: 04 October 2021

Citation:
Danyluk H, Lang S, Monchi O and Sankar T (2021) Pre-operative Limbic System Functional Connectivity Distinguishes Responders From Non-responders to Surgical Treatment for Trigeminal Neuralgia.
Front. Neurol. 12:716500.
doi: 10.3389/fneur.2021.716500

Background: Trigeminal neuralgia (TN) is a severe facial pain condition often requiring surgical treatment. Unfortunately, even technically successful surgery fails to achieve durable pain relief in many patients. The purpose of this study was to use resting-state functional magnetic resonance imaging (fMRI) to: (1) compare functional connectivity between limbic and accessory sensory networks in TN patients vs. healthy controls; and (2) determine if pre-operative variability in these networks can distinguish responders and non-responders to surgery for TN.

Methods: We prospectively recruited 22 medically refractory classic or idiopathic TN patients undergoing surgical treatment over a 3-year period, and 19 age- and sex-matched healthy control subjects. fMRI was acquired within the month prior to surgery for all TN patients and at any time during the study period for controls. Functional connectivity analysis was restricted to six pain-relevant brain regions selected *a priori*: anterior cingulate cortex (ACC), posterior cingulate cortex, hippocampus, amygdala, thalamus, and insula. Two comparisons were performed: (1) TN vs. controls; and (2) responders vs. non-responders to surgical treatment for TN. Functional connectivity was assessed with a two-sample *t*-test, using a statistical significance threshold of $p < 0.050$ with false discovery rate (FDR) correction for multiple comparisons.

Results: Pre-operative functional connectivity was increased in TN patients compared to controls between the right insular cortex and both the left thalamus [$t_{(39)} = 3.67$, $p = 0.0007$] and right thalamus [$t_{(39)} = 3.22$, $p = 0.0026$]. TN patients who were non-responders to surgery displayed increased functional connectivity between limbic structures, including between the left and right hippocampus [$t_{(18)} = 2.85$, $p = 0.0106$], and decreased functional connectivity between the ACC and both the left amygdala [$t_{(18)} = 2.94$, $p = 0.0087$] and right hippocampus [$t_{(18)} = 3.20$, $p = 0.0049$]. Across all TN patients, duration of illness was negatively correlated with connectivity between the ACC

and left amygdala ($r^2 = 0.34$, $p = 0.00437$) as well as the ACC and right hippocampus ($r^2 = 0.21$, $p = 0.0318$).

Conclusions: TN patients show significant functional connectivity abnormalities in sensory-salience regions. However, variations in the strength of functional connectivity in limbic networks may explain why some TN patients fail to respond adequately to surgery.

Keywords: trigeminal neuralgia (TN), fMRI, limbic system, surgical response, treatment resistance

INTRODUCTION

Trigeminal neuralgia (TN) is a chronic, neuropathic facial pain disorder characterized by intermittent, typically unilateral, electric shock-like or stabbing pain attacks in the distribution of one or more branches of the trigeminal nerve (cranial nerve V—CNV) (1). TN is severely disabling, often fails to respond over the long-term to medications against neuropathic pain, and historically has been associated with a high suicide rate (2). A variety of surgical treatment options are available for medically refractory TN patients—including microvascular decompression (MVD), percutaneous rhizotomy, and stereotactic radiosurgery—but technically successful surgical treatment does not result in durable pain relief in many cases (2, 3). Even following MVD—clearly the most efficacious surgical treatment for TN—pain recurrence occurs in > 25% of patients within 2 years of surgery, followed by a 4% per year recurrence rate thereafter (4). Thus, there is a need to better understand the mechanisms underlying durable response to surgery in patients with TN.

Many cases of TN are associated with vascular compression affecting the root entry zone (REZ) of CNV (so-called *classical TN*) (1), and as a result a primary focus in TN research has been the structure of CNV studied using magnetic resonance imaging (MRI), in particular diffusion tensor imaging (DTI) (5, 6). However, a nerve-centric conceptualization of TN inadequately explains many key features of the disease, notably the development of medication-refractoriness and variability in response to treatment (4). Several structural and functional brain abnormalities have been identified in TN patients, particularly within the limbic system and closely connected paralimbic or sensory-salience structures [e.g., anterior cingulate cortex (ACC), insula, thalamus, and hippocampus (7–13)]. Brain abnormalities in TN show overlap with those observed in other chronic pain and headache conditions: in particular, altered resting-state functional connectivity and atrophy of limbic system structures are recurrent observations (7, 8, 10, 14–17), as are alterations in functional connectivity of the right insula, exemplified in migraine (18) and temporomandibular joint pain (19). How structural and functional brain alterations relate specifically to treatment-resistance in TN, however, has been relatively understudied. We recently showed that structural variability in the limbic system—specifically in hippocampal volume—may predict durability of pain relief following surgical treatment in TN (9). However, to date, functional MRI (fMRI) studies explicitly comparing functional connectivity between responders and non-responders to surgery are lacking.

Our central hypothesis was that pre-operative functional connectivity differences exist between responders and non-responders to surgical treatment for TN. Our primary objective was to perform a focused functional connectivity analysis in TN patients and healthy control (HC) subjects, first identifying key networks which are altered in TN. We then evaluated how functional connectivity within these networks related to surgical outcome. Our analysis was restricted to six regions of interest (ROI) determined *a priori* (ACC, posterior cingulate cortex (PCC), hippocampus, amygdala, thalamus, and insula) that are part of previously characterized acute (sensory-salience related) or chronic (emotion-related) pain activity patterns (20, 21). In addition to examining pre-operative functional connectivity differences between eventual responders and non-responders, we further examined how functional connectivity within our selected ROIs correlated with time since initial TN diagnosis, given that surgical non-response has been linked to longer duration of TN (22).

METHODS

Study Participants

This was a single-center, prospective, longitudinal study of patients undergoing surgical treatment for TN between 2017 and 2020. This study was approved and performed in accordance with the rules and regulations by the Health Research Ethics Board—Health Panel of the University of Alberta. Potential study patients were identified in the neurosurgery clinic, then recruited by telephone. All participants provided written informed consent. *Inclusion criteria:* medically refractory classic or idiopathic TN defined using International Classification of Headache Disorders-III (ICHD-III) criteria (1); scheduled for surgical treatment by MVD or percutaneous balloon compression rhizotomy (BC). *Exclusion criteria:* history of multiple sclerosis or other lesional causes of TN; diagnosed psychiatric illness; history of any prior non-TN neurosurgical procedures. Additionally, we recruited 19 HC subjects matched to the TN group in mean age and sex distribution, and without chronic pain or psychiatric conditions.

Abbreviations: TN, trigeminal neuralgia; CNV, cranial nerve V; MVD, microvascular decompression; MRI, magnetic resonance imaging; ACC, anterior cingulate cortex; fMRI, functional magnetic resonance imaging; PCC, posterior cingulate cortex; ICHD-III, International Classification of Headache Disorders-III; BC, percutaneous balloon compression rhizotomy; HC, healthy control; VAS, visual analog scale; ROI, region of interest; ROC, receiver operator characteristic.

Data Acquisition

TN patients underwent MRI scanning within a one-month period prior to surgery, while HC subjects underwent a single MRI scanning session at any time during the study period. Scanning was carried out on a 3T Siemens Prisma Magnetom MRI scanner (Erlangen, Germany) with 64-channel head radiofrequency coil. Study participants underwent: *3D T1-weighted structural scan* [magnetization-prepared rapid acquisition gradient echo (MPRAGE)], field-of-view (FOV) = 250 × 250 mm^2, 208 slices, 0.85 mm isotropic, repetition time (TR) = 1800 ms, echo time (TE) = 2.37 ms, inversion time (TI) = 900 ms, 8° flip angle, 3:41 min) and *resting-state T2* functional MRI scan* (multiband gradient-echo echo-planar imaging sequence, FOV = 224 × 224 mm^2, 60 slices, 2.2 mm isotropic, TR = 1,830 ms, TE= 30 ms, matrix = 102 × 102, 80° flip angle, volumes = 252, multiband acceleration factor = 2, parallel imaging factor = GRAPPA factor 2, phase encoding direction = anterior-posterior, Bandwidth = 2450 Hz/pixel, 8:02 min). During resting-state fMRI acquisition, participants were instructed to keep their eyes closed but not to fall asleep or focus on anything in particular. Additionally, prior to MRI scanning TN patients completed a pain questionnaire to report the severity of pain attacks over the past week using a 0-100 mm Visual Analog Scale (VAS), and to accurately describe the frequency and location of attacks. TN patients were followed for at least 12-months after surgery (see below for details).

Clinical Characteristics and Outcome Assessment

The following demographic/clinical data were collected: sex; age; duration of TN since diagnosis; side-of-pain; pre-operative pain severity (measured using VAS); first (virgin) or repeat surgical treatment for TN; surgery type (MVD or BC); and medications (carbamazepine/oxcarbazepine (yes/no), gabapentin/pregabalin (yes/no), other antiepileptic (yes/no), antidepressant/anxiolytic (yes/no), baclofen (yes/no), opioid (yes/no), and cannabis oil (yes/no). Study participants were classified as responders or non-responders as follows: *responders*—(1) documented evidence of immediate and persistent pain relief for at least 1 year after surgery, as defined by a Barrow Neurological Institute (BNI) facial pain score (23) of 1, 2, or 3a; (2) no offer of or repeat surgical TN treatment within the 1 year following surgery; *non-responders*—(1) inadequate initial pain relief from surgery or early pain recurrence within 1 year of surgery, as defined by a BNI facial pain score of 3b, 4, or 5; or (2) offered or underwent repeat surgical treatment within 1 year of surgery. TN patients were followed-up longitudinally by in-person visits with study personnel at 7- and 30-days following surgery, and by phone follow-up at 6- and 12-months after surgery. BNI facial pain score was determined at each visit; any patient who had changed from an earlier post-operative BNI score of 1, 2, or 3a to 3b, 4, or 5, was immediately reclassified as a non-responder. Additionally, patients at a minimum underwent follow-up with their treating surgeon at 4-6 weeks post-operatively, and additional follow-up visits with treating surgeons thereafter were made on an *ad hoc* basis (usually because patients had developed recurrent pain).

fMRI Analysis

Pre-processing

All subjects underwent standard pre-processing in *SPM12*, including realignment, slice-time correction, and segmentation into gray matter, white matter, and cerebrospinal fluid (CSF) components using SPM's Unified Segmentation (24). Images were directly (non-linearly) normalized to MNI space using an EPI template (25). De-noising was performed using *Conn* v18.a software (https://web.conn-toolbox.org) (26), which included regression of six movement parameters and their first temporal derivatives and implementation of CompCor by performing PCA on eroded white matter and CSF masks with regression of the first 5 components (27). Volumes with large (>0.9 mm) frame-wise displacement or global signal change [>5 standard deviations (SD)] were also included as covariates of no interest. Linear de-trending was performed to remove signal drift, while high frequency noise was excluded by subjecting the residual signal to a high pass filter (>0.008 Hz).

Functional Connectivity

Ten ROIs made up of limbic system and paralimbic structures were selected *a priori* from previously characterized acute- and chronic-pain activity patterns to be used as nodes for a focused functional connectivity analysis (21): bilateral insular cortex, bilateral amygdala, bilateral hippocampus, bilateral thalamus, anterior cingulate cortex, and posterior cingulate cortex (**Figure 1**). Each ROI was generated from the Harvard-Oxford Atlas (28). The residual BOLD time-course was averaged within each ROI, and functional connectivity between each node of the limbic system was calculated as the Fisher transformed Pearson correlation coefficient. Differences in the pairwise connectivity of each limbic node between HC and TN patients was assessed with a two-sample *t*-test, using a threshold for statistical significance of $p < 0.050$ with a false discovery rate (FDR) correction for 10 seeds (9 comparisons). This was repeated for each individual node. Similarly, functional connectivity between the same 10 ROIs was used to compare responders ($n = 16$) and non-responders ($n = 6$) to surgical treatment for TN. In this latter analysis, we adjusted for the influence of the side of TN pain and immediate pre-scan VAS pain severity by including these as covariates in an ANCOVA model. Pre-scan VAS score was included to mitigate the influence of acute pain state on connectivity differences. ROI pairs demonstrating connectivity differences between surgical outcome groups were subsequently correlated with duration of pain using Pearson correlation.

Statistical Analysis

Clinical characteristics and demographic variables were compared between responders and non-responders to surgical treatment using the Mann-Whitney U test, as well as Chi-square or Fisher's exact test where appropriate. Statistical analyses were carried out with GraphPad Prism version 8 for Mac OS X (GraphPad Software, La Jolla California, USA). Statistical significance was set at $p < 0.050$ (2-tailed).

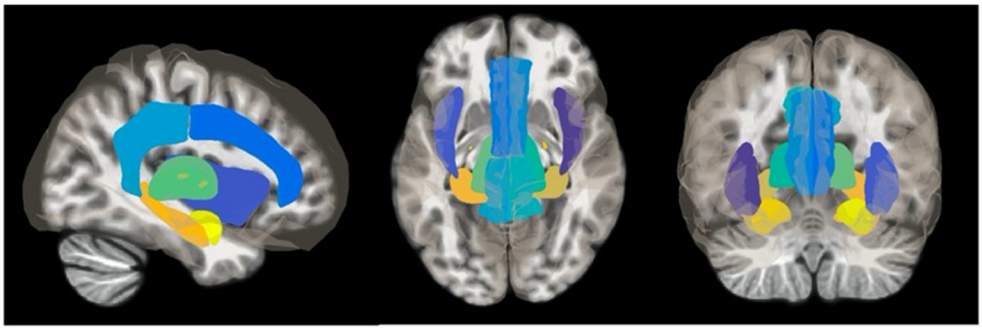


FIGURE 1 | Regions of interest (ROIs) used as seed points in fMRI analyses. Resting-state fMRI analysis was restricted to 10 ROIs composed of bilateral limbic and accessory sensory structures determined *a priori*: insula, thalamus, amygdala, hippocampus, anterior cingulate cortex, and posterior cingulate cortex. ROIs were generated from the Harvard-Oxford Atlas (28).

TABLE 1 | Comparison of demographic and clinical characteristics between TN patients (including responders and non-responders) and healthy controls.

	Responders	Non-Responders	*P*-value (2-tailed)	TN	HC	*P*-value (2-tailed)
Group	16	6	–	22	19	–
Sex (Female/Male)	7/9	5/1	0.16	12/10	10/9	0.90
Age (years)	60.4 ± 9.7	53.0 ± 12.9	0.12	56.5 ± 10.9	55.4 ± 9.3	0.72
Duration of TN (years)	4.6 ± 3.3	10.5 ± 5.9	0.021*	6.2 ± 4.8	N/A	–
Side of pain (right/left)	10/6	4/2	>0.99	14/8	N/A	–
Pre-op VAS (mm)	79.9 ± 24.1	72.3 ± 37.2	0.84	72.8 ± 27.5	N/A	–
Virgin (yes/no)	14/2	3/3	0.10	17/5	N/A	–
Surgery type (MVD/BC)	12/4	3/3	0.33	15/7	N/A	–
Carbamazepine/oxcarbazepine (yes/no)	15/1	6/0	>0.99	21/1	N/A	–
Gabapentin/pregabalin (yes/no)	6/10	5/1	0.15	11/11	N/A	–
Other antiepileptics (yes/no)	2/14	1/5	>0.99	3/19	N/A	–
Antidepressant/anxiolytic (yes/no)	2/14	1/5	>0.99	3/19	N/A	–
Baclofen (yes/no)	2/14	4/2	0.025*	6/16	N/A	–
Opioid (yes/no)	0/16	1/5	0.27	1/21	N/A	–
Cannabis oil (yes/no)	1/15	1/5	0.48	2/20	N/A	–

Mann-Whitney, Chi-square, or Fishers-exact tests used where appropriate. Means ± standard deviations are presented. Virgin (yes/no): first-time surgical treatment for TN; ***MVD****: microvascular decompression surgery;* ***BC****: percutaneous balloon compression rhizotomy; other antiepileptics: lamotrigine, topiramate; antidepressant/anxiolytic: amitriptyline, duloxetine. Threshold for statistical significance set at *p < 0.05.*

RESULTS

Study Participants

Twenty-two TN patients and 19 HCs were included in this study between 2017 and 2020 (**Table 1**).

Clinical Characteristics and Demographics

TN vs. HC Comparison

TN patients and HCs were well-matched in age (mean 56.5 ± 10.9 years and 55.4 ± 9.3 years respectively, $p = 0.72$) and sex distribution (12F/10M and 10F/9M, $p = 0.90$). Average duration of TN from diagnosis to surgery was 6.2 ± 4.8 years, with right-sided TN being more common than left-sided TN (14R/8L). Pre-operative VAS was 72.8 ± 27.5. Across TN patients, 15 underwent MVD and 7 underwent BC, with 17/22 undergoing virgin surgical treatments (14MVD, 3BC). All TN patients were on antiepileptic medication at the time of surgery, including carbamazepine/oxcarbazepine ($n = 21$) and/or gabapentin/pregabalin ($n = 11$). Three TN patients were also on antidepressant/anxiolytic medication, six were on baclofen, one was taking opioids, and two others were taking cannabis oil. Clinical characteristics and demographic features of all study participants are presented in **Table 1**.

Responders vs. Non-responders

In total, there were 16 responders to surgery and 6 non-responders. Most non-responders were female (5F/1M), while responders display a balanced sex distribution (7F/9M), though the difference was not statistically significant ($p = 0.16$). There was no difference in average age of responders and non-responders (60.4 ± 12.7 vs. 53.0 ± 12.9 years, $p = 0.12$). Non-responders had a longer duration of TN prior to surgical treatment than responders (10.5 ± 5.9 vs. 4.6 ± 3.3 years respectively, $p = 0.021$). Distribution of surgery type did not

TABLE 2 | Clinical characteristics of TN patients.

Patient ID	Sex	Age (years)	Side	Duration of TN (years)	Pre-op VAS (mm)	Branch(es)	SX type	# prev. SX	BNI	Medications
Responders										
1	M	57.5	R	6	66	3	MVD	0	1	Carbamazepine
2	M	49.0	R	1	100	1/2/3	BC	3	3a	Oxcarbazepine, baclofen
3	M	45.1	L	9	98	1	MVD	0	1	Carbamazepine, pregabalin
4	F	58.5	R	11	100	2/3	MVD	0	1	Carbamazepine
5	M	63.9	R	8	82	1/2/3	MVD	0	1	Carbamazepine
6	M	67.5	R	6	71	2/3	BC	0	3a	Carbamazepine
7	F	74.1	L	3	81	2	MVD	0	1	Oxcarbazepine, pregabalin
8	F	60.3	L	6	36	2/3	MVD	1	3a	Gabapentin, amitriptyline
9	F	64.9	L	7	100	2/3	MVD	0	1	Carbamazepine, gabapentin
10	F	60.4	L	7	86	2/3	MVD	0	3a	Carbamazepine, oxcarbazepine
11	F	60.4	R	1	80	2/3	BC	0	3a	Carbamazepine
12	M	41.8	R	2	89	1/2	MVD	0	1	Carbamazepine, gabapentin, topiramate
13	F	68.5	L	1	100	3	MVD	0	1	Carbamazepine
14	M	61.5	R	2.5	79	3	MVD	0	3a	Carbamazepine
15	M	63.3	R	2.5	95	2/3	MVD	0	1	Oxcarbazepine, lamotrigine, gabapentin
16	M	40.6	R	1	15	2/3	BC	0	2	Carbamazepine, baclofen, duloxetine, cannabis oil
Non-responders										
17	F	37.3	L	6	63	2/3	MVD	0	4	Oxcarbazepine, baclofen
18	F	48.9	L	8	2	1/2/3	MVD	0	5	Carbamazepine, gabapentin, baclofen
19	M	69.5	R	19	100	3	BC	1	4	Oxcarbazepine, gabapentin
20	F	57.1	R	14	80	1/2/3	BC	2	5	Carbamazepine, gabapentin, lamotrigine, baclofen, hydromorphone
21	F	57.5	R	13	100	1/2/3	BC	2	5	Carbamazepine, gabapentin
22	F	36.3	R	3	89	2/3	MVD	0	4	Carbamazepine, gabapentin, baclofen, amitriptyline, cannabis oil

***M**, male; **F**, female; **Side**, side of facial pain (**R**, right; **L**, left); **Branch(es)**: affected trigeminal nerve branches (i.e., V1, V2, V3, or combination); **SX**, surgical treatment; **MVD**, microvascular decompression; **BC**, percutaneous balloon compression rhizotomy; **# of prev. SX**, number of previous surgical treatments for TN; **BNI**, Barrow Neurological Institute facial pain intensity score.*

TABLE 3 | Functional connectivity differences between TN patients and healthy controls, and responders and non-responders to surgical treatment for TN.

Connectivity difference	Seed region	Connection	*T*-value	*P*-value (raw)	*P*-value (FDR adjusted)
TN vs. Healthy controls					
Increased connectivity	Thalamus (left)	Insular cortex (right)	$t_{(39)} = 3.67$	$p = 0.0007^*$	0.0065^*
Increased connectivity	Thalamus (right)	Insular cortex (right)	$t_{(39)} = 3.22$	$p = 0.0026^*$	0.0117^*
Non-responders vs. Responders					
Increased connectivity	Hippocampus (left)	Hippocampus (right)	$t_{(18)} = 2.85$	$p = 0.0106^*$	0.0477^*
Decreased connectivity	ACC	Amygdala (left)	$t_{(18)} = -2.94$	$p = 0.0087^*$	0.0392^*
Decreased connectivity	ACC	Hippocampus (right)	$t_{(18)} = -3.20$	$p = 0.0049^*$	0.0392^*

TN patients vs. healthy controls: patients with TN show increased resting-state functional connectivity between the thalamus (both left and right) and right insula. Responders vs. Non-responders: non-responders show increased resting-state functional connectivity between the left and right hippocampus. Non-responders also show decreased resting-state functional connectivity between the anterior cingulate cortex and left amygdala and right hippocampus. Two-sample Student's t-test used with false-discovery rate (FDR) correction. Threshold for statistical significance was set at $^*p < 0.05$. ACC, anterior cingulate cortex.

differ between outcome groups. The proportion of patients taking baclofen was higher in non-responders than responders ($p = 0.025$), while there were no other differences in medication use. Individual clinical profiles of TN patients are presented in **Table 2**, and post-operative variations in BNI facial pain score are indicated in **Supplementary Figures 1**, **2**.

Resting-State Connectivity Analyses

HC vs. TN

Resting-state functional connectivity was increased in TN patients between the right insular cortex and left thalamus [$t_{(39)} = 3.67$, $p = 0.0007$], as well as the right insular cortex and the right thalamus [$t_{(39)} = 3.22$, $p = 0.0026$]. *HC vs TN* connectivity results are presented in **Table 3** and **Figure 2**.

Responders vs. Non-responders

Non-responders to surgical treatment for TN showed increased resting-state functional connectivity between the left and right hippocampus [$t_{(18)} = 2.85$, $p = 0.0106$] compared to responders. Non-responders also showed decreased resting-state functional connectivity between the ACC and left amygdala [$t_{(18)} = -2.94$, $p = 0.0087$], as well as the ACC and right hippocampus [$t_{(18)} = -3.20$, $p = 0.0049$]. *Responder vs. non-responder* connectivity results are presented in **Table 3** and **Figure 2** (raw data in **Supplementary Table 1**).

Duration of Illness and Functional Connectivity

Based on the result that non-responders had characteristic differences in functional connectivity between three pairs of structures (i.e., ACC-left amygdala, ACC-right hippocampus, left hippocampus-right hippocampus), we examined whether the strength of functional connectivity for each of these pairs was related to duration of TN illness from the time of diagnosis. Indeed, across all TN patients, duration of illness was negatively correlated with connectivity between the ACC and the left amygdala ($r^2 = 0.34$, $p = 0.00437$). Similarly, duration of illness was also negatively correlated with connectivity between the ACC and the right hippocampus ($r^2 = 0.21$, $p = 0.0318$; **Figure 3**). However, there was no correlation between duration of illness and connectivity between the left and right hippocampus.

DISCUSSION

In this single-center prospective study, we used resting-state fMRI to analyse pre-operative functional connectivity—with a focus on sensory-salience and limbic networks—in patients with medically refractory TN. To our knowledge, this is the first direct comparison of functional connectivity prior to surgery between responders and non-responders to surgical treatment for TN. We observed increased functional connectivity between the bilateral thalamus and right insular cortex in TN patients compared to age- and sex-matched HC subjects, indicating that functional abnormalities in sensory-salience regions are present in TN. We also observed pre-operative functional connectivity differences between surgical responders and non-responders, though these differences were found within a network confined to the limbic system and included the ACC, amygdala, and hippocampus. Additionally, the magnitude of functional connectivity differences within this network of limbic structures was strongly correlated with duration of illness across all TN patients. Taken together, our results suggest that while functional abnormalities in sensory-salience structures characterize patients with TN, it may principally be variations in limbic network function that contribute to poor response to surgical treatment in TN.

Our patients were suitably representative of medically refractory TN sufferers who are offered surgery, and overall demonstrated a 73% surgical response rate at 1 year, in agreement with our previous work and the existing literature, notwithstanding differences in the categorization of surgical outcome across studies (4, 9). In line with previous reports, non-responders showed a female preponderance and on average suffered from TN for more than twice as long as responders at the time of surgery (22). All TN patients were taking antiepileptic medication, and medication use was largely the same between responders and non-responders at a medication-class level. However, it is worthwhile to note that 50% of responders were exclusively taking first-line medications (e.g., carbamazepine or oxcarbazepine), while all non-responders had progressed to second-line medication classes at the time of surgery, perhaps reflecting greater medical-refractoriness (3).

Compared to HC subjects, TN patients showed increased functional connectivity between the bilateral thalamus and right insula. These findings are in line with recent reports of thalamic hyperactivity compared to HCs both in TN (8) and in other pain conditions affecting the trigeminal system, such as migraine (29). The present study did not identify abnormal amygdala functional connectivity in TN patients. This contrasts with the findings of Zhang et al. (10), though it is possible that the discrepancy may be explained by different fMRI seed strategies used by their study compared to ours. We have previously reported that thalamus volume is enlarged in TN contralateral to the side-of-pain, which may reflect a structural consequence of sustained hyperactivity (9, 30). The present findings add support to the notion that abnormalities in sensory-relay architecture are indeed a robust feature in patients with TN, though it must be pointed out that thinking of the thalamus exclusively as a sensory-relay structure would be an oversimplification. While the insula certainly participates in sensory-relay, it also has a key role in higher-order functions such as salience and the redirection of attention/focus (16). The right insula in particular has been shown to have increased functional activity in TN (12) and acute pain states (16, 31), as well as reduced volume in patients with chronic pain conditions (7, 10, 15). Given the complementary functions of the thalamus and insula in sensory-relay and salience, respectively, and because these two structures have direct structural connections (32), we speculate that our findings suggest increased sensory load coming from, and therefore increased focus on, the painful region of the face in TN. It is impossible to know from our data whether abnormalities in the thalamus and insula are the cause or an effect of medically refractory TN. However, the previously reported findings that right insular structure normalizes following successful surgical treatment for TN supports the latter interpretation (7).

As mentioned above, this is first the study to our knowledge to compare pre-operative resting-state functional connectivity between responders and non-responders to surgical treatment for TN. Non-responders showed increased functional connectivity between the left and right hippocampus. Our observation that hippocampus activity is altered in non-responders overlaps with

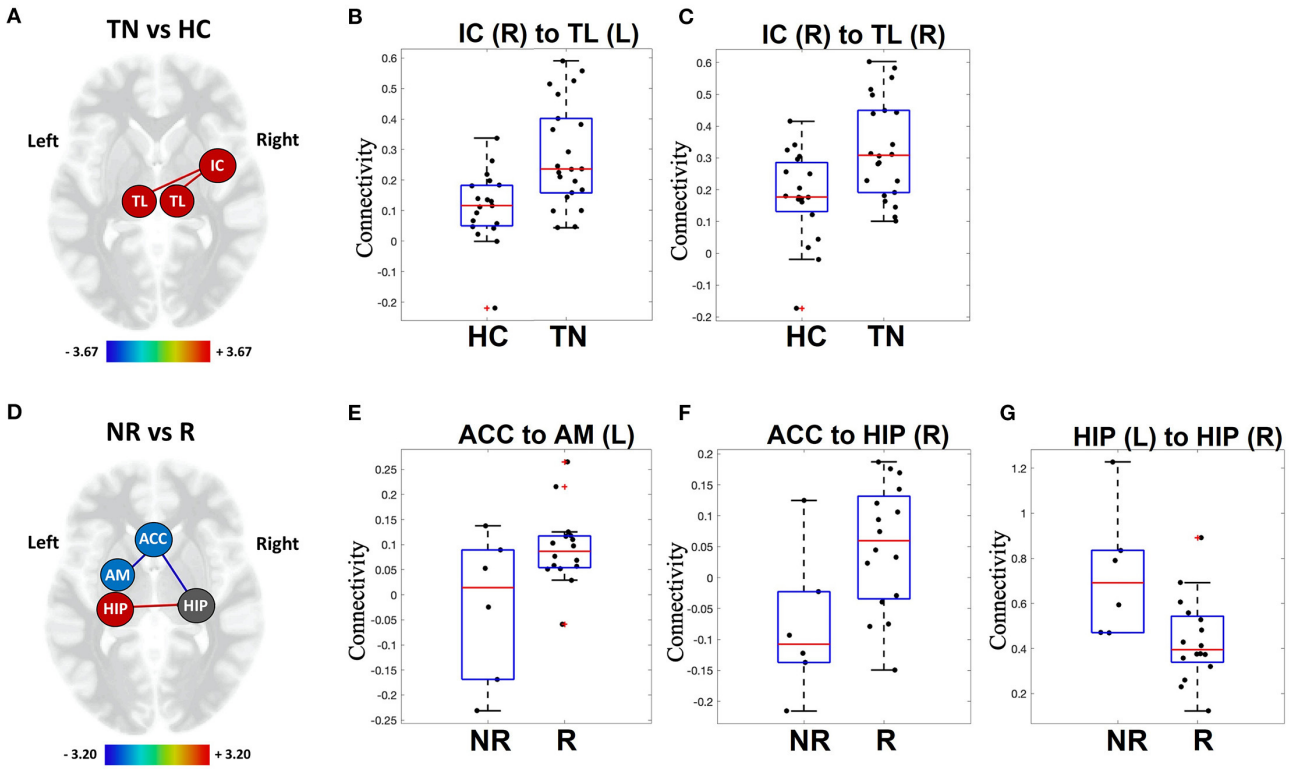


FIGURE 2 | Visual representation of functional connectivity differences. *TN patients (TN) vs. healthy controls (HC)*: patients with TN show increased resting-state functional connectivity in sensory-relay and salience structures **(A)**. Individual patient connectivity is displayed on scatter-plot graphs for right insular cortex to left thalamus **(B)** and right insular cortex to right thalamus connections **(C)**. *Responders (R) vs. Non-responders (NR)*: non-responders show altered resting-state functional connectivity in limbic structures **(D)**. Individual patient connectivity is displayed on scatter-plot graphs for the anterior cingulate cortex to left amygdala **(E)** and right hippocampus **(F)**, as well as between the left and right hippocampus **(G)**. Increased connectivity, red line; decreased connectivity, blue line; TL, thalamus; IC, insular cortex; HIP, hippocampus; AM, amygdala; ACC, anterior cingulate cortex. Heat scales indicate the relative strength of connection between nodes (i.e., edge color). Red crosses represent patients with functional connectivity beyond 1.5 times the group inter-quartile range (IQR).

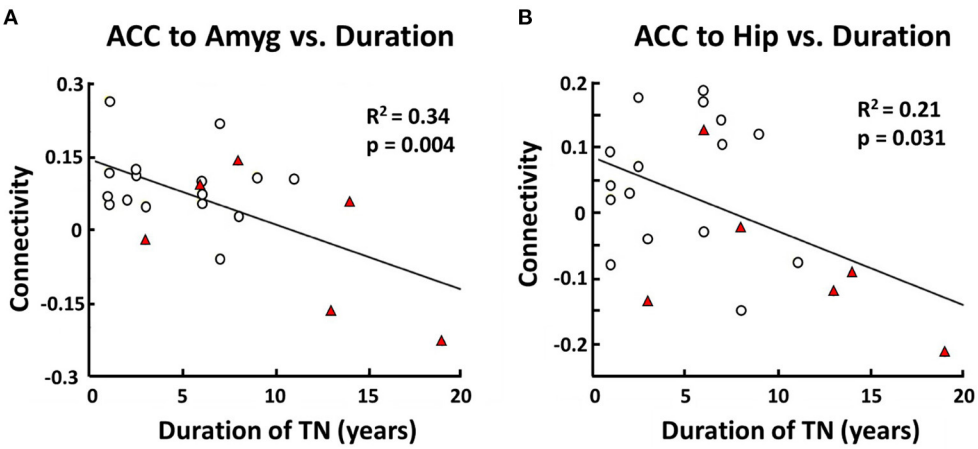


FIGURE 3 | Correlation between functional connectivity (responders vs. non-responders) and duration of TN. In TN patients there is a negative correlation between anterior cingulate cortex (ACC) and left amygdala (Amyg) resting-state functional connectivity and duration of TN in years ($R^2 = 0.34$, $p = 0.004$) **(A)**. There is also a negative correlation between ACC and right hippocampus (Hip) resting-state functional connectivity and duration of TN in years ($R^2 = 0.21$, $p = 0.031$) **(B)**. Pearson Correlation was used with a threshold for statistical significance set at $p < 0.05$.

previous findings that hippocampus structure is associated with pain severity and durability of pain relief in TN (9, 33), and possibly that hippocampal neurogenesis may directly influence pain persistence (at least in animal models) (34). It is plausible that increased left-right hippocampal connectivity may reflect or contribute to an increased capacity for pain memory recall (35). We also observed that the ACC in non-responders showed decreased functional connectivity to both the left amygdala and right hippocampus. The pre-operative difference in this ACC-hippocampus-left amygdala network (i.e., a limbic network) between responders and non-responders suggests that limbic system contributions to the chronification of pain may also be relevant in treatment-resistant TN (17, 35, 36). Interestingly, functional connectivity within this limbic network correlates negatively with duration of illness. While functional connectivity in TN patients has previously been shown to correlate with duration of illness (8), this is the first time that variability in pre-operative network connectivity associated with duration of TN has been shown to correlate with actual treatment response. Similarly, Hashmi et al. showed that the transition of back pain patients from an acute- to a longer-term chronic-pain phenotype paralleled the evolution of resting-state abnormalities from acute-pain "sensory" to "emotion-related" brain regions (21). Thus, it would appear that a longer-duration of TN—itself related to poorer surgical outcome—is associated with limbic system changes increasing treatment-resistance, and rendering less effective any peripheral surgical treatments aimed at CNV. In turn, this would argue in favor of earlier surgical intervention in TN, which has been suggested to produce more durable pain relief (37). Furthermore, the functional networks identified in the present study may serve as potential pre-operative biomarkers of surgical outcome for TN and may also represent potential neurosurgical targets for TN or other pain conditions (38–40). We are currently carrying out further studies in which functional connectivity of the limbic system is compared between short-duration and longer-duration TN patients, and longitudinal studies in which functional connectivity is evaluated before and after TN surgery, in order to better understand the impact of limbic networks on treatment-resistance, the utility of limbic network connectivity as a biomarker of surgical outcome, and the extent to which altered limbic networks can actually be normalized by surgical intervention.

LIMITATIONS

This study is not without limitations, most notably the small sample size with relatively few non-responders. We aimed to mitigate this limitation to some extent with a hypothesis-driven approach in which the analysis was restricted to only six pain-relevant brain structures chosen *a priori*. Our focused approach, however, limited our capacity to identify other brain regions whose function may also influence surgical response; larger sample studies with the statistical freedom to evaluate the whole-brain will allows us to replicate, and build on, our findings here. The small size and unbalanced nature of our cohort also prohibited receiver-operator characteristic (ROC) curve analysis to evaluate the sensitivity and specificity of functional connectivity in classifying surgical responders and non-responders (41, 42). To illustrate another limitation, it is worth pointing out that one patient in the non-responder group reported a VAS pain score of only 2/100 in the week preceding MRI scanning as they were experiencing a short period of remission. This patient has since been treated surgically three additional times—one of the most severe treatment-resistant cases of TN in our cohort—illustrating the challenge of accurately measuring pain severity in a fluctuating disease with periods of remission. To at least partially mitigate this limitation, we did adjust for pre-scan VAS as highlighted in the Methods. While medication class use did not differ between responders and non-responders at the group level, it must be pointed out that 50% of responders were exclusively taking first-line medications for their TN at the time of scanning. Therefore, we cannot rule out the possibility that the collective addition of second- and third-line medications in non-responders could be contributing to between-group connectivity differences. Another possible limitation is that we included a small number of patients undergoing repeat surgical treatments, in which functional connectivity may have been altered by prior surgery. That being said, it is noteworthy that repeat surgery patients were not distinguishable from virgin patients by any specific clinical attributes, nor did the proportion of repeat patients differ between response groups. Finally, the binarization of response to surgical treatment for TN (i.e., responder vs. non-responder) is an oversimplification, though common practice in the TN literature.

CONCLUSION

We report a novel functional connectivity analysis in patients with TN undergoing surgical treatment. As in other chronic pain conditions, functional abnormalities in sensory-salience regions are also present in patients with TN. However, alterations in functional connectivity within limbic networks—which are correlated with increasing duration of illness—may be associated with the development of treatment-resistant pain that responds more poorly to surgery in certain patients with TN.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Alberta Health Research Ethics Board—Health Panel. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the

publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

HD designed the project, was responsible for all patient data collection, contributed to ethics approval, performed data analysis and results interpretation, and wrote the manuscript. SL contributed to data analysis, results interpretation, and wrote parts of the methods section. OM contributed to results interpretation and manuscript generation. TS oversaw all aspects of the study and directly contributed to study design, ethics approval, data analysis, results interpretation, and manuscript generation. All authors reviewed the manuscript and agreed to its submission.

FUNDING

This work was funded by University of Alberta Hospital Foundation Sankar Research Establishment Grant, Edmonton Civic Employees Charitable Assistance Fund, Backman Family Fund (TS). Canada Research Chair in Non-Motor Symptoms of Parkinson's disease and the Tourmaline Chair in Parkinson's disease (OM).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.716500/full#supplementary-material

REFERENCES

1. Olesen J. Headache classification committee of the international headache society (IHS) the international classification of headache disorders, 3rd edition. *Cephalalgia.* (2018) 38:1–211. doi: 10.1177/0333102417738202
2. Zakrzewska JM, Akram H. Neurosurgical interventions for the treatment of classical trigeminal neuralgia. *Cochrane Database Syst Rev.* (2011). 9:CD007312. doi: 10.1002/14651858.CD007312.pub2
3. Obermann M. Treatment options in trigeminal neuralgia. *Ther Adv Neurol Disord.* (2010) 3:107–15. doi: 10.1177/1756285609359317
4. Burchiel KIMJ, Clarke H, Haglund M, Loeser J. Long-term efficacy of microvascular decompression in trigeminal neuralgia. *J Neurosurg.* (1988) 69:35–8. doi: 10.3171/jns.1988.69.1.0035
5. Desouza DD, Hodaie M, Davis KD. Abnormal trigeminal nerve microstructure and brain white matter in idiopathic trigeminal neuralgia. *Pain.* (2014) 155:37–44. doi: 10.1016/j.pain.2013.08.029
6. Lutz J, Thon N, Stahl R, Lummel N, Tonn J-C, Linn J, et al. Microstructural alterations in trigeminal neuralgia determined by diffusion tensor imaging are independent of symptom duration, severity, and type of neurovascular conflict. *J Neurosurg.* (2015) 124:823–30. doi: 10.3171/2015.2.JNS142587
7. DeSouza DD, Davis KD, Hodaie M. Reversal of insular and microstructural nerve abnormalities following effective surgical treatment for trigeminal neuralgia. *Pain.* (2015) 156:1112–23. doi: 10.1097/j.pain.0000000000000156
8. Tsai YH, Yuan R, Patel D, Chandrasekaran S, Weng HH, Yang JT, et al. Altered structure and functional connection in patients with classical trigeminal neuralgia. *Hum Brain Mapp.* (2018) 39:609–21. doi: 10.1002/hbm.23696
9. Danyluk H, Lee EK, Wong S, Sajida S, Broad R, Wheatley M, et al. Hippocampal and trigeminal nerve volume predict outcome of surgical treatment for trigeminal neuralgia. *Cephalalgia.* (2020) 40:586–96. doi: 10.1177/0333102419877659
10. Zhang Y, Mao Z, Pan L, Ling Z, Liu X, Zhang J, et al. Dysregulation of pain- and emotion-related networks in trigeminal neuralgia. *Front Hum Neurosci.* (2018) 12:107. doi: 10.3389/fnhum.2018.00107
11. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci.* (2007) 27:2349–56. doi: 10.1523/JNEUROSCI.5587-06.2007
12. Wang Y, Cao DY, Remeniuk B, Krimmel S, Seminowicz DA, Zhang M. Altered brain structure and function associated with sensory and affective components of classic trigeminal neuralgia. *Pain.* (2017) 158:1561–70. doi: 10.1097/j.pain.0000000000000951
13. Henssen D, Dijk J, Knepflé R, Sieffers M, Winter A, Vissers K. Alterations in grey matter density and functional connectivity in trigeminal neuropathic pain and trigeminal neuralgia: a systematic review and meta-analysis. *NeuroImage Clin.* (2019) 24:102039. Available from: doi: 10.1016/j.nicl.2019.102039
14. Obermann M, Yoon MS, Ese D, Maschke M, Kaube H, Diener HC, et al. Impaired trigeminal nociceptive processing in patients with trigeminal neuralgia. *Neurology.* (2007) 69:835–41. doi: 10.1212/01.wnl.0000269670.30045.6b
15. Rodriguez-Raecke R, Niemeier A, Ihle K, Ruether W, May A. Brain gray matter decrease in chronic pain is the consequence and not the cause of pain. *J Neurosci.* (2009) 29:13746–50. doi: 10.1523/JNEUROSCI.3687-09.2009
16. (Bud) Craig AD. How do you feel — now? The anterior insula and human awareness. *Nat Rev Neurosci.* (2009) 10:59–70. doi: 10.1038/nrn2555
17. Shackman AJ, Salomons T V, Slagter HA, Fox AS, Winter JJ, Davidson RJ. The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nat Rev Neurosci.* (2011) 12:154–67. doi: 10.1038/nrn2994
18. Tso AR, Trujillo A, Guo CC, Goadsby PJ, Seeley WW. The anterior insula shows heightened interictal intrinsic connectivity in migraine without aura. *Neurology.* (2015) 84:1043–50. doi: 10.1212/WNL.0000000000001330
19. Lickteig R, Lotze M, Kordass B. Successful therapy for temporomandibular pain alters anterior insula and cerebellar representations of occlusion. *Cephalalgia.* (2013) 33:1248–57. doi: 10.1177/0333102413491028
20. Yarkoni T, Poldrack RA, Nichols TE, Van Essen DC, Wager TD. Large-scale automated synthesis of human functional neuroimaging data. *Nat Methods.* (2011) 8:665–70. doi: 10.1038/nmeth.1635
21. Hashmi JA, Baliki MN, Huang L, Baria AT, Torbey S, Hermann KM, et al. Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits. *Brain.* (2013) 136:2751–68. doi: 10.1093/brain/awt211
22. Heinskou TB, Rochat P, Maarbjerg S, Wolfram F, Brennum J, Olesen J, et al. Prognostic factors for outcome of microvascular decompression in trigeminal neuralgia: a prospective systematic study using independent assessors. *Cephalalgia.* (2019) 39:197–208. doi: 10.1177/0333102418783294
23. Han PP, Shetter AG, Smith KA, Fiedler JA, Rogers CL, Speiser B, et al. Gamma knife radiosurgery for trigeminal neuralgia: experience at the barrow neurological institute. *Int J Radiat Oncol Biol Phys.* (2000) 47:1013–9. doi: 10.1016/S0360-3016(00)00513-7
24. Ashburner J, Friston K. Unified segmentation. *Neuroimage.* (2005) 26:839–51. doi: 10.1016/j.neuroimage.2005.02.018
25. Calhoun V, Wager T, Krishan A, Rosch K, Seymour K, Nebel M, et al. The impact of T1 versus EPI spatial normalization templates for fMRI data analyses. *Human.* (2017) 38:5331–42. doi: 10.1002/hbm.23737
26. Whitfield-Gabrieli S, Nieto-Castanon A. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connect.* (2012) 2:125–41. doi: 10.1089/brain.2012.0073
27. Behzadi Y, Restom K, Liu T. A component based noise correction method for BOLD and perfusion based fMRI. *Neuroimage.* (2007) 37:90–101. doi: 10.1016/j.neuroimage.2007.04.042

28. Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage.* (2006) 31:968–80. doi: 10.1016/j.neuroimage.2006.01.021
29. Lim M, Jassar H, Kim DJ, Nascimento TD, DaSilva AF. Differential alteration of fMRI signal variability in the ascending trigeminal somatosensory and pain modulatory pathways in migraine. *J Headache Pain.* (2021) 22:4. doi: 10.1186/s10194-020-01210-6
30. Danyluk H, Andrews J, Kesarwani R, Seres P, Broad R, Wheatley BM. The thalamus in trigeminal neuralgia : structural and metabolic abnormalities, and influence on surgical response. *BMC Neurol.* (2021) 21:290. doi: 10.1186/s12883-021-02323-4
31. Kong J, White NS, Kwong KK, Vangel MG, Rosman IS, Gracely RH, et al. Using fMRI to dissociate sensory encoding from cognitive evaluation of heat pain intensity. *Hum Brain Mapp.* (2006) 27:715–21. doi: 10.1002/hbm.20213
32. Ghaziri J, Tucholka A, Girard G, Boucher O, Houde JC, Descoteaux M, et al. Subcortical structural connectivity of insular subregions. *Sci Rep.* (2018) 8:8596. doi: 10.1038/s41598-018-26995-0
33. Wang Y, Yang Q, Cao D, Seminowicz D, Remeniuk B, Gao L, et al. Correlation between nerve atrophy, brain grey matter volume and pain severity in patients with primary trigeminal neuralgia. *Cephalalgia.* (2018) 39:515–25. doi: 10.1177/0333102418793643
34. Apkarian AV, Mutso AA, Centeno MV, Kan L, Wu M, Levinstein M, et al. Role of adult hippocampal neurogenesis in persistent pain. *Pain.* (2016) 157:418–28. doi: 10.1097/j.pain.0000000000000332
35. Berger SE, Vachon-Presseau É, Abdullah TB, Baria AT, Schnitzer TJ, Apkarian AV. Hippocampal morphology mediates biased memories of chronic pain. *Neuroimage.* (2018) 166:86–98. doi: 10.1016/j.neuroimage.2017.10.030
36. Shimo K, Ueno T, Younger J, Nishihara M, Inoue S, Ikemoto T, et al. Visualization of painful experiences believed to trigger the activation of affective and emotional brain regions in subjects with low back pain. *PLoS ONE.* (2011) 6:2–7. doi: 10.1371/journal.pone.0026681
37. Mousavi SH, Niranjan A, Huang MJ, Laghari FJ, Shin SS, Mindlin JL, et al. Early radiosurgery provides superior pain relief for trigeminal neuralgia patients. *Neurology.* (2015) 85:2159–65. doi: 10.1212/WNL.0000000000002216
38. Russo JF, Sheth SA. Deep brain stimulation of the dorsal anterior cingulate cortex for the treatment of chronic neuropathic pain. *Neurosurg Focus.* (2015) 38:E11. doi: 10.3171/2015.3.FOCUS1543
39. Yen CP, Kung SS, Su YF, Lin WC, Howng SL, Kwan AL. Stereotactic bilateral anterior cingulotomy for intractable pain. *J Clin Neurosci.* (2005) 12:886–90. doi: 10.1016/j.jocn.2004.11.018
40. Gallay MN, Moser D, Jeanmonod D. MR-Guided focused ultrasound central lateral thalamotomy for trigeminal neuralgia. Single center experience. *Front Neurol.* (2020) 11:271. doi: 10.3389/fneur.2020.00271
41. Saito T, Rehmsmeier M. The precision-recall plot is more informative than the ROC plot when evaluating binary classifiers on imbalanced datasets. *PLoS ONE.* (2015) 10:e0118432. doi: 10.1371/journal.pone.0118432
42. Fawcett T. An introduction to ROC analysis. *Patt Recog. Lett.* (2006) 27:861–74. doi: 10.1016/j.patrec.2005.10.010

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2021 Danyluk, Lang, Monchi and Sankar. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Neurology

ORIGINAL RESEARCH
published: 08 October 2021
doi: 10.3389/fneur.2021.711880

Identification and Therapeutic Outcome Prediction of Cervical Spondylotic Myelopathy Based on the Functional Connectivity From Resting-State Functional MRI Data: A Preliminary Machine Learning Study

Qian Su[1†], Rui Zhao[2†], ShuoWen Wang[3], HaoYang Tu[4], Xing Guo[2] and Fan Yang[5*]*

[1] Tianjin Key Laboratory of Cancer Prevention and Therapy, Department of Molecular Imaging and Nuclear Medicine, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin's Clinical Research Center for China, Tianjin, China, [2] Department of Orthopedics Surgery, Tianjin Medical University General Hospital, Tianjin, China, [3] School of Basic Medical Sciences, Tianjin Medical University, Tianjin, China, [4] School and Hospital of Stomatology, Tianjin Medical University, Tianjin, China, [5] Department of Radiology, Tianjin Medical University General Hospital, Tianjin, China

OPEN ACCESS

Edited by:
Marie-Eve Hoeppli,
Cincinnati Children's Hospital Medical Center, United States

Reviewed by:
Ailish Malone,
Royal College of Surgeons in Ireland, Ireland
Takashi Kaito,
Osaka University, Japan

***Correspondence:**
Qian Su
suqian0510@126.com
Fan Yang
yf491801633@sina.com

[†] These authors have contributed equally to this work

Specialty section:
This article was submitted to Applied Neuroimaging, a section of the journal Frontiers in Neurology

Received: 19 May 2021
Accepted: 19 August 2021
Published: 08 October 2021

Citation:
Su Q, Zhao R, Wang S, Tu H, Guo X and Yang F (2021) Identification and Therapeutic Outcome Prediction of Cervical Spondylotic Myelopathy Based on the Functional Connectivity From Resting-State Functional MRI Data: A Preliminary Machine Learning Study. Front. Neurol. 12:711880. doi: 10.3389/fneur.2021.711880

Currently, strategies to diagnose patients and predict neurological recovery in cervical spondylotic myelopathy (CSM) using MR images of the cervical spine are urgently required. In light of this, this study aimed at exploring potential preoperative brain biomarkers that can be used to diagnose and predict neurological recovery in CSM patients using functional connectivity (FC) analysis of a resting-state functional MRI (rs-fMRI) data. Two independent datasets, including total of 53 patients with CSM and 47 age- and sex-matched healthy controls (HCs), underwent the preoperative rs-fMRI procedure. The FC was calculated from the automated anatomical labeling (AAL) template and used as features for machine learning analysis. After that, three analyses were used, namely, the classification of CSM patients from healthy adults using the support vector machine (SVM) within and across datasets, the prediction of preoperative neurological function in CSM patients *via* support vector regression (SVR) within and across datasets, and the prediction of neurological recovery in CSM patients *via* SVR within and across datasets. The results showed that CSM patients could be successfully identified from HCs with high classification accuracies (84.2% for dataset 1, 95.2% for dataset 2, and 73.0% for cross-site validation). Furthermore, the rs-FC combined with SVR could successfully predict the neurological recovery in CSM patients. Additionally, our results from cross-site validation analyses exhibited good reproducibility and generalization across the two datasets. Therefore, our findings provide preliminary evidence toward the development of novel strategies to predict neurological recovery in CSM patients using rs-fMRI and machine learning technique.

Keywords: rs-fMRI, machine learning, cervical spondylotic myelopathy, support vector machine, functional connectivity

INTRODUCTION

Cervical spondylotic myelopathy (CSM) is the most common cause of non-traumatic spinal cord injury (1–3). As a non-invasive and effective approach for evaluating structural damage of CSM, several neuroimaging techniques targeting the cervical spine to diagnose and to predict neurological recovery in CSM have been investigated. Currently, cervical structural MRI is regarded as a gold standard for diagnostic and prognostic imaging for CSM in clinical practice (4, 5). However, there are insufficient empirical data, due to limited anatomical information from the cord structure, to support the usage of conventional structural cervical MRI (e.g., T1-weighted and T2-weighted images) as a predictive biomarker of postoperative neurological recovery (6). Therefore, the need for simple, accurate, and non-invasive imaging biomarkers for diagnosing and predicting neurological function recovery in CSM patients is warranted (5).

As a non-invasive imaging technique measuring the functional changes in CSM, the brain resting-state functional MRI (rs-fMRI) has been proved to successfully identify the CSM patients from healthy participants (7–13). In contrast to conventional MRI technique, which only measures the structural damages within the conduction pathway, rs-fMRI measures the brain activities that encompass information for all motor and cognitive functions as the brain functions as a "control and data center." Therefore, CSM-associated information is distributed in widespread regions of the brain (8, 11, 14). Therefore, several studies conducted the rs-fMRI to predict the neurological recovery of CSM patients following decompression surgery. Takenaka et al. found that the functional connectivity (FC) between certain brain regions associated with postoperative gain in the 10-s test might be sufficient to provide a prediction formula for potential recovery (11). Moreover, they also found that the resting-state amplitude of low-frequency fluctuation is also a potentially prognostic functional biomarker in cervical myelopathy (15).

Their studies provided new insights for developing a novel method for diagnostic and prognostic imaging in CSM patients. However, a major limitation is that their results were mainly using mass univariate analyses (e.g., correlation analysis and linear regression), which can simply measure the association between average regional activity amplitude and clinical measures. Given that the rs-fMRI data consist of massive variables measuring the functional state of the brain and the interrelationship between these variables, the univariate analyses thus may miss the information associating with the CSM pathology. Rapid advancement of multivariate pattern analysis (MVPA) of fMRI data (16, 17) offers the unprecedented ability to detect small differences in spatial patterns of functional brain changes and reorganizations between disease-state and disease-free conditions (18, 19). Also, MVPA approaches evaluate the complexity interaction among massive variables, hence making accurate predictions (16, 20–22). The support vector machine (SVM) has been regarded as one of the MVPA techniques showing high accuracy in diagnosing and predicting clinical measures in various diseases using fMRI data (20, 23). The SVM is a supervised-learning model that analyzes data used for classification and regression analysis. The SVM technique has a great potential in defining a set of features from various regions of the brain, allowing the classification of healthy controls (HCs) and patients, and yields a potential translational impact (16, 24).

Therefore, to establish a model with potential diagnostic and prediction properties of clinical outcomes in patients with CSM, we aimed to test the utility of FC, which integrates spatial relationships among different brain regions and is the most widely used metric among other analytical methods in rs-fMRI studies (9, 25–27), as a potential biomarker for diagnosing and predicting surgical outcomes in CSM patients using the SVM approach. Moreover, FC has been shown to be one of the most reliable metrics (i.e., cross-scan stability) in fMRI studies (28–30). In this study, we performed an MVPA to classify CSM patients and HCs, both with and without feature selection *via* SVM. We then used support vector regression (SVR) to predict the preoperative Japanese Orthopedic Association (JOA) scores, JOA recovery rate, and the JOA recovery scores following spinal cord decompression surgery. We also tested the reproducibility and generalizability of our results by cross-validation between the two independent datasets. To the best of our knowledge, this is the first study testing the utility of combining rs-FC and machine learning method for diagnosing and predicting surgical outcomes in CSM patients.

MATERIALS AND METHODS

Study Subjects

The local Institutional Review Board of Tianjin Medical University General Hospital (Tianjin, China) approved this cross-sectional, retrospective study. Written informed consent was obtained from all participants before each procedure during the data collection.

In this study, two datasets (i.e., two pre-established databases) obtained in Tianjin Medical University General Hospital at two different time frames were included: the first dataset involved 27 right-handed CSM patients pooled from 2015 to 2016. The inclusion criteria of CSM patients into this dataset (dataset 1) included the following: (1) meet a criterion for diagnosing the CSM (i.e., clear evidence of cord compression on cervical spine MRI, explicit clinical manifestations of sensorimotor extremities' deficits or bladder, and bowel dysfunction); (2) no clinical evidence or history of any other diseases including neurological diseases, psychiatric diseases, ocular diseases, systematic diseases, brain diseases, extracranial vertebral artery, and carotid artery; (3) no history of alcohol and substance abuse; (4) the patients agreed to undergo decompression of spinal canal, had no previous history of cervical spinal surgery, and are able to complete the functional MRI studies. Furthermore, 11 healthy subjects with similar age, gender, and academic years (i.e., with differences for age, academic years all below 2 years from a given subject in the patient group) were recruited through advertisements. Only the healthy subjects with no evidence of spinal compression, no ocular disease, no other spinal or brain neurological disorders or systemic disease, and able to complete the fMRI studies were included—details of study participants

were as per our previous study (31). In the second dataset (dataset 2), 26 CSM patients and 36 HCs sampled from 2019 to 2020 were recruited in our study using the inclusion criteria for the first dataset; details of study participants were as per our previous study (32). Therefore, a total of 53 CSM patients and 47 healthy participants were included in our current study.

The detailed order for data collection were as follows: (1) the patients were first examined and evaluated by a senior orthopedic surgeon 1 week before surgery for acquiring preoperative JOA scores; subsequently, the patients underwent fMRI scan for acquiring preoperative fMRI data; (2) the patients underwent spinal cord decompression surgery; and (3) all patients were reevaluated by the same surgeon at the clinics 6 months after surgery to acquire the postoperative JOA scores.

Acquisition of MRI Data and Preprocessing

For dataset 1, data were acquired using a 3.0T magnetic resonance scanner (Discovery MR750; General Electric Healthcare, Chicago, IL, USA) with an eight-channel phased-array head coil. Before scanning, earplugs were placed inside the subjects' ears to keep out noise. The subjects were then instructed to fix their heads with sponge pads to minimize unconscious activity. Subjects could keep their eyes closed but remain awake and avoid specific and strong ideological activities during scanning. We made clear instruction to the participants that they should not fall asleep during the entire scan. We also confirmed with the participants that they have been awake during the entire scan after they completed the scan. Afterward, functional images of the brain were captured using a gradient echo-planar imaging (EPI) sequence at the following parameters: repetition time (TR) = 2,000 ms; echo time (TE) = 30 ms; flip angle (FA) = 90°; field of view (FOV) = 240 mm × 240 mm; matrix = 64 × 64; the number of slices = 38 slices; and slice thickness = 3.0 mm. A total of 180 images were obtained within 6 min. Structural images were captured using a three-dimensional T1-weighted image (3D T1WI) for co-registration and normalization of functional images. The parameters of the 3D T1WI were as follows: sagittal acquisition; TR = 7.8 ms; TE = 3.0 ms; inversion time = 450 ms; FA = 13°; FOV = 256 mm × 256 mm; matrix, 256 × 256; number of slices = 180; and slice thickness = 1.0 mm.

For the second dataset (dataset 2), the 3T fMRI data were acquired using a MAGNETOM Prisma 3T MR scanner (Siemens, Erlangen, Germany) with a 64-channel phase-array head-neck coil. Preparation of the study subjects was identical to that described in dataset 1. Blood oxygenation level-dependent (BOLD) signals were detected with a simultaneous multi-slice gradient EPI sequence at the following parameters: TE = 30 ms; TR = 800 ms; FOV = 222 mm × 222 mm; matrix = 74 × 74; in-plane resolution = 3 mm × 3 mm; FA = 54°; slice thickness = 3 mm; gap = 0 mm; number of slices = 48; slice orientation = transversal; bandwidth = 1,690 Hz/pixel; parallel acquisition technique (PAT) mode; slice acceleration factor = 4; and phase-encoding acceleration factor = 2. A total of 450 images were captured in a period of 6 min. A high-resolution 3D T1 structural image [two inversion contrast magnetization-prepared rapid gradient echo (MP2RAGE)] was also acquired at the following parameters: TR/TE = 4,000 ms/3.41 ms; inversion times (TI1/TI2) = 700 ms/2,110 ms; FA1/FA2 = 4°/5°; matrix = 256 × 240; FOV = 256 mm × 240 mm; number of slices = 192; in-plane resolution = 1 mm × 1 mm; slice thickness = 1 mm; slice orientation = sagittal; and total duration = 6 min 42 s.

All MRI data were preprocessed using the toolbox Data Processing Assistant for rs-fMRI (DPARSF; http://www.restfmri.net/forum/DPARSF) procedure from which 180 volumes were acquired for functional scan in dataset 1 and 450 volumes in dataset 2. The first 10 volumes from each functional scan were excluded from the subjects to correct acclimatization to the scanning environment and magnetization stabilization. A slice-timing correction was performed (not done in dataset 2 since the TR of dataset 2 was significantly shortened); and motion correction was performed to remove timing differences and head movement. The functional images were co-registered with the structural images and spatially normalized to the Montreal Neurological Institute template, where each voxel was resampled to 3 × 3 × 3 mm^3. Subsequently, the resampled images were smoothed with an 8-mm full-width-at-half-maximum isotropic Gaussian kernel. After that, the linear trend and bandpass filter (0.01∼0.08 Hz) were applied to remove the effects of high-frequency noise. Finally, six motion parameters, the mean global signal, the white matter signal, and the cerebrospinal fluid (CSF) signal were extracted as covariates to reduce the non-neural signal. The resulting data were subjected to further analysis.

Clinical Assessment

A group of senior spine surgeons performed clinical assessments including JOA evaluation (33). The clinical diagnosis of CSM was based on the neurological signs and symptoms in patients together with relevant radiological findings of stenosis. The JOA was used preoperatively and postoperatively after 6 months for clinical evaluation. The JOA recovery scores were calculated for the study group by subtracting preoperative JOA scores from postoperative JOA scores.

The JOA recovery rate was defined as follows:

$$JOA\ recovery\ rate = \frac{(Postoperative\ JOA\ scores - Preoperative\ JOA\ scores)}{(17 - Preoperative\ JOA\ scores)}$$

And the JOA recovery was defined as follows:

$$JOA\ recovery = Postoperative\ JOA\ scores - Preoperative\ JOA\ scores$$

Functional Connectivity Analysis

A total of 116 functionally defined regions of interest (ROIs) were selected using an automated anatomical labeling (AAL) template (34). The average resting-state BOLD time series for each ROI were then extracted and then correlated with the BOLD time series of every other ROI using Pearson's correlation for every subject. From the resulting square (116 × 116) symmetric matrix of correlation coefficients for each subject, only 6,670 ROI-pair correlation values from the lower triangular part of the matrix were retained, and the redundant elements from the upper triangular part of the matrix (i.e., the upper triangular part

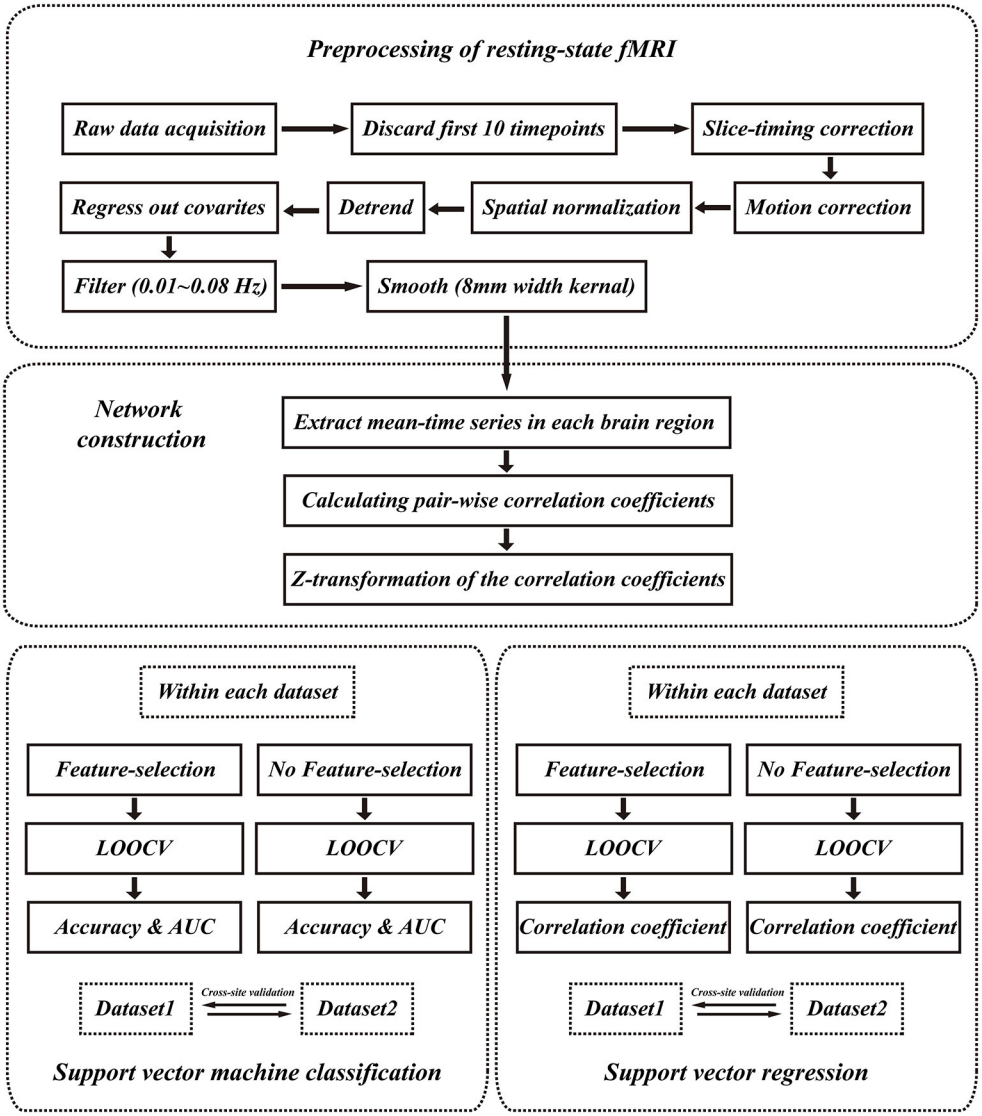


FIGURE 1 | Analysis pipeline. The analysis pipeline of our study. LOOCV, leave-one-out cross-validation.

is identical to the lower triangular part), and diagonal elements were excluded. The 6,670 ROI pairs were subjected to Fisher's z-transformation for normalization and used as features for further analyses. **Figure 1** shows a series of steps in a representative pipeline of the classification method used in this study.

Mass Univariate Analyses

Mass univariate analyses were performed to reveal the FC differences between CSM patients and HCs. The two-sample *t*-test was performed for each FC (i.e., FCs calculated between each pair of brain regions) using age, gender, scan parameters, and education as covariates. Therefore, 6,670 *p*-values were obtained. Subsequently, all *p*-values were corrected for multiple comparisons with false discovery rate (FDR), corresponding to a corrected $q < 0.05$. This analysis was also repeated within each dataset to give a detailed result of each dataset.

Classification of Cervical Spondylotic Myelopathy From Healthy Adults

The pattern classification was performed to classify patients with CSM and HCs based on FC using the MVPANI toolbox (http://funi.tmu.edu.cn) and LibSVM's implementation of linear SVM using the default parameters (35). A large vector with 6,670 features was extracted from each subject.

For within-dataset analyses, the leave-one-out-validation (LOOCV) technique was employed to overcome the loss of generalization due to the small training and testing sample size in this study. The bias of LOOCV error was expected to be small

since almost the entire dataset was used for training, and the trained model was close to the real one.

In LOOCV, for example (e.g., within dataset 1), (1) one data point in dataset 1 was held out (i.e., treated as the testing sample), and the model was trained vis-à-vis the rest of the data within this dataset and then tested with that held-out data point (i.e., one fold). Subsequently, the classification accuracy for the testing sample was obtained (i.e., the classification accuracy of this fold). (2) This procedure was repeated until all data points were held out once as the testing sample, (3) The average classification accuracy across all folds was obtained for this dataset. A feature selection procedure embedded within the LOOCV procedure was also performed. For each fold in LOOCV, all features were initially used to train a classifier using the training dataset and then ranked from high to low according to the resultant feature weights (e.g., absolute value). Then, the top 5% of the features with the highest weights were selected and used to train a new classifier using the training dataset. Afterward, the obtained classifier was tested using the test dataset, resulting in classification accuracy for this LOOCV step. Therefore, classification accuracy was obtained for every LOOCV step, and then the absolute accuracy was calculated as the average across all LOOCV steps. The feature selection procedure was repeated for a series of selected features from 5 to 100% with a step of 5% increment, resulting in 20 selected feature sets with 20 averaged classification accuracies. For each of the 20 classification accuracies, the corresponding p-value was calculated from the null distribution obtained from 1,000 random permutation tests by randomly shuffling the labels of subjects in the training dataset, with the selected corresponding feature set in each LOOCV step. The p-values were calculated as a proportion of the number of permutations generated that were greater than or equal to actual classification accuracy, and the total number of permutations. If none of the 1,000 permutations reached the actual accuracy, the p-value was labeled as $p < 0.001$. Note that in this procedure, 20 independent MVPAs were analyzed with a different percentage in feature selection. Thus, the p-values that were calculated from the permutation tests were further corrected for multiple comparisons using the Bonferroni correction method, where $p < 0.05/20 = 0.0025$ was considered statistically significant. All LOOCV and feature-selection steps were also performed within dataset 2.

Generalization of the SVM model was evaluated by a cross-site validation test between two datasets, where each dataset was treated as a testing set once, and not involved in the training process. The brief description of the cross-site validation test was as follows: (1) the SVM model was trained using the data of dataset 1 and then tested on the data of dataset 2. (2) Subsequently, the classification accuracy was obtained for this validation step. (3) The SVM model was trained using the data of dataset 2 and then tested on the data of dataset 1. (4) The classification accuracy was also obtained for this validation step. (5) The mean classification accuracy of all validation steps (i.e., two accuracies) were obtained for cross-site validation analysis. In addition to classification accuracy, the receiver operating characteristic (ROC) curves and the corresponding area the under curve (AUC) for within-dataset and cross-dataset classification were also calculated.

Prediction of Preoperative Japanese Orthopedic Association Scores, Japanese Orthopedic Association Recovery Rate, and Japanese Orthopedic Association Recovery Scores in Cervical Spondylotic Myelopathy

The presurgical FC of each subject, as the training feature, was used to establish and evaluate SVR models. The SVR models were used to predict the preoperative JOA scores, JOA recovery rate, and JOA recovery scores. The SVR analyses embedded with LOOCV were also performed within each dataset and across datasets.

In within-dataset analyses, LOOCV procedure was also performed (e.g., within dataset 1): (1) one data point in dataset 1 was held out, and the model was trained vis-à-vis the rest data within the dataset; (2) then the trained model was tested with that held-out data point. For this procedure, a predicted value was obtained, representing a predicted value for this subject (i.e., held-out data point). This procedure was repeated until all data points were held out once. A feature selection procedure that was embedded within the LOOCV procedure was performed. The detailed procedure was similar to the description in *Classification of Cervical Spondylotic Myelopathy From Healthy Adults* in the *Materials and Methods*. In this section, the correlation coefficients between the predicted labels and actual labels were calculated and used for deriving the corresponding p-values from null distribution. The detailed information of the LOOCV and feature-selection procedures was as follows: for each LOOCV step, all features were initially correlated with the actual label, and the corresponding R and p-values were obtained. Features with a p-value of <0.05 were selected and used to train a regression model with the training dataset. The regression model was tested using the test dataset, thereby yielding the predicted labels for the test data.

Evaluation of the generalizability of the SVM model was performed using a cross-site validation test between two datasets where each dataset that was not involved in the training process was held as testing set once.

The brief description of the cross-site validation is as follows: (1) the SVR model was trained using the data of dataset 1 and then tested on the data of dataset 2. (2) Subsequently, the predicted labels of each data point in dataset 2 (i.e., testing sample) were obtained for calculating the correlation coefficients and root mean square error (RMSE) (e.g., between predicted labels and actual labels; dataset 1 as the training data). (3) The SVM model was trained using the data of dataset 2 and then tested on the data of dataset 1. (4) Subsequently, the predicted labels of each data point in dataset 1 (i.e., testing sample) were obtained for calculating the correlation coefficients and RMSE (e.g., between predicted labels and actual labels; dataset 2 as the training set). The corresponding p-value was derived from the null distribution that was obtained from 1,000 random permutation tests, by randomly shuffling the labels of the subjects in the training dataset, with the corresponding feature set. Specifically, the p-values were determined as a proportion of the number of permutations greater than or equal to the

TABLE 1 | Demographic data and clinical assessment.

Dataset 1				Dataset 2			
Characteristic	**CSM (n = 27)**	**HC (n = 11)**	***p*-value**	**Characteristic**	**CSM (n = 26)**	**HC (n = 36)**	***p*-value**
Age (years)	57.9 ± 9.1	54.8 ± 8.4	0.34	Age (years)	54.7 ± 8.8	53.7 ± 8.3	0.54
Gender (female/male)	12/15	5/6	0.96	Gender (female/male)	12/14	17/19	0.93
Education (years)	10.8 ± 2.7	11.6 ± 2.5	0.42	Education (years)	10.7 ± 2.5	11.2 ± 23	0.41
Pre-JOA	11.8 ± 1.5			Pre-JOA	11.0 ± 1.8		
Post-JOA	15.7 ± 2.3			Post-JOA	14.2 ± 2.6		
JOA recovery	3.9 ± 1.8			JOA recovery	3.1 ± 2.4		

JOA, Japanese Orthopedic Association score; Pre, preoperative; Post, postoperative; CSM, cervical spondylotic myelopathy; HC, healthy control.
JOA recovery = Postoperative JOA scores – Preoperative JOA scores.

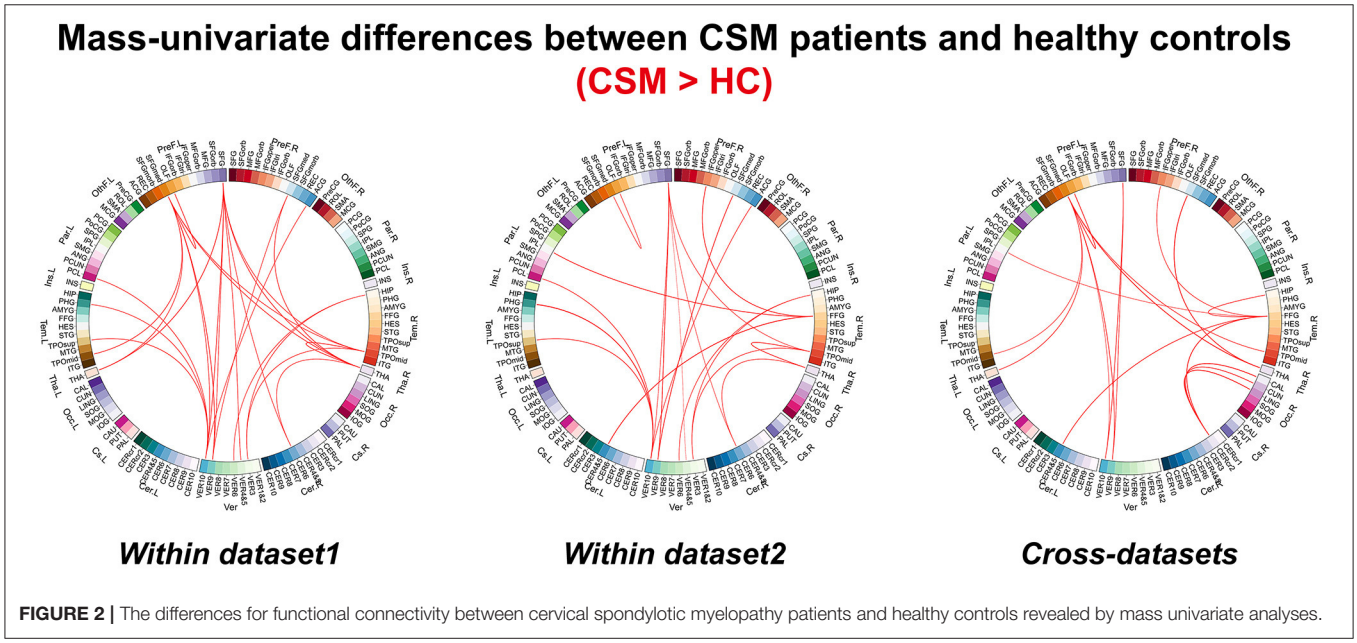


FIGURE 2 | The differences for functional connectivity between cervical spondylotic myelopathy patients and healthy controls revealed by mass univariate analyses.

actual correlation coefficient (and the proportion of the number of permutations smaller than or equal to the RMSE) and the total permutations. If none of the 1,000 permutations reached the actual correlation coefficient (or smaller than the actual RMSE), the p-value was considered to be $p < 0.001$. Pearson's correlation analysis can only provide the linear association between the predicted labels and actual labels, while the Bland–Altman analysis could further describe the agreement between two variables (i.e., predicted label and actual label) and help to determine the true limits of agreement (LOA) for each prediction procedure. Therefore, the Bland–Altman analyses would significantly aid interpretation of the clinical impact of these analyses.

RESULTS

Clinical Measures and Demographic Data

The preoperative, postoperative, and recovery JOA scores are presented in **Table 1**. No significant differences in age, gender, and academic years were observed between CSM patients and HCs.

Mass Univariate Analyses

The FC differences between CSM patients and HCs are shown in **Figure 2**. Increased FCs (i.e., FCs were increased in CSM in comparison with HC participants) were obtained both within dataset and across dataset analyses. In dataset 1, increased FCs are mainly between the frontal lobe and cerebellum, frontal lobe and thalamus, and temporal lobe and thalamus. In dataset 2, increased FCs are mainly between the frontal lobe and cerebellum, and temporal lobe and cerebellum.

Classification of Cervical Spondylotic Myelopathy From Healthy Adults

The SVM results are shown in **Figure 3**. The classification accuracies that were obtained from a no-feature selection procedure for each dataset and cross-site validation were 81.6% ($p < 0.001$, with Bonferroni correction) for dataset 1, 85.5% ($p < 0.001$) for dataset 2, and 72.0% ($p = 0.002$, with Bonferroni

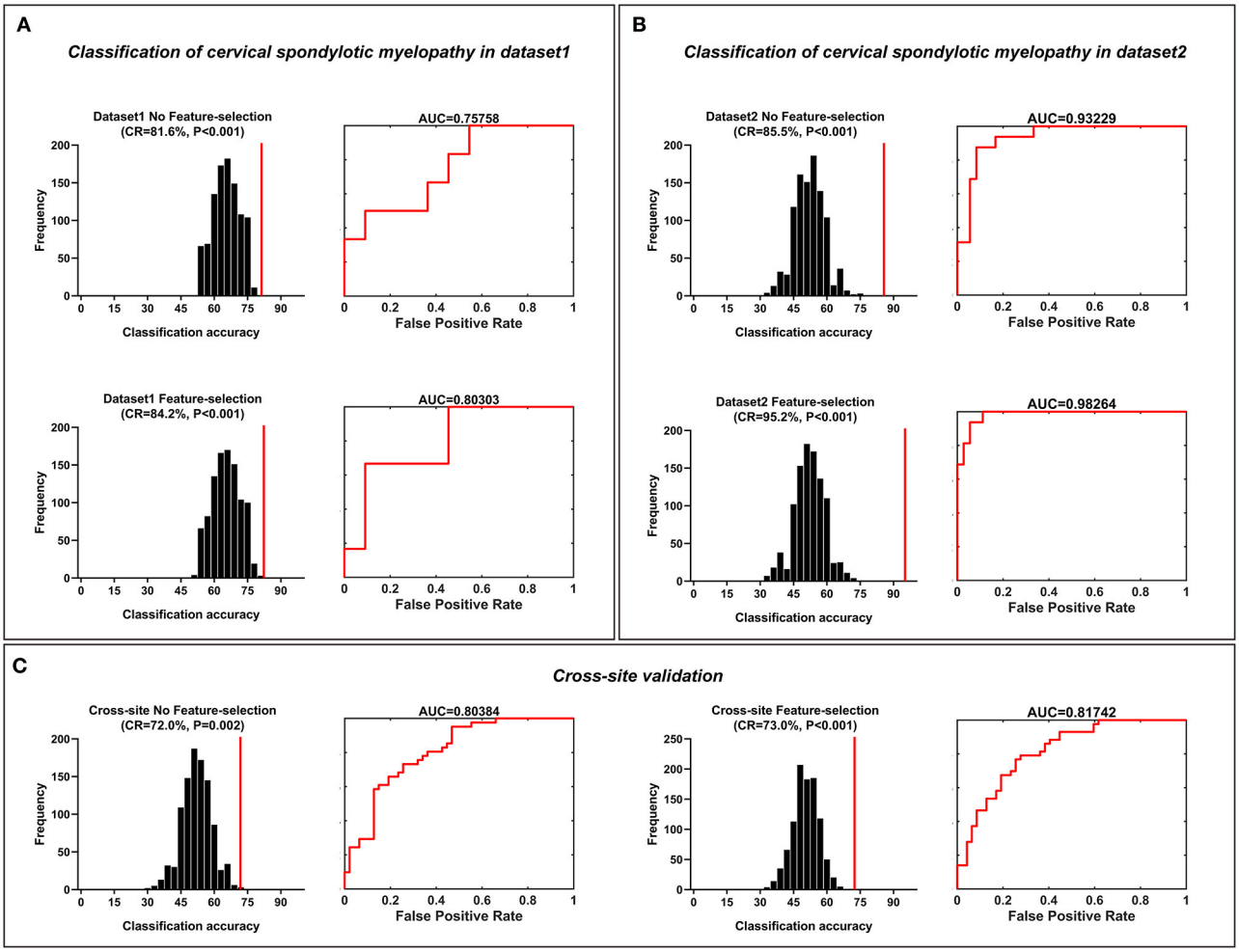


FIGURE 3 | Classification of cervical spondylotic myelopathy patients from healthy controls. Classification of cervical spondylotic myelopathy from healthy adults. **(A)** The classification accuracies obtained from both feature-selection and no-feature-selection models in dataset 1. **(B)** The classification accuracies obtained from both the feature-selection model and the no-feature-selection model in dataset 2. **(C)** The classification accuracies obtained both from both the feature-selection and no-feature-selection models during the cross-site validation procedure. The corresponding ROC curve and AUC were also illustrated. CR, correct rate; ROC, receiver operating characteristic; AUC, area the under curve.

correction) for cross-site validation. The corresponding AUCs of ROC curves were 0.76 for dataset 1, 0.93 for dataset 2, and 0.80 for cross-site validation. The highest classification accuracies that were obtained with a feature selection procedure for each dataset and cross-site validation were 84.2% ($p < 0.001$, with Bonferroni correction) for dataset 1 (the model trained with top 25% features, 1,668 FC pairs), 95.2% ($p < 0.001$, with Bonferroni correction) for dataset 2 (the model trained with top 30% features, 2,001 FC pairs), and 73.0% ($p < 0.001$, with Bonferroni correction) for cross-site validation (the model trained with top 15% features, 1,001 FC pairs). The corresponding AUCs of ROC curves were 0.80 for dataset 1, 0.98 for dataset 2, and 0.82 for cross-site validation.

Prediction of Preoperative Japanese Orthopedic Association Scores, Japanese Orthopedic Association Recovery Rate, and Japanese Orthopedic Association Recovery Scores in Cervical Spondylotic Myelopathy

The SVR results of preoperative JOA score predictions are shown in **Figure 4**. The correlation coefficients obtained with a no-feature selection procedure, between the predicted preoperative JOA scores and the actual preoperative JOA scores, were 0.40 ($p = 0.02$) for dataset 1 and 0.64 ($p = 0.001$) for dataset 2. The RMSE obtained with a no-feature selection procedure, between the predicted preoperative JOA scores and the actual preoperative

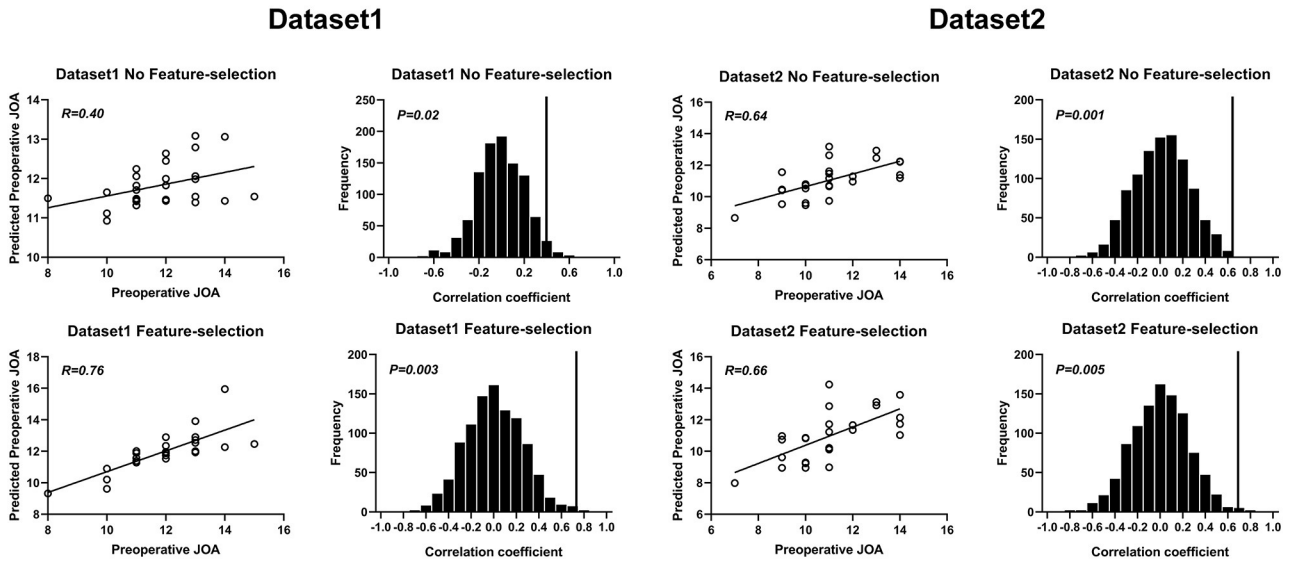


FIGURE 4 | Prediction of preoperative JOA scores using rs-FC. Prediction of preoperative JOA scores. JOA, Japanese Orthopedic Association; rs-FC, resting-state functional connectivity.

TABLE 2 | The root mean square error (RMSE) for prediction analyses.

	Pre-JOA		JOA recovery		JOA recovery rate	
	Feature selection	No feature selection	Feature selection	No feature selection	Feature selection	No feature selection
			Within site			
Dataset 1	**0.179****	**0.259***	**0.131****	**0.193***	**1.549****	**1.831***
Dataset 2	**0.257****	**0.262****	**0.365***	**0.349***	**4.342****	**4.752***
			Cross-site validation			
Dataset 1 as training set	**0.326*****	0.347	**0.260****	0.363	**3.560*****	6.736
Dataset 2 as training set	**0.236****	0.326	**0.258***	0.263	**4.475***	5.860

The root mean square error for the within-site and cross-site predictions of preoperative JOA scores, JOA recovery, and JOA recovery rate.
**p < 0.05, **p < 0.005, ***p < 0.001. Correlation coefficients with significant P values (P < 0.05) were shown in bold format.*

JOA scores, were 0.259 ($p < 0.05$, **Table 2**) for dataset 1 and 0.262 ($p < 0.005$, **Table 2**) for dataset 2.

The correlation coefficients obtained with a feature selection procedure, between the predicted preoperative JOA scores and the actual preoperative JOA scores, were 0.76 ($p = 0.003$) for dataset 1 (46 FC pairs) and 0.66 ($p = 0.005$) for dataset 2 (22 FC pairs). The RMSE obtained with a feature selection procedure, between the predicted preoperative JOA scores and the actual preoperative JOA scores, was 0.179 ($p < 0.005$, **Table 2**) for dataset 1 and 0.257 ($p < 0.005$, **Table 2**) for dataset 2.

The SVR results of JOA recovery prediction are shown in **Figure 5**. The correlation coefficients obtained with a no-feature selection procedure, between the predicted JOA recovery scores and the actual JOA recovery scores, were 0.32 ($p = 0.04$) for dataset 1 and 0.34 ($p = 0.035$) for dataset 2. The correlation coefficients obtained with a feature selection procedure, between the predicted preoperative JOA scores and the actual preoperative JOA scores, were 0.73 ($p = 0.003$) for dataset 1 (51 FC pairs) and 0.36 ($p = 0.04$) for dataset 2 (18 FC pairs). The RMSE obtained with a no-feature selection procedure, between the predicted JOA recovery scores and the actual JOA recovery scores, was 0.193 ($p < 0.05$, **Table 2**) for dataset 1 and 0.349 ($p < 0.05$, **Table 2**) for dataset 2. The RMSE obtained with a feature selection procedure, between the predicted JOA recovery scores and the actual JOA recovery scores, was 0.131 ($p < 0.005$, **Table 2**) for dataset 1 and 0.365 ($p < 0.05$, **Table 2**) for dataset 2.

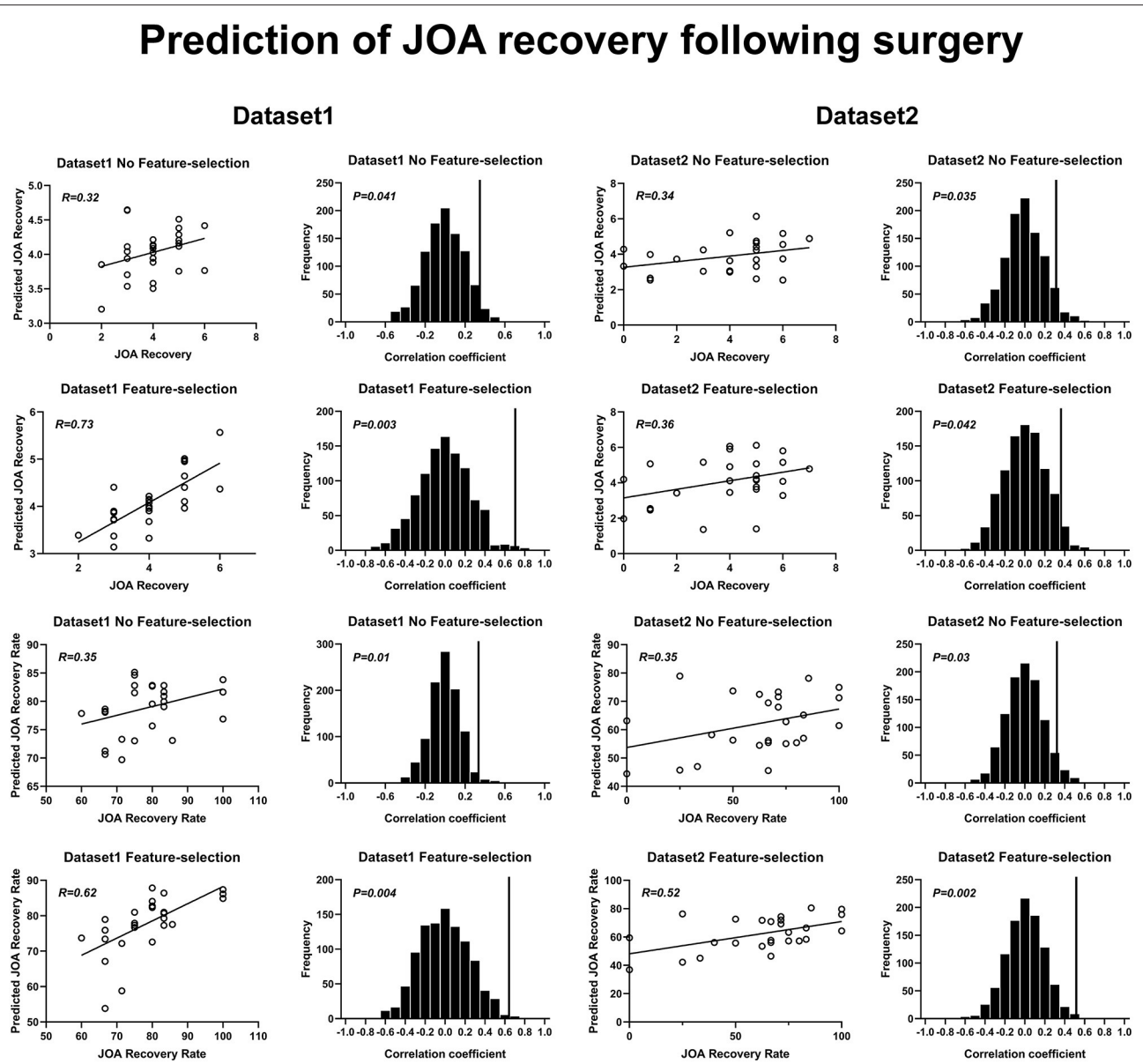


FIGURE 5 | Prediction of JOA recovery using rs-FC. Prediction of preoperative JOA scores. JOA, Japanese Orthopedic Association; rs-FC, resting-state functional connectivity. JOA recovery = postoperative JOA scores minus preoperative JOA scores.

The correlation coefficients obtained with a no-feature selection procedure, between the predicted JOA recovery rate and the actual JOA recovery rate, were 0.35 ($p = 0.01$) for dataset 1 and 0.35 ($p = 0.03$) for dataset 2. The correlation coefficients obtained with a feature selection procedure, between the JOA recovery rate and the actual JOA recovery rate, were 0.62 (35 FC pairs) ($p = 0.004$) for dataset 1 and 0.52 (27 FC pairs) ($p = 0.002$) for dataset 2. The RMSE obtained with a no-feature selection procedure, between the predicted JOA recovery rate and the actual JOA recovery rate, was 1.831 ($p < 0.05$, **Table 2**) for dataset 1 and 4.752 ($p < 0.05$, **Table 2**) for dataset 2. The RMSE obtained with a feature selection procedure, between the JOA recovery rate and the actual JOA recovery rate, was 1.549 ($p < 0.005$, **Table 2**) for dataset 1 and 4.342 ($p < 0.005$, **Table 2**) for dataset 2.

Figure 6 presents the results for cross-site validation. The correlation coefficients between the predicted preoperative JOA scores and the actual preoperative JOA scores for training sets were 0.40 ($p = 0.01$) for dataset 1 and 0.32 ($p = 0.05$) for dataset 2, respectively. The RMSE between the predicted preoperative JOA scores and the actual preoperative JOA scores for training sets was 0.347 ($p > 0.05$, **Table 2**) for dataset 1 and 0.326 ($p > 0.05$, **Table 2**) for dataset 2. After feature selection, the correlation coefficients of the training sets were 0.72 (42 FC pairs) ($p < 0.001$)

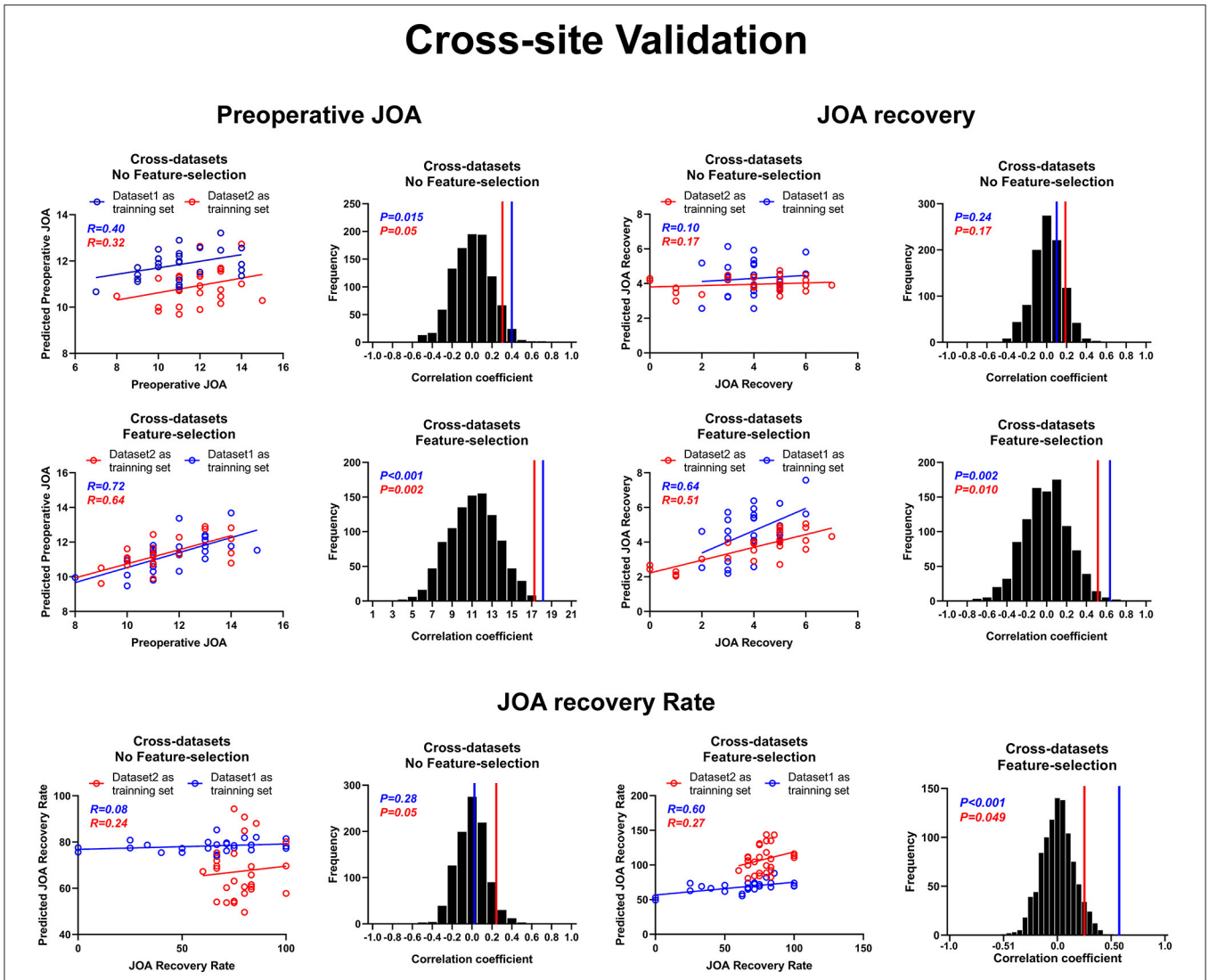


FIGURE 6 | Cross-site validation for prediction analyses. Cross-site validation of the prediction of both preoperative JOA scores and JOA recovery. JOA, Japanese Orthopedic Association. JOA recovery = postoperative JOA scores minus preoperative JOA scores.

for dataset 1 and 0.64 ($p = 0.002$) (37 FC pairs) for dataset 2. The RMSE of the training sets was 0.326 ($p < 0.001$, **Table 2**) for dataset 1 and 0.236 ($p < 0.005$, **Table 2**) for dataset 2.

The correlation coefficients between the predicted JOA recovery scores and the actual JOA recovery scores for the training sets were 0.10 ($p = 0.24$) for dataset 1 and 0.17 ($p = 0.17$) for dataset 2. The RMSE between the predicted JOA recovery scores and the actual JOA recovery scores for the training sets was 0.363 ($p > 0.05$) for dataset 1 and 0.263 ($p > 0.05$) for dataset 2. After feature selection, the correlation coefficients for the training sets were 0.64 ($p = 0.002$) for dataset 1 (31 FC pairs) and 0.51 ($p = 0.01$) for dataset 2 (26 FC pairs). After feature selection, the RMSE for the training sets was 0.260 ($p < 0.005$) for dataset 1 and 0.258 ($p < 0.05$) for dataset 2.

The correlation coefficients between the predicted JOA recovery rate and the actual JOA recovery rate for the training sets were 0.08 ($p = 0.28$) for dataset 1 and 0.24 ($p = 0.05$) for dataset 2. The RMSE between the predicted JOA recovery rate and the actual JOA recovery rate for the training sets was 6.736 ($p > 0.05$, **Table 2**) for dataset 1 and 5.860 ($p > 0.05$, **Table 2**) for dataset 2. After feature selection, the correlation coefficients for the training sets were 0.60 ($p = 0.001$) for dataset 1 (33 FC pairs) and 0.27 ($p = 0.049$) for dataset 2 (15 FC pairs). The RMSE for the training sets was 3.560 ($p < 0.001$, **Table 2**) for dataset 1 and 4.475 ($p < 0.05$, **Table 2**) for dataset 2. Further, Bland–Altman analyses revealed that 95% of points of all prediction analyses were within the LOA (see **Supplementary Materials**, **Supplementary Figures 1–3**).

The actual LOA of JOA prediction for dataset 1 was from −2.67 to 2.71 and was from −1.76 to 1.93 after feature selection. The LOA of JOA recovery prediction for dataset 1 was from −1.97 to 2.02 and was from 1.32 to 1.39 after feature selection.

The LOA of JOA recovery rate prediction for dataset 1 was from −18.44 to 19.51 and was from −16.62 to 15.46 after feature selection. The LOA of JOA prediction for dataset 2 was from −2.71 to 2.74 and was from −2.83 to 2.71 after feature selection. The LOA of JOA recovery prediction for dataset 2 was from −3.73 to 3.65 and was from −3.65 to 3.93 after feature selection. The LOA of JOA recovery rate prediction for dataset 2 was from −50.16 to 50.43 and was from −45.52 to 46.22 after feature selection.

For cross-site validation, the LOA of JOA prediction for dataset 1 as training set was from −2.40 to 4.02 and was from −3.85 to 2.17. The LOA of JOA recovery prediction for dataset 1 as training set was from −2.91 to 2.36 and was from −3.77 to 3.79 after feature selection. The LOA of JOA recovery rate prediction for dataset 1 as training set was from −40.74 to 18.86 and was from −7.23 to 66.70 after feature selection. The LOA of JOA prediction for dataset 2 as training set was from −3.83 to 1.97 and was from −2.79 to 1.75. The LOA of JOA recovery prediction for dataset 2 as training set was from −1.70 to 3.04 and was from −2.37 to 3.02 after feature selection. The LOA of JOA recovery rate prediction for dataset 2 as training set was from −36.48 to 69.07 and was from −39.63 to 51.88 after feature selection.

DISCUSSION

In this study, we conducted MVPAs of FC in patients with CSM, including (1) univariate analyses for revealing the differences for FC between CSM patients and HCs; (2) classification between CSM patients and HCs; (3) prediction of preoperative JOA scores; and (4) prediction of JOA recovery rate and JOA recovery scores. Our results demonstrated that rs-FC combined with SVM could successfully classify CSM patients from HCs and that rs-FC combined with SVR could successfully predict the neurological recovery in CSM patients. These results further indicated that MVPA approach could capture the rs-FC pattern abnormalities in CSM patients and could be used as a potential biomarker for predicting the surgical outcomes in CSM patients.

CSM is commonly seen in practice, and the preoperative grading of CSM severity and prognosis prediction are matters of great concern for clinical surgeons. Conventional cervical MRI (i.e., T1 and T2) has been used to diagnose CSM for the past decades; however, its utility for predicting CSM prognosis has been controversial (36). Several metrics measuring the morphologic changes of the spinal cord has been shown to be not so reliable for predicting surgical outcomes (37). To resolve this issue, several neuroimaging approaches, including diffusion tensor imaging (DTI) (38–40), proton magnetic resonance spectroscopy (41, 42), and electromyography combined with conventional MRI (43), have been proposed for prognostic use in CSM. It has been shown that the DTI analysis of spinal tracts might provide additional information for prognosis of CSM (39, 40). Moreover, it has been also shown that the metabolic changes of the sensorimotor cortices were also associated with the neurological recovery following decompression surgery (41, 42, 44). Other approaches, such as electromyography, have also been shown to provide prognostic information for CSM (43). However, these techniques were not easily accessible in clinical practices (i.e., long acquisition time and being invasive). Therefore, the need for simple, accurate, and non-invasive imaging biomarkers for prognostic use in CSM patients is warranted.

In recent years, researchers turned their attention to brain rs-fMRI, which is easily acquired and non-invasive in clinical practice. At the first glance, it seems surprising to develop a prognostic biomarker based on brain rs-fMRI given that CSM is not a primary cortical disorder. However, previous studies have shown that the resting-state and task fMRI were useful for developing potential neural biomarkers for assessing preoperative sensorimotor deficits in CSM patients (11). A seed-based FC study conducted by Peng et al. showed that the FCs between the anterior and the cerebellum, the anterior thalamus, and the cuneus significantly increased and positively correlated with preoperative JOA scores. Furthermore, Zhou et al. and Peng et al. observed that increased FCs between the anterior thalamus and precentral gyrus positively correlated with the upper limb motor function in CSM patients. Moreover, the resting-state FC between the thalamus and the pre/postcentral gyrus was correlated with the severity of long-term spinal cord injury (12, 45).

Recently, Takenaka and Kan (11) reported that the FC between the visual cortex and the frontal gyrus is associated with the 10-s test results and could predict postoperative neurological recovery in CSM patients. Besides, in our previous study, we demonstrated a significant correlation between the increased FC and preoperative JOA scores (46). Despite these studies demonstrating that several rs-fMRI metrics may be useful for presurgical evaluation in CSM patients, these studies only conducted univariate correlation analysis for revealing the linear association between brain metrics and outcome measures. Therefore, the pattern (i.e., consisted of multi-voxels or multi-connections) information, which could be detected by the MVPA, may be ignored by conventional approach.

In this study, we conducted an FC analysis and constructed the whole-brain network. We tested the utility of classification of CSM patients from HCs using FCs as features *via* an SVM. We obtained good performance both within datasets and across two independent datasets. Moreover, the model's performances were also increased after feature selection. Our findings indicated that the classification accuracies were high within each dataset and could be generalized between two independent datasets acquired by different MR machines. Therefore, our findings suggest that the rs-FC may be instrumental in the diagnosis of CSM in patients.

Moreover, we assessed the potential utility of rs-FC in the presurgical evaluation of CSM using the SVR. We obtained successful regression between rs-FC and the preoperative neurological function (e.g., preoperative JOA scores) in CSM patients since all correlation coefficients were above 0.4 before feature selection and above 0.6 after feature selection (all p-values < 0.05 after permutation test and family-wise error (FWE) correction). These findings also showed good generalization across the two datasets. Therefore, our current results provided preliminary evidence that the pattern of rs-FC is associated

with the presurgical neurological function in CSM patients and may aid the evaluation of CSM patients for research purposes. It is obvious that there are differences in the predicted and actual JOA scores. Two main reasons may contribute to these differences. First, rs-fMRI data constitute multiple sources of noise during data collection (e.g., respiratory or cardiac noise). Despite that the preprocessing steps could largely increase the noise-to-signal ratio of rs-fMRI data. There still were unexpected noises, which may affect the accuracy of the prediction analysis. Second, although JOA scale is the most commonly used and robust clinical measure for evaluating the severity of CSM, it only measures the sensorimotor aspect of the CSM patients (e.g., sensory, motor, and bowel and bladder deficits). Other psychological factors (e.g., cognitive deficits and depression), which have also shown to be associated with the CSM, could not be evaluated by the JOA scale. Therefore, such measurement error may also contribute to the prediction error between actual JOA scores and predicted JOA scores.

Besides, we explored the association between the rs-FC and prognosis of CSM *via* SVR, using preoperative rs-FCs as features and the sensorimotor recovery following spinal cord decompression surgery (JOA recovery or JOA recovery rate) as labels. Despite the successful prediction of the JOA recovery scores in each dataset, the correlation coefficients were relatively low except for the prediction of JOA scores after feature selection in dataset 1. The cross-site prediction performances were also relatively poor ($R = 0.10/0.17$ before feature selection; $R = 0.51/0.64$ after feature selection) compared with the prediction of preoperative JOA scores. This may be attributable to various factors such as age, disease duration, presurgical neurological state, spinal cord DTI signal, and surgical approaches, which affect the prognosis of CSM (2, 4, 47, 48); thus, it would make the prediction harder than we expected. It is worth mentioning that the outcome of the JOA recovery prediction by SVR is generally poor. Interestingly, within the low performance, the model appears to perform better on dataset 1 than on dataset 2, though the opposite was true in classifying patients from HCs. This is likely to reflect the fact that myriad factors in postoperative recovery may not be captured by the rs-FC data. Moreover, the non-generalizability of the cross-site prediction before feature selection may be due to the different sets of features selected during the training process, thus making the cross-site prediction harder. It is also worth mentioning that the poor prediction for JOA recovery could also be attributed to the SVR itself. Before feature selection, there were 6,670 features included in the SVR model; however, there were only <100 samples for training the model. Overfitting of these models could also be a major cause of poor prediction. The improvements of prediction accuracy after feature selection could further support this speculation due to the fact that feature selection procedure could remove redundant features to some extent.

For clinical significance, the Bland–Altman analyses were performed to reveal the clinical significance of the prediction analyses. In the case for JOA prediction, the minimum clinically important difference of the JOA has been shown to be 1–2 points (49); and the minimum clinically important difference of the JOA recovery rate has shown to be 52.8% in CSM patients (50). In our current analysis, the 95% LOA exceeded these, meaning that the predicted data could deviate from the actual JOA score (or actual JOA recovery rate) by more than what is accepted as a clinically meaningful change. These results indicated that predicting CSM-related outcomes is not yet robust enough for accurate predictions (e.g., for clinical purpose), though it does show promise and could be developed with a bigger dataset or with other outcome variables.

LIMITATIONS

Since our study only used rs-FC as features to classify CSM patients and predict clinical measures, other rs-fMRI metrics and feature fusion approach are needed in the future to develop more accurate diagnostic and prognostic models for CSM. Moreover, our current study is a retrospective study and lack repeatability analysis (when tested on the same individual at two different time points under the same conditions). Therefore, it may be a potential confounder of unknown significance. As mentioned above, our study is a retrospective study; therefore, the sample size and the statistical power have not been estimated, and the prediction analyses were performed after the data collection of follow-up information. Prospective study using more rigorous statistical analyses and directly comparing the prediction accuracy between orthopedic surgeon and machine learning techniques is required in the future. Furthermore, we did not collect postoperative fMRI data due to possible artifacts and MRI heating of implants. Therefore, we recommend long-term follow-up before postoperative data collection for safety. Additionally, spinal cord MR data, including the DTI, diffusion spectrum imaging (DSI), and functional scan, should be collected in the future to obtain more information on CSM. Future studies may need to add the clinical information and spinal cord MR data to the prediction model to improve the prediction performance.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Tianjin Medical University General Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

QS and FY designed this study. SW, RZ, and HT collected the data. RZ wrote the manuscript. XG revised the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This study was funded by the Tianjin Medical University Cancer Institute and Hospital Fund (Grant No. B19 02).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.711880/full#supplementary-material

REFERENCES

1. Boogaarts HD, Bartels RH. Prevalence of cervical spondylotic myelopathy. *Euro Spine J.* (2015) 2:139–41. doi: 10.1007/s00586-013-2781-x
2. Iyer A, Azad TD, Tharin S. Cervical spondylotic myelopathy. *Clin Spine Surg.* (2016) 29:408–14. doi: 10.1097/BSD.0000000000000397
3. Karadimas SK, Gatzounis G, Fehlings MG. Pathobiology of cervical spondylotic myelopathy. *Euro Spine J.* (2015) 2:132–8. doi: 10.1007/s00586-014-3264-4
4. Kalsi-Ryan S, Karadimas SK, Fehlings MG. Cervical spondylotic myelopathy: the clinical phenomenon and the current pathobiology of an increasingly prevalent and devastating disorder. *Neuroscientist.* (2013) 19:409–21. doi: 10.1177/1073858412467377
5. Lebl DR, Bono CM. Update on the diagnosis and management of cervical spondylotic myelopathy. *J Am Acad Orthopaedic Surg.* (2015) 23:648–60. doi: 10.5435/JAAOS-D-14-00250
6. Machino M, Yukawa Y, Ito K, Nakashima H, Kato F. Dynamic changes in dural sac and spinal cord cross-sectional area in patients with cervical spondylotic myelopathy: cervical spine. *Spine.* (2011) 36:399–403. doi: 10.1097/BRS.0b013e3181d2510b
7. Aleksanderek I, McGregor SMK, Stevens TK, Goncalves S, Bartha R, Duggal N. Cervical spondylotic myelopathy: metabolite changes in the primary motor cortex after surgery. *Radiology.* (2017) 282:817–25. doi: 10.1148/radiol.2016152083
8. Bhagavatula ID, Shukla D, Sadashiva N, Saligoudar P, Prasad C, Bhat DI. Functional cortical reorganization in cases of cervical spondylotic myelopathy and changes associated with surgery. *Neurosurg Focus.* (2016) 40:E2. doi: 10.3171/2016.3.FOCUS1635
9. Biswal BB, Kylen JV, Hyde JS. Simultaneous assessment of flow and BOLD signals in resting-state functional connectivity. *NMR Biomed.* (1997) 10:165–70. doi: 10.1002/(SICI)1099-1492(199706/08)10:4/5<165::AID-NBM454>3.0.CO;2-7
10. Liu X, Qian W, Jin R, Li X, Luk KD, Wu EX, et al. Amplitude of low frequency fluctuation (ALFF) in the cervical spinal cord with stenosis: a resting state fMRI study. *PLoS ONE.* (2016) 11:e0167279. doi: 10.1371/journal.pone.0167279
11. Takenaka S, Kan S. Towards prognostic functional brain biomarkers for cervical myelopathy: a resting-state fMRI study. (2019) 9:10456. doi: 10.1038/s41598-019-46859-5
12. Tan Y, Zhou F, Wu L, Liu Z, Zeng X, Gong H, et al. Alteration of regional homogeneity within the sensorimotor network after spinal cord decompression in cervical spondylotic myelopathy: a resting-state fMRI study. *BioMed Research Int.* (2015) 2015:647958. doi: 10.1155/2015/647958
13. Zhou FQ, Tan YM, Wu L, Zhuang Y, He LC, Gong HH. Intrinsic functional plasticity of the sensory-motor network in patients with cervical spondylotic myelopathy. *Sci Rep.* (2015) 5:9975. doi: 10.1038/srep09975
14. Kuang C, Zha Y. Abnormal intrinsic functional activity in patients with cervical spondylotic myelopathy: a resting-state fMRI study. *Neuropsychiatric Dis Treatment.* (2019) 15:2371–83. doi: 10.2147/NDT.S209952
15. Takenaka S, Kan S, Seymour B, Makino T, Sakai Y, Kushioka J, et al. Resting-state amplitude of low-frequency fluctuation is a potentially useful prognostic functional biomarker in cervical myelopathy. *Clin Orthopaedics Related Res.* (2020) 478:1667–80. doi: 10.1097/CORR.0000000000001157
16. Khosla M, Jamison K, Ngo GH, Kuceyeski A, Sabuncu MR. Machine learning in resting-state fMRI analysis. *Magnetic Resonance Imaging.* (2019) 64:101–21. doi: 10.1016/j.mri.2019.05.031
17. Matthews M, Fair DA. Research review: functional brain connectivity and child psychopathology - overview and methodological considerations for investigators new to the field. *J Child Psychol Psychiatry.* (2015) 56:400–14. doi: 10.1111/jcpp.12335
18. Fernandez Rojas R, Huang X, Ou KL. A machine learning approach for the identification of a biomarker of human pain using fNIRS. *Sci Rep.* (2019) 9:5645. doi: 10.1038/s41598-019-42098-w
19. Harper DE, Shah Y, Ichesco E, Gerstner GE, Peltier SJ. Multivariate classification of pain-evoked brain activity in temporomandibular disorder. *Pain Rep.* (2016) 1:e572. doi: 10.1097/PR9.0000000000000572
20. Chen H, Duan XJ, Liu F, Lu FM, Ma XJ, Zhang YX, et al. Multivariate classification of autism spectrum disorder using frequency-specific resting-state functional connectivity-a multi-center study. *Progress Neuro-Psychopharmacol Biol Psychiatry.* (2016) 64:1–9. doi: 10.1016/j.pnpbp.2015.06.014
21. Liu F, Guo WB, Fouche JP, Wang YF, Wang WQ, Ding JR, et al. Multivariate classification of social anxiety disorder using whole brain functional connectivity. *Brain Struct Funct.* (2015) 220:101–15. doi: 10.1007/s00429-013-0641-4
22. Vergun S, Gaggle W, Nair VA, Suhonen JI, Birn RM, Ahmed AS, et al. Classification and extraction of resting state networks using healthy and epilepsy fMRI data. *Front Neurosci.* (2016) 10:440. doi: 10.3389/fnins.2016.00440
23. Meier TB, Desphande AS, Vergun S, Nair VA, Song J, Biswal BB, et al. Support vector machine classification and characterization of age-related reorganization of functional brain networks. *Neuroimage.* (2012) 60:601–13. doi: 10.1016/j.neuroimage.2011.12.052
24. Sundermann B, Herr D, Schwindt W, Pfleiderer B. Multivariate classification of blood oxygen level-dependent fMRI data with diagnostic intention: a clinical perspective. *Am J Neuroradiol.* (2014) 35:848–55. doi: 10.3174/ajnr.A3713
25. Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc Natl Acad Sci USA.* (2003) 100:253–8. doi: 10.1073/pnas.0135058100
26. Hutchison RM, Womelsdorf T, Allen EA, Bandettini PA, Calhoun VD, Corbetta M, et al. Dynamic functional connectivity: promise, issues, and interpretations. *Neuroimage.* (2013) 80:360–78. doi: 10.1016/j.neuroimage.2013.05.079
27. Tomasi D, Volkow ND. Functional connectivity hubs in the human brain. *Neuroimage.* (2011) 57:908–17. doi: 10.1016/j.neuroimage.2011.05.024
28. Chen B, Xu T, Zhou C, Wang L, Yang N, Wang Z, et al. Individual variability and test-retest reliability revealed by ten repeated resting-state brain scans over one month. *PLoS ONE.* (2015) 10:e0144963. doi: 10.1371/journal.pone.0144963
29. Huang L, Huang T, Zhen Z, Liu J. A test-retest dataset for assessing long-term reliability of brain morphology and resting-state brain activity. *Sci Data.* (2016) 3:160016. doi: 10.1038/sdata.2016.16
30. Zhang H, Chen X, Zhang Y, Shen D. Test-retest reliability of "high-order" functional connectivity in young healthy adults. *Front Neurosci.* (2017) 11:439. doi: 10.3389/fnins.2017.00439
31. Chen Z, Wang Q, Liang M, Zhao R, Zhu J, Xiong W, et al. Visual cortex neural activity alteration in cervical spondylotic myelopathy patients: a resting-state fMRI study. *Neuroradiology.* (2018) 60:921–932. doi: 10.1007/s00234-018-2061-x
32. Zhao R, Su Q, Chen Z, Sun H, Liang M, Xue Y. Neural correlates of cognitive dysfunctions in cervical spondylotic myelopathy patients: a resting-state fMRI study. *Front Neurol.* (2020) 11:596795. doi: 10.3389/fneur.2020.596795
33. Fukui M, Chiba K, Kawakami M, Kikuchi S, Konno S, Miyamoto M, et al. Japanese orthopaedic association cervical myelopathy evaluation questionnaire: part 3. Determination of reliability. *J Orthopaedic Sci.* (2007) 12:321–6. doi: 10.1007/s00776-007-1131-4

34. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage.* (2002) 15:273–89. doi: 10.1006/nimg.2001.0978
35. Peng Y, Zhang X, Li Y, Su Q, Wang S, Liu F, et al. MVPANI: a toolkit with friendly graphical user interface for multivariate pattern analysis of neuroimaging data. *Front Neurosci.* (2020) 14:545. doi: 10.3389/fnins.2020.00545
36. Li XY, Lu SB, Sun XY, Kong C, Guo MC, Sun SY, et al. Clinical and magnetic resonance imaging predictors of the surgical outcomes of patients with cervical spondylotic myelopathy. *Clin Neurol Neurosurg.* (2018) 174:137–43. doi: 10.1016/j.clineuro.2018.09.003
37. Vedantam A, Jonathan A, Rajshekhar V. Association of magnetic resonance imaging signal changes and outcome prediction after surgery for cervical spondylotic myelopathy. *J Neurosurg Spine.* (2011) 15:660–6. doi: 10.3171/2011.8.SPINE11452
38. Jones JG, Cen SY, Lebel RM, Hsieh PC, Law M. Diffusion tensor imaging correlates with the clinical assessment of disease severity in cervical spondylotic myelopathy and predicts outcome following surgery. *Am J Neuroradiol.* (2013) 34:471–8. doi: 10.3174/ajnr.A3199
39. Wang KY, Idowu O, Thompson CB, Orman G, Myers C, Riley LH, et al. Tract-specific diffusion tensor imaging in cervical spondylotic myelopathy before and after decompressive spinal surgery: preliminary results. *Clin Neuroradiol.* (2017) 27:61–9. doi: 10.1007/s00062-015-0418-7
40. Wen CY, Cui JL, Mak KC, Luk KD, Hu Y. Diffusion tensor imaging of somatosensory tract in cervical spondylotic myelopathy and its link with electrophysiological evaluation. *Spine J.* (2014) 14:1493–500. doi: 10.1016/j.spinee.2013.08.052
41. Aleksanderek I, Stevens TK, Goncalves S, Bartha R, Duggal N. Metabolite and functional profile of patients with cervical spondylotic myelopathy. *J Neurosurg Spine.* (2017) 26:547–53. doi: 10.3171/2016.9.SPINE151507
42. Craciunas SC, Gorgan MR, Ianosi B, Lee P, Burris J, Cirstea CM. Remote motor system metabolic profile and surgery outcome in cervical spondylotic myelopathy. *J Neurosurg Spine.* (2017) 26:668–78. doi: 10.3171/2016.10.SPINE16479
43. Liu FJ, Sun YP, Shen Y, Ding WY, Wang LF. Prognostic value of magnetic resonance imaging combined with electromyography in the surgical management of cervical spondylotic myelopathy. *Exp Ther Med.* (2013) 5:1214–8. doi: 10.3892/etm.2013.934
44. Dong Y, Holly LT, Albistegui-Dubois R, Yan X, Marehbian J, Newton JM, et al. Compensatory cerebral adaptations before and evolving changes after surgical decompression in cervical spondylotic myelopathy. *J Neurosurg Spine.* (2008) 9:538–51. doi: 10.3171/SPI.2008.10.0831
45. Peng X, Tan Y, He L, Ou Y. Alterations of functional connectivity between thalamus and cortex before and after decompression in cervical spondylotic myelopathy patients: a resting-state functional MRI study. *Neuroreport.* (2020) 31:365–71. doi: 10.1097/WNR.0000000000001346
46. Chen Z, Zhao R, Wang Q, Yu C, Li F, Liang M, et al. Functional connectivity changes of the visual cortex in the cervical spondylotic myelopathy patients: a resting-state fMRI study. *Spine.* (2020) 45:E272–9. doi: 10.1097/BRS.0000000000003245
47. Lv Y, Tian W, Chen D, Liu Y, Wang L, Duan F. The prevalence and associated factors of symptomatic cervical Spondylosis in Chinese adults: a community-based cross-sectional study. *BMC Musculoskeletal Disord.* (2018) 19:325. doi: 10.1186/s12891-018-2234-0
48. Toledano M, Bartleson JD. Cervical spondylotic myelopathy. *Neurol Clin.* (2013) 31:287–305. doi: 10.1016/j.ncl.2012.09.003
49. Tetreault L, Nouri A, Kopjar B, Côté P, Fehlings MG. The minimum clinically important difference of the modified japanese orthopaedic association scale in patients with degenerative cervical myelopathy. *Spine.* (2015) 40:1653–9. doi: 10.1097/BRS.0000000000001127
50. Kato S, Oshima Y, Matsubayashi Y, Taniguchi Y, Tanaka S, Takeshita K. Minimum clinically important difference and patient acceptable symptom state of japanese orthopaedic association score in degenerative cervical myelopathy patients. *Spine.* (2019) 44:691–7. doi: 10.1097/BRS.0000000000002928

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2021 Su, Zhao, Wang, Tu, Guo and Yang. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Neurology

ORIGINAL RESEARCH
published: 20 October 2021
doi: 10.3389/fneur.2021.733035

Altered Brain Structure in Chronic Visceral Pain: Specific Differences in Gray Matter Volume and Associations With Visceral Symptoms and Chronic Stress

*Hanna Öhlmann[1], Laura Ricarda Koenen[2], Franziska Labrenz[1], Harald Engler[2], Nina Theysohn[3], Jost Langhorst[4,5] and Sigrid Elsenbruch[1,6]**

[1] Department of Medical Psychology and Medical Sociology, Ruhr University Bochum, Bochum, Germany, [2] Institute of Medical Psychology and Behavioral Immunobiology, Center for Translational Neuro-and Behavioral Sciences, University Hospital Essen, University of Duisburg-Essen, Essen, Germany, [3] Institute of Diagnostic and Interventional Radiology and Neuroradiology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany, [4] Department for Internal and Integrative Medicine, Sozialstiftung Bamberg, Bamberg, Germany, [5] Department for Integrative Medicine, Medical Faculty, University of Duisburg-Essen, Essen, Germany, [6] Department of Neurology, Center for Translational Neuro- and Behavioral Sciences, University Hospital Essen, University of Duisburg-Essen, Essen, Germany

OPEN ACCESS

Edited by:
Susanne Becker,
University of Zurich, Switzerland

Reviewed by:
Ravi Bhatt,
University of Southern California,
United States
Luke Henderson,
The University of Sydney, Australia

***Correspondence:**
Sigrid Elsenbruch
sigrid.elsenbruch@ruhr-uni-bochum.de

Specialty section:
This article was submitted to
Applied Neuroimaging,
a section of the journal
Frontiers in Neurology

Received: 29 June 2021
Accepted: 21 September 2021
Published: 20 October 2021

Citation:
Öhlmann H, Koenen LR, Labrenz F, Engler H, Theysohn N, Langhorst J and Elsenbruch S (2021) Altered Brain Structure in Chronic Visceral Pain: Specific Differences in Gray Matter Volume and Associations With Visceral Symptoms and Chronic Stress. Front. Neurol. 12:733035. doi: 10.3389/fneur.2021.733035

Structural brain alterations in chronic pain conditions remain incompletely understood, especially in chronic visceral pain. Patients with chronic-inflammatory or functional bowel disorders experience recurring abdominal pain in concert with other gastrointestinal symptoms, such as altered bowel habits, which are often exacerbated by stress. Despite growing interest in the gut-brain axis and its underlying neural mechanisms in health and disease, abnormal brain morphology and possible associations with visceral symptom severity and chronic stress remain unclear. We accomplished parallelized whole-brain voxel-based morphometry analyses in two patient cohorts with chronic visceral pain, i.e., ulcerative colitis in remission and irritable bowel syndrome, and healthy individuals. In addition to analyzing changes in gray matter volume (GMV) in each patient cohort vs. age-matched healthy controls using analysis of covariance (ANCOVA), multiple regression analyses were conducted to assess correlations between GMV and symptom severity and chronic stress, respectively. ANCOVA revealed reduced GMV in frontal cortex and anterior insula in ulcerative colitis compared to healthy controls, suggesting alterations in the central autonomic and salience networks, which could however not be confirmed in supplemental analyses which rigorously accounted for group differences in the distribution of sex. In irritable bowel syndrome, more widespread differences from healthy controls were observed, comprising both decreased and increased GMV within the sensorimotor, central executive and default mode networks. Associations between visceral symptoms and GMV within frontal regions were altered in both patient groups, supporting a role of the central executive network across visceral pain conditions. Correlations with chronic stress, on the other hand, were only found for irritable bowel syndrome, encompassing numerous brain regions and networks. Together, these findings complement and expand existing brain imaging evidence in

chronic visceral pain, supporting partly distinct alterations in brain morphology in patients with chronic-inflammatory and functional bowel disorders despite considerable overlap in symptoms and comorbidities. First evidence pointing to correlations with chronic stress in irritable bowel syndrome inspires future translational studies to elucidate the mechanisms underlying the interconnections of stress, visceral pain and neural mechanisms of the gut-brain axis.

Keywords: chronic visceral pain, gut-brain axis, inflammatory bowel disease, ulcerative colitis, irritable bowel syndrome, gray matter volume, voxel-based morphometry, chronic stress

INTRODUCTION

Despite substantial individual and societal burden, chronic pain is often overlooked and remains incompletely understood, especially with respect to brain mechanisms relevant to pathophysiology, disease course, and treatment. Clinical conditions characterized by chronic visceral or pelvic pain are particularly understudied using brain imaging techniques. Dedicated visceral pain research is warranted not only given the unique clinical presentation of chronic visceral pain. Many afflicted patients do not experience pain arising from the viscera (i.e., inner organs such as the thorax, pelvis or abdomen) in isolation, but rather suffer from recurring episodes of abdominal pain or discomfort in concert with other gastrointestinal (GI) symptoms, such as bowel disturbances. Work in visceral pain is also called for in light of increasing knowledge about the specificity of visceral pain both in terms of psychological as well as central mechanisms. In contrast to somatic pain, visceral pain is perceived as more diffuse and more unpleasant, provokes more pain-related fear, may be more sensitive to stress (1–4), and, importantly, engages partly distinct functional brain responses, at least during acute experimental pain (2, 5). Finally, the clinical relevance of chronic visceral pain is enormous, with a prevalence that likely surpasses even that of chronic low back and neck-shoulder pain. Indeed, intermittent abdominal pain is experienced by 25 % of adults in the general population (6), and also constitutes the most prevalent GI symptom that causes outpatient clinic visits in the United States (7).

Numerous GI conditions are characterized by visceral pain and pain-related symptoms arising from the GI tract, together contributing to substantial psychological distress, functional disability, and healthcare costs (8). The most prominent GI conditions are traditionally classified as either structural diseases with a clear organic pathology, such as chronic-inflammatory bowel diseases (IBD), or as functional disorders lacking a clearly identifiable organic cause, like irritable bowel syndrome (IBS). IBD is a relapsing-remitting disease mainly characterized by chronic intestinal inflammation, with the localization of intestinal inflammation defining the specific diagnosis of ulcerative colitis (UC; primarily affecting the colon) and Crohn's disease (affecting various GI sites) (9). Of note, about 35% of patients with IBD experience abdominal pain and changes in bowel habits not only during active but also in phases of inactive disease, when the clinical presentation can mirror that of IBS (10). IBS is considered a bio-psycho-social disorder of gut-brain interaction, with unclear etiology yet long-standing appreciation for a crucial role of brain mechanisms relevant to visceral hypersensitivity and hypervigilance, interacting with peripheral factors like increased gut permeability and low-grade inflammation (11). Despite differences in etiology and pathophysiology, psychological factors, especially stress, play a major role in both IBD and IBS, in line with evolving concepts of the gut-brain axis (12, 13).

The role of psychological factors in acute and chronic visceral pain has inspired translational research elucidating the complex signaling pathways between the GI system and the brain, both in health and disease. There exist multiple connections between the gut and the central nervous system involving microbial, immunological, metabolic, hormonal, and neural processes (14). Chronic abdominal pain can be conceptualized as a dysregulation in this complex interplay (15). As the brain is a highly dynamic system, this dysregulation conceivably implies not only changes in functional but also structural brain imaging measures, in line with broad evidence of morphological brain alterations in various somatic chronic pain conditions (16–18). A meta-analysis by Cauda and colleagues revealed that different chronic pain conditions share alterations of gray matter volume (GMV) in regions of the default-mode, thalamus-basal ganglia and attention networks, while GMV changes in sensory networks are more variable and depend on the specific chronic pain condition (19). In chronic visceral pain, the presence and putative role of morphological brain changes has been much more extensively studied in IBS than in IBD. For IBS, systematic reviews support structural alterations in regions of the prefrontal, salience, emotional arousal and sensorimotor networks, with GMV decreases in the insular cortex and GMV increases in sensorimotor cortices as most consistent findings (20–22). In IBD, knowledge about altered brain morphology is very limited, especially in UC. Results are inconsistent, and mostly available for cohorts comprising only patients with Crohn's disease (23–27) or mixed samples of Crohn's disease and UC (28, 29). Only a single study focused exclusively on patients with UC (30), despite indications for differences in brain morphology and function between UC and Crohn's disease (29).

Furthermore, efforts to elucidate correlations between structural brain abnormalities and relevant pain-related GI symptoms, as well as with chronic stress as a major psychological factor relevant to the pathophysiology, disease course, and treatment in both IBS and IBD (31, 32), have rarely been accomplished. In IBS, structural alterations have been shown to

correlate not only with GI symptoms, but also with psychological variables, including psychiatric comorbidities (33, 34), pain catastrophizing (34), and early trauma (35), but perceived chronic stress as a major factor has not been studied. This research gap also exists for IBD, with only a single existing study testing correlations between brain function (rather than structure) and acute stress (36). Given long-standing knowledge that chronic rather than acute stress is relevant to symptom exacerbation (37, 38) as well as to pain and health-related quality of life in IBD (39), attention to chronic stress in brain imaging studies is urgently called for.

To close research gaps in structural neuroimaging studies focused on patients with chronic visceral pain, we herein present results of parallelized voxel-based morphometry analyses accomplished in patients with UC and patients with IBS, compared to matched healthy control groups. In order to minimize effects of acute inflammation and severe symptoms characterizing phases of active disease, we only included patients in full remission or with very mild and stable disease activity, at the same time minimizing possible effects of medical treatments routinely necessary in these patients, especially during exacerbations. As a first step in the analysis strategy, voxel-based morphometry was accomplished to determine changes in GMV in each patient group compared to healthy controls, using whole-brain analyses given variability of findings and the widespread structural alterations observed in previous studies. Although alterations in GMV compared to controls were expected in both disorders, differences were hypothesized to be more pronounced and widespread in IBS than in UC given differences in the etiology and pathophysiology, especially regarding the presumably more prominent role of central mechanisms along the gut-brain axis in IBS. As a second step, we performed analyses aiming to address associations with symptom severity and chronic stress in each patient cohort compared to controls using multiple regression analyses. Given overlap in symptoms experienced by patients with UC and IBS and evidence for the role of stress in both disorders (12), it was hypothesized that both symptom severity and chronic stress are differentially related to GMV in both patient groups compared to healthy controls. Here, we expected effects in neural networks previously shown to be relevant to symptom intensity and psychological modulation of acute and chronic visceral pain [e.g., sensorimotor and emotional arousal networks; (20)].

METHODS

Overview and Procedures

For the purposes of the present analyses, we used data from a total of $N = 96$ adult volunteers ($N = 31$ UC, $N = 23$ IBS, $N = 44$ healthy controls), acquired within two comprehensive visceral pain studies conducted by our group between the years 2015 and 2020 at the University Hospital Essen, Germany. Primary studies involved different emotional learning/memory tasks (data will be presented elsewhere), all accomplished subsequent to the acquisition of data analyzed herein. Importantly, all participants underwent sociodemographic, psychological and clinical characterization and structural magnetic resonance imaging (MRI) prior to other experimental manipulations. Highly standardized and parallelized procedures were implemented for recruitment, screening and all other assessments that are part of this report, all accomplished within the same biomedical research setting using the same MR scanner. Work was conducted in accordance with The Declaration of Helsinki, and studies were approved by the local Ethics Committee of the University Hospital Essen (protocol numbers. 10-4493; 16-7237). All volunteers gave written informed consent and received monetary compensation for participation.

Inclusion and Exclusion Criteria

The screening process consisted of a standardized telephone screening, followed by an on-site visit with study staff, and completion of questionnaires (for details on questionnaires, see below). General exclusion criteria for all participants included age <18 or >65 years, body mass index <18 or >30, MRI-specific criteria like claustrophobia, pregnancy or ferromagnetic implants, and any evidence of structural brain abnormalities, verified by a neuroradiologist (author NT). Pregnancy was ruled out using a commercially available pregnancy test on the day of the MRI (Biorepair GmbH, Sinsheim, Germany, sensitivity 10 mIU/ml). For healthy controls, additional exclusion criteria included any known somatic or mental health condition, clinically-relevant anxiety or depression symptoms based on Hospital Anxiety and Depression Scale (HADS), or regular use of medications (except hormonal contraceptives, hormone replacement therapy, thyroid medication, irregular over-the-counter non-prescription drugs). For the UC group, only patients in clinical remission or with very low ongoing disease activity were included to avoid interference of active disease with study-related procedures, and to minimize putative effects of acute inflammation (or medical treatments required during phases of disease exacerbation) on study-related measures of interest acquired herein. Clinical disease activity was assessed based on symptom reports, initially evaluated in a structured screening interview, and then quantified with the Clinical Colitis Activity Index [CAI; (40)]. In addition, levels of fecal calprotectin were quantified, providing a non-invasive marker of intestinal inflammation (41), with an established reliable cut-off value indicating clinical remission below 150 μg (42). Treatment with systemic glucocorticoids within 4 weeks of the study were exclusionary. Other concomitant medications, which were continued as prescribed by the treating physician, were recorded. For IBS, symptom-based confirmation of diagnostic criteria was based on ROME IV criteria (43). Regular prescribed or non-prescribed IBS-related medications including low-dose treatment with antidepressants were not discontinued for the study. While minor and stable (or successfully treated) psychological symptoms, such as mild anxiety or depression symptoms (including elevated HADS scores) were not exclusionary, patients with diagnosed, more severe psychiatric comorbidities were excluded. Note that given frequent reporting of additional extraintestinal pain symptoms in IBS and IBD (44, 45), patients who reported such symptoms in addition to symptoms of their primary GI diagnoses were not excluded, but other types of

TABLE 1 | Sociodemographic, clinical, and psychological self-report data.

	UC (*N* = 31)	HC_{UC} (*N* = 31)	*p**	IBS (*N* = 23)	HC_{IBS} (*N* = 23)	*p**
Sex (Females, *N*)	26 F	31 F	–	23 F	23 F	–
Age, years	41.45 ± 12.82	41.61 ± 11.91	0.959	46.91 ± 10.92	43.74 ± 12.17	0.357
BMI	23.61 ± 3.80	22.33 ± 2.53	0.124	23.13 ± 4.02	23.31 ± 2.72	0.861
Gastrointestinal symptoms (total sum)	8.45 ± 6.47	3.35 ± 2.68	<0.001	15.09 ± 4.88	3.70 ± 3.15	<0.001
Lower abdominal pain (1 item)	1.06 ± 1.06	0.32 ± 0.54	0.001	1.87 ± 1.06	0.43 ± 0.66	0.001
Upper abdominal pain (1 item)	0.48 ± 0.89	0.16 ± 0.37	0.07	0.78 ± 0.85	0.13 ± 0.34	0.002
Psychological distress (HADS total)	9.65 ± 4.72	6.42 ± 3.82	0.004	15.09 ± 6.09	6.48 ± 4.38	<0.001
Anxiety symptoms (HADS_A)	6.32 ± 2.82	3.77 ± 2.32	<0.001	9.09 ± 3.27	3.61 ± 2.54	<0.001
Depression symptoms (HADS_D)	3.32 ± 2.83	2.65 ± 2.17	0.295	6.00 ± 3.30	2.87 ± 2.47	0.001
Chronic stress (TICS)	19.32 ± 8.98	16.32 ± 9.22	0.199	25.17 ± 8.58	15.04 ± 9.44	<0.001

**Results of two-tailed independent-samples t-tests comparing each patient group and the matched control group. Data are shown as mean ± standard deviation, unless otherwise specified. UC, ulcerative colitis; HC_{UC}, matched healthy control group for UC group; IBS, irritable bowel syndrome; HC_{IBS}, matched healthy control group for IBS group; BMI, body mass index; HADS, hospital anxiety and depression scale; HADS_A, HADS anxiety subscale; HADS_D, HADS depression subscale; TICS, trier inventory of chronic stress.*

chronic or recurring pain symptoms and chronic pain diagnoses were recorded. For all patients, an existing and confirmed diagnosis (of the respective GI disorder) established at least 1 year prior to recruitment for this study was required.

Clinical Symptom Questionnaires

In all participants, GI symptoms were quantified with a standardized questionnaire that we routinely use in our group as it is applicable across visceral pain conditions as well as in healthy volunteers [who also experience such symptoms, albeit less frequently or intensely; (46)]. A range of typical GI symptoms (i.e., diarrhea, constipation, vomiting, nausea, lower abdominal pain, upper abdominal pain, heartburn, post-prandial fullness, bloating, loss of appetite) in the previous 3 months is assessed using a Likert-type response scale (0 = experience never, 1 = experience once or twice per month, 2 = experience once or twice per week, 3 = experience more than twice a week). The total sum score was calculated for analyses. Given the specific interest in visceral pain herein, individual responses on the items for upper and lower abdominal pain, respectively, are additionally provided for a more specific characterization of GI symptoms in each group (**Table 1**). For patients with IBS, current bowel alteration(s) and bowel symptom subtyping (i.e., diarrhea-predominant, constipation-predominant, mixed) were also accomplished based on the GI symptom questionnaire. Patients with UC additionally completed the CAI (40) to assess clinical disease activity. The CAI consists of 6 items capturing a range of typical UC symptoms (i.e., increase in stool frequency, bloody stools, abdominal pain, temperature due to colitis, extraintestinal manifestations, and the investigator's global assessment of symptomatic state) as well as 1 item concerning laboratory results (i.e., erythrocyte sedimentation rate and hemoglobin). Hemoglobin is relevant, as anemia is the most common complication in IBD associated with disease activity, and the erythrocyte sedimentation rate is a biomarker of inflammation. Based on the total sum score, disease activity can be classified into inactive (i.e., remission; ≤4), mild activity (5–10), moderate activity (11–17) and high activity (≥18) with a maximum score of 26 (47). However, laboratory assessments were not available for the entire sample of UC patients (missing for $N = 13$ patients), which is why we provide CAI average scores computed based on 6 items for all patients for consistency. In results, we refer to this measure as symptom-based CAI for clarity.

Chronic Stress and Psychological Distress

Chronic stress was assessed by the 12-item screening scale of the Trier Inventory of Chronic Stress [TICS-SSCS; (48)]. The scale evaluates individual experiences with chronic stressors in everyday life and provides a reliable global measure of perceived stress during the last 3 months (49). Likert-scale response options are "never" (0), "rarely" (1), "sometimes" (2), "often" (3), and "very often" (4), with a total score ranging from 0 to 48, and higher scores indicating greater perceived presence and frequency of chronic stressors. Note that we chose this questionnaire specifically for its applicability not only to research in clinical populations but also in healthy volunteers, expanding on our early work on the role of chronic stress in the context of visceral pain (50).

In addition, the Hospital Anxiety and Depression Scale [HADS; (51)] was used as screening tool, and to provide a clinically-relevant and widely-used measure suitable for a characterization of patient groups with respect to psychological distress. The HADS consists of two subscales with 7 items measuring anxiety (HADS_A) and depression (HADS_D), respectively. For each subscale, available cut-off values differentiate between non-cases (subscale score <8), potential cases (subscale score 8–10), and probable cases (subscale score ≥11) of anxiety and depression (52). For the purposes of sample characterization, in addition to the two subscale scores, we provide mean total scores (HADS Total), which can range from 0 to 42 with higher scores indicating higher levels of overall psychological distress.

All questionnaire data and other self-report variables were analyzed using IBM SPSS Statistics 27 (IBM Corporation, Armonk, NY). Group comparisons were accomplished using

independent-samples *t*-tests, and data are reported as mean ± standard deviation, unless indicated otherwise.

Magnetic Resonance Imaging and Voxel-Based Morphometry

Structural images were acquired on a 3 Tesla MR scanner using a 32-channel head coil (Skyra, Siemens Healthcare, Erlangen, Germany). All data were acquired on the identical scanner, and used one of two 3D-MPRage T1-weighted sequences with very similar yet not identical acquisition parameters: sequence 1 [repetition time (TR) 1,900 ms, echo time (TE) 2.13 ms, flip angle 9°, field of view (FOV) 239 × 239 mm^2, voxel size 0.9 × 0.9 × 0.9 mm^3]; sequence 2 [TR 1,770 ms, TE 3.24 ms, flip angle 8°, FOV 256 × 256 mm^2, voxel size 1 × 1 × 1 mm^3]. All group analyses were accomplished after a matching of healthy controls (based on the entire sample of $N = 44$) to each individual patient group, providing dedicated control groups for UC and IBS, respectively, referred to subsequently as HC_{UC} and HC_{IBS}. The matching procedure was based on MR scanning sequence and age, accounting for the slightly different acquisition parameters of the two sequences. Note that the data included for analyses of IBS vs. HC_{IBS} were all acquired with sequence 1; analyses of UC vs. HC_{UC} had equal number of patients and healthy controls measured with sequence 1 ($N = 13$ UC, $N = 13$ HC_{UC}) and 2 ($N = 18$ UC, $N = 18$ HC_{UC}). The acquired images were pre-processed and analyzed with the CAT12 toolbox (Structural Brain Mapping group, Jena University Hospital, Jena, Germany) and SPM12 (Statistical Parametric Mapping, Wellcome Center for Human Neuroimaging, UCL Queen Square Institute of Neurology, London, UK) implemented in Matlab R2020a (MathWorks Inc., Natick, MA, USA). The analysis followed the standard protocol for this toolbox (http://www.neuro.uni-jena.de/cat12/CAT12-Manual.pdf) using default settings and parameters, unless otherwise specified. The main processing steps included the segmentation of voxels into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF), and normalization using optimized shooting registration. After pre-processing, the homogeneity of the sample was checked by inspecting the correlation between all volumes to ensure data quality. As all images showed high correlation values (>0.86), no images were excluded from further analysis. Modulated normalized GM maps were smoothed with a Gaussian kernel of 8 mm (FWHM). The smoothed images were used for further analysis to test for regional GMV differences between groups. Atlas labeling was based on MRI scans originating from the Open Access Series of Imaging Studies (OASIS) project. The labeled data were provided by Neuromorphometrics under academic subscription (Neuromorphometrics, Inc., Somerville, MA, USA). The total intracranial volume was determined for each subject, as it is an important confounding variable in voxel-based morphometry.

All whole-brain statistical analyses were performed within the CAT12 environment. To increase sensitivity and to avoid the arbitrary choice of an initial cluster-forming threshold, the Threshold Free Cluster Enhancement [TFCE; (53, 54)] toolbox was used for all analyses (Structural Brain Mapping group, Jena University Hospital, Jena, Germany). In a first step, two analyses of covariance (ANCOVA) were run to compare the GMV between each patient group and matched healthy controls with total intracranial volume and age as covariates of no interest. Note that T1-sequence was additionally included as covariate of no interest for the comparison of UC vs. HC_{UC}. For all ANCOVAs, we report significant results corrected for multiple comparisons [using family-wise error (FWE) correction of alpha, set at $p < 0.05$].

In a second step, four multiple regressions were calculated (i.e., two for each patient group vs. controls) to test for group interactions in the correlation of GMV with GI symptoms and chronic stress, respectively, controlling for total intracranial volume, age (and sequence where appropriate) as covariates of no interest. For these analyses, we report FWE-corrected results as well as results without correction applying an alpha level of $p < 0.001$. For each cluster identified by multiple regression analysis, the estimated GMV of its peak brain region was extracted and transferred to SPSS. As exploratory analysis, we examined correlations of GMV within brain regions identified by multiple regression analyses and GI symptoms and chronic stress, respectively, within each group using partial correlation analyses. To this end, the extracted tissue volumes within anatomical regions and GI symptoms and chronic stress were regressed based on total intracranial volume, age, and sequence (where appropriate). Correlational analyses were then accomplished and plotted using RStudio (version 1.2.5001, RStudio PBC).

Supplemental analyses were carried out as follows (all results reported within **Supplementary Material**): Firstly, as sex was not equally distributed in patients with UC and HC_{UC}, all analyses were re-computed in a subsample comprising only women, i.e., after exclusion of 5 male patients and their 5 age-matched female controls. Secondly, to indirectly address whether patterns of GMV alterations in patients with UC and IBS are disease-specific, further data and results are provided (details on approach provided in **Supplementary Material**). The approach included extracting and plotting GMV of the clusters identified in the comparison of one patient group and matched healthy controls in the other patient group and matched healthy controls, and using these clusters as regions of interest (ROI) in ROI-based analyses.

RESULTS

Sociodemographic, Clinical, and Psychological Characteristics

As per matching of healthy controls to patient group based on age and T1-scanning sequence, the final samples we report upon consisted of $N = 31$ UC vs. $N = 31$ HC_{UC} and $N = 23$ IBS vs. $N = 23$ HC_{IBS} (with $N = 2$ healthy controls excluded during matching and an overlap of $N = 12$ healthy controls in both control groups). As intended by matching and consistent with stringent screening for abnormal BMI, no differences between the patient and control groups were evident in age or BMI (**Table 1**). In both patient groups, GI symptoms were expectedly

TABLE 2 | Results of whole-brain ANCOVAs comparing gray matter volume in the two patient groups to healthy controls.

Brain region	H	k	TFCE	p_{FWE}	x	y	z
UC < HC_{UC}							
Middle frontal gyrus	L	521	323.01	0.029	−42	20	45
Anterior insula	L	334	273.41	0.032	−23	23	−9
IBS < HC_{IBS}							
Postcentral gyrus	L	2,936	553.22	0.002	−29	−30	72
Precuneus	L	2,703	243.29	0.02	2	−75	53
Inferior temporal gyrus	R	755	255.01	0.018	51	−41	−32
Middle temporal gyrus	R	144	155.41	0.046	48	−41	−3
Lateral orbital gyrus	R	201	170.81	0.04	47	29	−18
Inferior occipital gyrus	R	805	226.23	0.023	56	−69	−12
	R	264	180.43	0.036	44	−89	5
IBS > HC_{IBS}							
Superior frontal gyrus	L	9,185	644.58	0.001	12	11	72
	R	631	208.35	0.028	24	45	47
	R	236	189.4	0.033	23	35	30
Middle frontal gyrus	L	109	176.01	0.038	−42	41	33
	L	110	170.45	0.04	−38	23	20
Inferior frontal gyrus (opercular part)	L	184	173.6	0.039	−59	14	21
Temporal pole	L	3,005	230	0.022	−24	3	−17
	R	383	196.58	0.031	33	26	−39
	R	254	178.35	0.037	35	−2	−30
Superior parietal lobule	R	163	205.23	0.028	9	−54	69
Middle cingulate gyrus	L	519	179.19	0.037	−11	24	26
Occipital pole	L	296	191.12	0.032	−14	−96	8

Results are FWE-corrected at $p < 0.05$ and the total intracranial volume, age, and sequence (where appropriate) were included as covariates of no interest. H, hemisphere; L, left; R, right; k, cluster size; TFCE, threshold-free cluster enhancement; x, y, z, MNI coordinates; UC, ulcerative colitis; HC_{UC}, matched healthy control group for UC group; IBS, irritable bowel syndrome; HC_{IBS}, matched healthy control group for IBS group.

significantly increased compared to healthy controls, as were reports of abdominal pain, especially in the lower abdominal region. For the UC patient group, inclusion of patients in remission or with only mild disease activity was successful, as confirmed by a symptom-based average CAI of 1.48 (SD = 1.99), and a median fecal calprotectin concentration of 41.88 μg (IQR = 83.74 μg). IBD-related medications continued as prescribed by the treating physician included aminosalicylates (N = 20), local corticosteroids (N = 2), TNF-α blocker (N = 2), and azathioprine (N = 2). Few patients reported additional extraintestinal pain symptoms (fibromyalgia, N = 2; migraine, N = 2; arthritis, N = 1). Patients with IBS reported different bowel habit disturbances, as is typical for this condition, with diarrhea-predominant (N = 9), constipation-predominant (N = 4), mixed IBS (N = 9), or unspecified (N = 1). IBS-related medications included selective serotonin reuptake inhibitors (N = 1), muscarine receptor antagonists (N = 2), and loop diuretics (N = 1). Extraintestinal pain symptoms were reported by some patients (fibromyalgia, N = 3; migraine, N = 1, arthritis, N = 2). Regarding psychological variables, significantly higher levels of psychological distress based on HADS total score were observed in both patient groups, while only patients with IBS reported significantly more chronic stress when compared to controls (**Table 1**).

Group Differences in Brain Morphology

For the comparison between patients with UC and healthy controls, the ANCOVA identified two clusters in which GMV was significantly lower in patients with UC (**Table 2**). These clusters comprised the left middle frontal gyrus and left anterior insula, respectively. In addition to a rendered view (**Figure 1A**), the two clusters are visualized on axial slices to enable a more precise localization (**Supplementary Figure 1**). Each cluster's extracted GMV was plotted for patients with UC and matched control groups to provide data on the single-subject level (**Supplementary Figure 2**). However, it should be kept in mind that these plots cannot visualize the correction for total intracranial volume, age, and sequence that was applied in the ANCOVA. In the reversed contrast, no clusters demonstrating higher GMV in patients with UC compared to healthy controls yielded significance.

For the comparison between patients with IBS and healthy controls, the ANCOVA identified seven clusters with significantly lower GMV in patients with IBS (**Table 2**). These clusters encompassed the left postcentral gyrus, left precuneus, right lateral orbital gyrus, right inferior temporal gyrus, right middle temporal gyrus, and right inferior occipital gyrus, respectively. Clusters are depicted in a rendered view (**Figure 1B**, blue color scale) as well as axial slices (**Supplementary Figure 3**). Again,

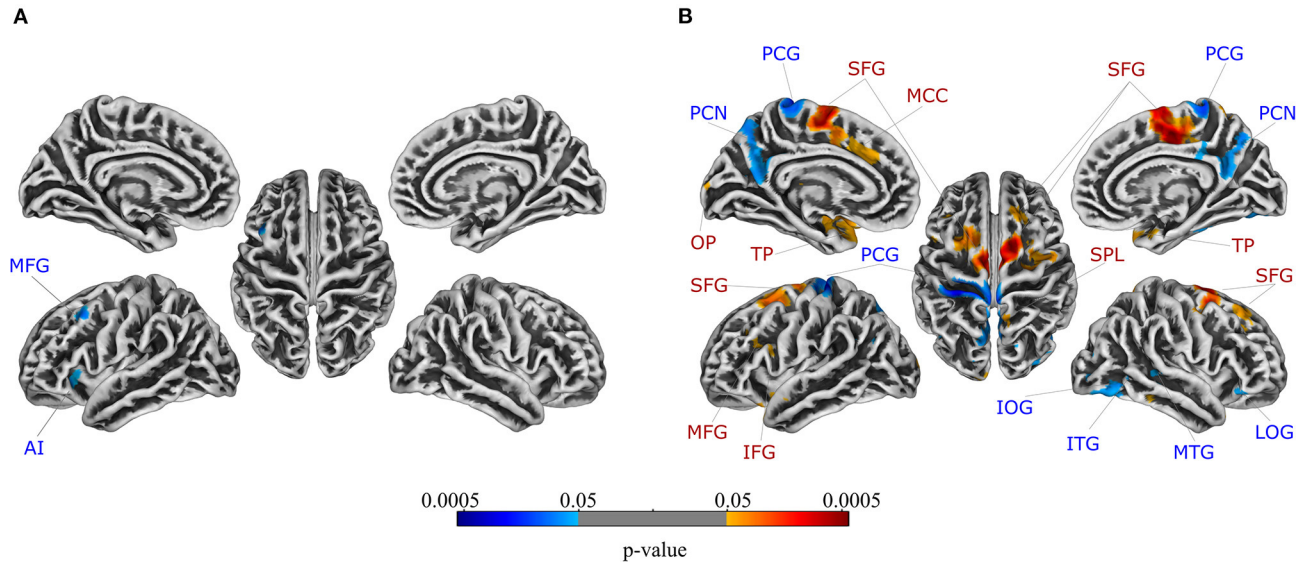


FIGURE 1 | Regions in which gray matter volume was lower in patients compared to healthy controls are depicted in blue, while regions in which gray matter volume was higher in patients compared to healthy controls are shown in red for patients with **(A)** ulcerative colitis and **(B)** irritable bowel syndrome. FWE-correction was applied at the significance level of $p < 0.05$. Axial slices are provided in **Supplementary Figures 1, 3**, respectively. For details, see **Table 2**. AI, anterior insula; IFG, inferior frontal gyrus; IOG, inferior occipital gyrus; ITG, inferior temporal gyrus; LOG, lateral orbital gyrus; MCC, middle cingulate gyrus; MFG, middle frontal gyrus; MTG, middle temporal gyrus; OP, occipital pole; PCG, postcentral gyrus; PCN, precuneus; SFG, superior frontal gyrus; SPL, superior parietal lobule; TP, temporal pole.

each cluster's GMV was extracted and plotted for patients with IBS as well as matched controls (**Supplementary Figure 4A**). In contrast, GMV was significantly higher in patients with IBS compared to healthy controls in 12 clusters including the bilateral temporal pole, bilateral superior frontal gyrus, left middle cingulate gyrus, left middle frontal gyrus, left opercular part of the inferior frontal gyrus, left occipital pole, and right superior parietal lobule, respectively. These results are visualized using a rendered view (**Figure 1B**, red color scale) and axial slices (**Supplementary Figure 3**), and GMV of these clusters was extracted and plotted for IBS patients as well as matched controls (**Supplementary Figure 4B**).

Associations Between Gray Matter Volume and Gastrointestinal Symptoms

Multiple regression analysis testing correlations of GMV and GI symptoms in patients with UC and HC_{UC} revealed a significant interaction effect between group and GI symptoms in two clusters located in the right superior frontal gyrus (**Table 3**). Supplemental partial correlational analyses between extracted GMV for this region and GI symptoms revealed a negative correlation in UC and a positive correlation in HC_{UC}, suggesting that greater GI symptoms correlated with reduced GMV in superior frontal gyrus only in patients (details and partial correlation plots in **Supplementary Figure 8**). Note that multiple regression analysis performed without correction for multiple comparisons revealed an interaction effect between group and GI symptoms in nine clusters (at $p < 0.001$), comprising additional frontal and occipital regions (**Figure 2A**, **Table 3**). These results are additionally visualized on axial slices to enable a more precise localization (**Supplementary Figure 5**).

In patients with IBS and controls, multiple regression analysis testing correlations between GMV and GI symptoms resulted in a significant interaction effect between group and GI symptoms in one cluster in the right occipital pole (**Table 3**). Supplemental partial correlational analyses between extracted GMV for this region and GI symptoms revealed a negative correlation in IBS and a positive correlation in HC_{IBS}, suggesting that greater GI symptoms correlated with reduced GMV in the occipital pole only in patients (details and correlation plots in **Supplementary Figure 9**). Note that multiple regression analysis performed without correction for multiple comparisons revealed an interaction effect between group and GI-symptoms in seven clusters (at $p < 0.001$, uncorrected for multiple comparisons), comprising additional frontal and temporal regions as well as the left posterior cingulate gyrus (**Figure 2B**, **Table 3**). These results are additionally visualized on axial slices (**Supplementary Figure 6**).

Associations Between Gray Matter Volume and Chronic Stress

Multiple regression analysis evaluating correlations of GMV with chronic stress did not yield significant interaction effects for the analysis including patients with UC and controls (neither with FWE-correction nor with a more liberal threshold). Conversely, the same analysis in patients with IBS and controls revealed a significant interaction effect between group and chronic stress in a total of 10 clusters, encompassing the bilateral angular gyrus, bilateral temporal pole, left superior

TABLE 3 | Results of whole-brain multiple regression correlating gray matter volume and gastrointestinal symptoms in patients with UC and patients with IBS compared to healthy controls.

Brain region	H	k	TFCE	*p**	x	y	z
UC < HC_{UC}							
Superior frontal gyrus	R	462	1,359.98	0.037	12	56	24
	R	130	1,338.89	0.039	18	39	35
Middle frontal gyrus	L	726	1,073.7	<0.001	−35	2	59
	L	113	871.09	0.001	−47	53	−3
Frontal pole	R	126	866.6	0.001	32	65	−8
Superior occipital gyrus	R	178	1,051.01	0.001	30	−87	20
Occipital pole	L	462	1,013.21	<0.001	−18	−95	−5
	R	165	1,050.94	0.001	17	−96	9
IBS < HC_{IBS}							
Occipital pole	R	130	1,538.2	0.038	20	−93	6
Middle frontal gyrus	L	328	1,135.04	0.001	−44	17	41
	R	109	1,112.4	0.001	38	62	2
Inferior frontal gyrus (orbital part)	L	350	1,490.26	0.001	−42	23	−5
Precentral gyrus	L	860	1,131.42	<0.001	9	−27	66
Middle temporal gyrus	L	151	829	0.001	−69	−42	9
Posterior cingulate gyrus	L	117	684.76	0.001	−8	−48	15
Inferior occipital gyrus	R	3,859	1,538.9	<0.001	20	−93	6

**P-values from FWE-corrected analyses are underlined; all other values indicate results from uncorrected analyses (interaction group × GI symptoms). H, hemisphere; L, left; R, right; k, cluster size; TFCE, threshold-free cluster enhancement; x, y, z, MNI coordinates; UC, ulcerative colitis; HC_{UC}, matched healthy control group for UC group; IBS, irritable bowel syndrome; HC_{IBS}, matched healthy control group for IBS group.*

frontal gyrus (medial segment), right middle frontal gyrus, right inferior frontal gyrus (triangular part), right postcentral gyrus, right thalamus, and right inferior occipital gyrus (**Table 4**). Supplemental partial correlational analyses between extracted GMV for regions identified by multiple regression and chronic stress suggested that associations were consistently negative in IBS, supporting that more stress was related to lower GMV, while correlations were overall positive in healthy controls (details and correlation plots in **Supplementary Figure 10**). Note that multiple regression analysis performed without correction for multiple comparisons resulted in an interaction effect between group and chronic stress in 15 clusters at $p < 0.001$, comprising additional frontal regions, left middle cingulate gyrus, right anterior insula, left basal forebrain, and left caudate (**Figure 2C**, **Table 4**). These results are additionally visualized on axial slices (**Supplementary Figure 7**).

Supplemental Analyses

For details on methods and results, see **Supplementary Material** (Chapter 2). In sum, the first set of supplemental analyses in the subsample of female UC and controls revealed no significant differences in GMV between patients and controls, but largely unchanged results of multiple regression analyses. For GI symptoms, significant interaction effects were observed in comparable clusters (**Supplementary Table 1**). For chronic stress, no significant interaction effects were demonstrated (neither with FWE-correction nor with a more liberal threshold), in line with the original analysis. The second set of analyses on GMV plots and results of ROI-based analyses indirectly addressing the question whether the observed GMV alterations are disease-specific are presented in the (**Supplementary Figures 11, 12**, respectively). Results revealed disease-specific GMV changes, especially for IBS, together with shared GMV alterations for a small subset of brain regions for both disorders.

DISCUSSION

Structural brain alterations in chronic pain conditions remain incompletely understood, especially in chronic visceral pain. We herein included UC as a chronic-inflammatory bowel disease and IBS as a disorder of gut-brain interactions as two distinct and clinically-relevant patient cohorts, together comprising the most prominent clinical conditions associated with chronic visceral pain and other burdening GI symptoms of the gut-brain axis. To elucidate structural brain alterations, we accomplished parallelized whole-brain voxel-based morphometry analyses in UC and IBS, each compared to an age-matched healthy control group. In addition to assessing altered GMV using analysis of covariance, multiple regression analyses were accomplished testing associations with symptom severity and chronic stress as a crucial psychological factor relevant to the pathophysiology and treatment of both conditions.

In our UC patient cohort, we observed decreased GMV in the anterior insula and middle frontal cortex when compared to age-matched healthy controls, in line with findings reported for patients with Crohn's disease (24, 25) and for mixed IBD samples including both UC and Crohn's disease patients (28, 29). Conversely, the only other existing study addressing brain morphology specifically in patients with UC found no alterations in GMV when compared to controls (30). However, while we successfully matched UC patients to controls with respect to age, our recruitment did not control for sex, resulting in an unequal distribution of males and females. A supplemental analysis testing group differences in a smaller subset of data that only included women failed to confirm group differences observed in the larger sample. This could indicate a role of sex/gender, or reflect limited statistical power due to the reduced sample size. Clearly, small sample sizes are a major limitation not only of the present study but also of existing previous work in IBD, precluding more conclusive answers on altered brain morphology in UC in remission, which may be very subtle and/or exist only in specific subsets of patients. A related concern are challenges faced by brain imaging research in IBD produced by the waxing and waning nature of symptoms and underlying inflammatory processes, and large interindividual

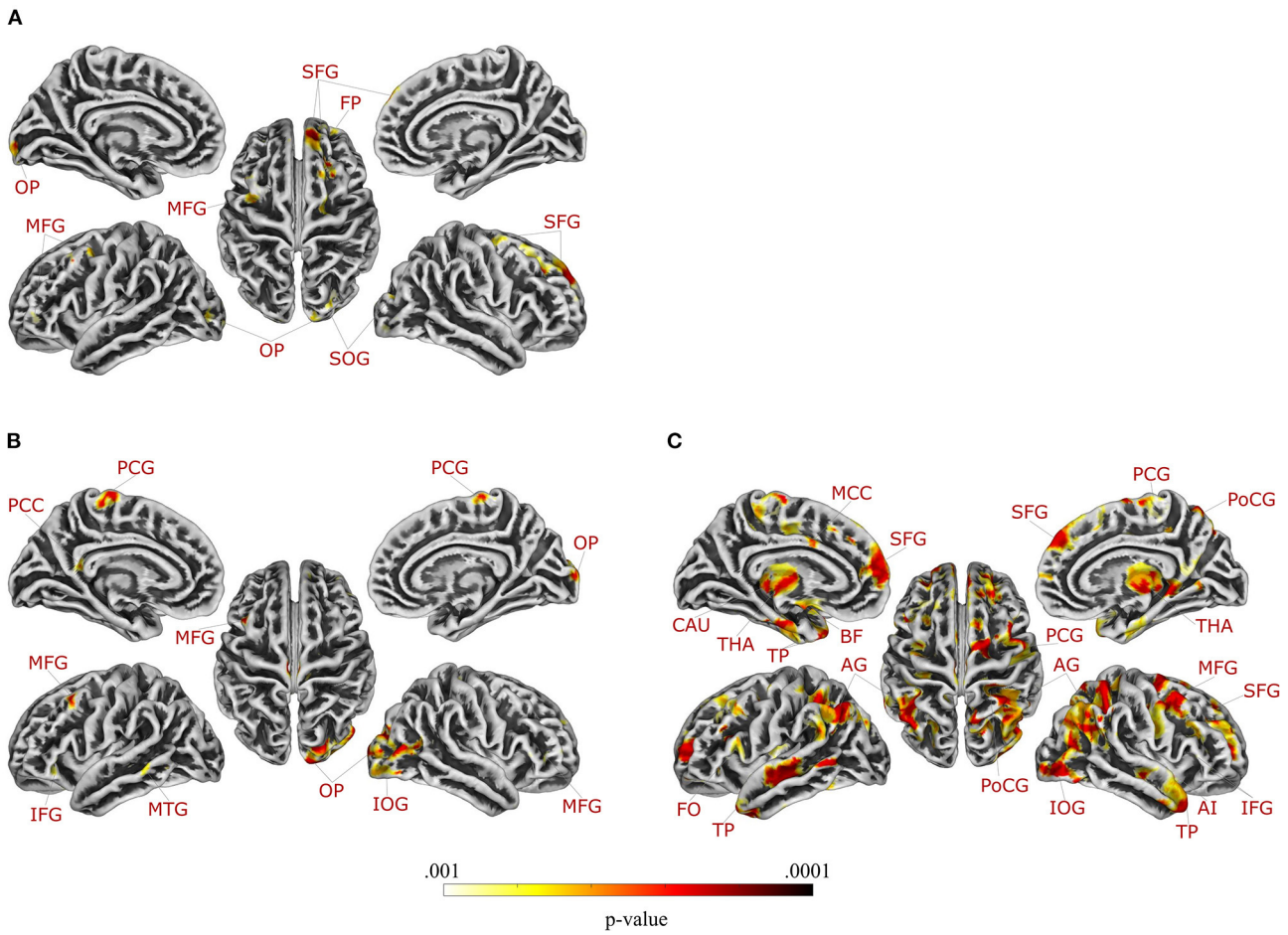


FIGURE 2 | Regions in which gray matter volume was differentially correlated with gastrointestinal symptoms in patients with **(A)** ulcerative colitis and **(B)** irritable bowel syndrome compared to healthy controls, and **(C)** regions in which gray matter volume was differentially correlated with chronic stress in patients with irritable bowel syndrome compared to healthy controls (applying a significance level of $p < 0.001$, uncorrected for multiple comparisons). Axial slices are provided in **Supplementary Figures 5–7**. For details, see **Tables 3**, **4**. AI, anterior insula; AG, angular gyrus; BF, basal forebrain; CAU, caudate nucleus; FO, frontal operculum; FP, frontal pole; IFG, inferior frontal gyrus; IOG, inferior occipital gyrus; MCC, middle cingulate gyrus; MFG, middle frontal gyrus; MTG, middle temporal gyrus; OP, occipital pole; PCC, posterior cingulate gyrus; PCG, precentral gyrus; PoCG, postcentral gyrus; SFG, superior frontal gyrus; SOG, superior occipital gyrus; THA, thalamus; TP, temporal pole.

differences in disease course and treatment, calling for decisions about inclusion and exclusion that are never unequivocal. The only other existing study specifically addressing patients with UC focused on a highly-selected sample of patients ($N = 18$) without any disease activity for at least 6 months, and with no more than one inflammatory flare since diagnosis (30). While we similarly excluded patients with active disease, the exclusion criteria for our somewhat larger sample ($N = 31$) were not as restrictive, allowing recruitment of a sample with disease ranging from full remission to low and well-managed disease activity, without restrictions with respect to number of previous flares or medication history. Consistent with this strategy, UC patients in our study reported significantly more GI symptoms, including lower abdominal pain, as well as greater psychological distress, when compared to healthy controls. This clinical presentation is arguable more representative of the typical patient population with UC outside of acute exacerbations, consistent with evidence that patients with IBD often report GI symptoms and a psychological disease impact during remission.

Bearing the critical considerations described above in mind, it is nevertheless interesting to discuss our findings suggesting possibly reduced GMV in the anterior insula and the middle frontal cortex in UC. The anterior insula is part of the salience network, which is highly relevant to pain anticipation and pain modulation in acute and chronic visceral pain [e.g., (4, 20, 23)]. Interestingly, in IBD with and without abdominal pain, resting state functional MRI revealed differences in the insula, and correlations with daily pain scores (55). Furthermore, transcranial direct current stimulation over the motor cortex demonstrably resulted in modified insula connectivity and reduced pain (56), and functional brain imaging revealed altered insula activation in anticipation of painful rectal distensions

TABLE 4 | Results of multiple regression correlating gray matter volume and chronic stress in patients with IBS and healthy controls.

Brain region	H	k	TFCE	*p**	x	y	z
IBS < HC_{IBS}							
Angular gyrus	L	2,006	2,566.1	0.001	−44	−50	48
	R	5,402	2,119.6	0.004	44	−38	41
Temporal pole	L	7,230	1,836.4	0.01	−47	8	−14
	R	6,535	2,320.7	0.002	41	8	−27
Superior frontal gyrus	L	5,205	2,010.2	0.006	−20	51	8
Middle frontal gyrus	R	428	1,565.7	0.023	36	8	54
Inferior frontal gyrus (triangular part)	R	112	1,341.4	0.045	41	32	5
Postcentral gyrus	R	957	1,481.8	0.03	44	−5	32
Thalamus proper	R	6,057	1,696.7	0.016	6	−17	−2
Inferior occipital gyrus	R	430	1,362.4	0.042	44	−75	−8
Superior frontal gyrus	R	9,925	2,010.2	<0.001	−20	51	8
Inferior frontal gyrus (orbital part)	R	158	1,323.5	0.001	35	35	0
	L	120	1,280.1	<0.001	−42	26	2
Anterior orbital gyrus	L	314	1,048.9	0.001	−30	41	−6
Precentral gyrus	R	7,445	1,565.7	<0.001	36	8	54
Middle cingulate gyrus	L	642	1,192.4	0.001	−9	−11	39
Anterior insula	R	497	1,530.2	0.001	36	−11	9
Basal forebrain	L	191	1,427.6	<0.001	−9	5	−12
Caudate	L	113	1,310	0.001	−14	20	−3

**P-values from FWE-corrected analysis are underlined; all other values indicate results from uncorrected analysis (interaction group x chronic stress). H, hemisphere; L, left; R, right; k, cluster size; TFCE, threshold-free cluster enhancement; x, y, z, MNI coordinates; IBS, irritable bowel syndrome; HC_{IBS}, matched healthy control group for IBS group.*

(57). The anterior insula together with frontal regions is also part of the central autonomic network, with a broad role in diverse GI sensorimotor functions along the gut-brain axis (20), including adaptive responses to the experience of recurring pain (58). This is particularly interesting given evidence supporting specific alterations in autonomic nervous system function in IBD [e.g., (59, 60)], also in relation to stress [reviewed in Labanski et al. (12)].

Our parallelized analyses in a patient cohort with IBS, which we consider an interesting disease control group for UC, revealed largely distinct and much more widespread structural brain alterations when compared to healthy controls. Brain alterations comprised both decreases as well as increases in GMV in multiple regions of the sensorimotor, central executive, and default mode networks, all demonstrably relevant to different facets of chronic visceral pain (20) and largely consistent with published findings in the literature (21, 22). We performed the present analyses with the intention to provide evidence in UC and IBS as the most prominent chronic visceral pain conditions together within one report, complementing our earlier functional brain imaging efforts in this direction (61), here aiming to discern a possible specificity of brain structural alterations to chronic visceral pain condition. While we abstained from direct patient group comparisons for methodological and conceptual reasons, the pattern of alterations in UC and IBS, respectively, when compared to controls appears to be rather dissimilar, in line with our hypothesis and further supported by supplemental ROI-based analyses. Together, these suggest mostly distinct and IBS-specific GMV alterations, with only minor putative overlap in a few subregions in UC. There exist very few neuroimaging studies that applied brain imaging techniques in IBS and IBD within one study, and ours is the first to use VBM to elucidate brain morphology. These studies collectively support disease-specific alterations (61–65), which is intriguing given the ongoing debate on overlapping and distinguishing features of these disorders (66, 67).

For a better understanding of GMV alterations, elucidating their relation with clinical as well as psychological factors is an important step. Associations of GMV changes with symptom severity have previously been demonstrated in patients with IBS and patients with Crohn's disease in terms of disease duration (24, 27, 68), pain duration (34), and daily pain scores (25). As GI symptoms are not only experienced by patients suffering from a bowel disorder, but also (obviously less frequently and/or intensively) by healthy volunteers, the question arises whether differences exist in the way these symptoms relate to GMV in patients. Results of our multiple regression analyses, specifically addressing interaction effects in patient samples and controls, support the hypothesis that the correlation between GI symptoms and brain structure is altered in patients. Differences from healthy controls were mainly observed in frontal brain regions (i.e., within the central executive network) in both patient groups. In addition, in patients with IBS, the relation of symptom severity and GMV, as expected, differed from that in healthy volunteers in regions of the sensorimotor network and default mode network. Thus, the present study confirms and expands previous findings on the relation of symptom severity and GMV in patients suffering from a chronic-inflammatory or functional bowel disorder.

In addition, the present study is the first to investigate whether structural brain measures are related to chronic stress in patients with chronic visceral pain. This question arises given the broad role of stress and stress mediators in normal visceroception (50), visceral pain sensitivity (3), visceral pain modulation (69), and altered brain processing of acute visceral pain in IBS (70). Even more importantly, stress shapes GI symptom experience and disease course both in IBS (71, 72) and IBD (37, 38), and is incorporated in treatment approaches in both conditions (73, 74). Results revealed a differential association of chronic stress with GMV in patients with IBS and healthy

volunteers, encompassing numerous brain regions involved in networks relevant to the psychological modulation of visceral pain (20). In addition to regions of the sensorimotor network, central executive network, and default mode network (in which associations with symptom severity were also observed), the relation of chronic stress and GMV in regions of the salience network was significantly altered in patients with IBS, which is interesting given recent evidence indicating the unique salience of pain arising from the visceral modality (4, 5). Supplemental partial correlational analyses accomplished within each group, pointed to consistently negative associations within the group of IBS patients but not the control group, suggesting that higher chronic stress was associated with lower regional brain volumes exclusively within patients. While exploratory, these results are intriguing and may indicate that chronic stress constitutes a vulnerability factor only in patients, which in concert with additional disease-relevant mechanisms contributes to disturbed gut-brain interactions.

The same analysis of patients with UC, on the other hand, unexpectedly yielded no differences in the association of GMV changes and chronic stress. However, this negative result is difficult to interpret given the absence of group differences in chronic stress levels in our UC cohort, indicating essentially normal perceived chronic stress in this sample despite elevated clinical symptoms of anxiety as quantified with the HADS. While sample characteristics of UC were in this respect similar to an earlier study in a different sample of UC that used a comparable recruitment strategy (75), other studies from our own group (76) and other groups [e.g., (63)] reported more psychological impairment in patients, including elevated chronic stress levels. The lack of elevated chronic stress in this UC sample obviously limits the interpretation of these results, although owing to our approach to test the interaction this does not *per se* exclude an impact but rather a disease-specific differential association compared to controls. Clearly, our data do not provide conclusive answers, and hopefully inspire further study, possibly in selected patient groups presenting with higher stress levels or other impairment in psychological health, as recently accomplished by our group in a treatment trial (75), or in concert with biological measures relevant to neuroendocrine stress mediators and inflammation (76), both accomplished without concurrent brain imaging. Longitudinal studies already elucidated the relation between stress and disease course (37, 38). Including structural MRI as additional non-invasive measure in such studies appears feasible and attractive in order to further advance knowledge about the brain as "central hub" of the gut-brain axis and its interconnections with the central and peripheral stress systems, and its role in different conditions characterized by chronic visceral pain. This would promote translational efforts in the field to advance our understanding of brain measures relevant to perception and pain.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: Neurovault (https://neurovault.org/collections/EIGBDJQK/).

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the University Hospital Essen. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HÖ and LK: acquired data. SE, HE, JL, and LK: designed the study. HÖ, FL, and NT: analyzed the data. HÖ and SE: wrote the first draft of the paper. SE and HE: acquired funding. All authors contributed to the interpretation of the data, revised the manuscript for critical content, and approved the final version of the manuscript.

FUNDING

This work was supported by funding from the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation; Project Nos. 316803389–SFB 1280 and 422744262—TRR 289). The funding organization was not involved in study design; in collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Marcel Gratz for excellent technical support and Dr. Alexandra Labanski for help with patient recruitment and screening. The authors also thank Sopiko Knuf-Rtveliashvili and Dr. Liubov Petrakova for support in data acquisition.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.733035/full#supplementary-material

REFERENCES

1. Grundy L, Erickson A, Brierley SM. Visceral pain. *Annu Rev Physiol.* (2019) 81:261–84. doi: 10.1146/annurev-physiol-020518-114525
2. Koenen LR, Icenhour A, Forkmann K, Pasler A, Theysohn N, Forsting M, et al. Greater fear of visceral pain contributes to differences between visceral and somatic pain in healthy women. *Pain.* (2017) 158:1599–608. doi: 10.1097/j.pain.0000000000000924
3. Benson S, Siebert C, Koenen LR, Engler H, Kleine-Borgmann J, Bingel U, et al. Cortisol affects pain sensitivity and pain-related emotional learning in experimental visceral but not somatic pain: a randomized controlled study in healthy men and women. *Pain.* (2019) 160:1719–28. doi: 10.1097/j.pain.0000000000001579
4. Koenen LR, Pawlik RJ, Icenhour A, Petrakova L, Forkmann K, Theysohn N, et al. Associative learning and extinction of conditioned

threat predictors across sensory modalities. *Commun Bio.* (2021) 4:553. doi: 10.1038/s42003-021-02008-1
5. Van Oudenhove L, Kragel PA, Dupont P, Ly HG, Pazmany E, Enzlin P, et al. Common and distinct neural representations of aversive somatic and visceral stimulation in healthy individuals. *Nat Commun.* (2020) 11:5939. doi: 10.1038/s41467-020-19688-8
6. Collett B. Visceral pain: the importance of pain management services. *Br J Pain.* (2013) 7:6–7. doi: 10.1177/2049463713480138
7. Peery AF, Dellon ES, Lund J, Crockett SD, McGowan CE, Bulsiewicz WJ, et al. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology.* (2012) 143:1179–87. doi: 10.1053/j.gastro.2012.08.002
8. Aziz Q, Giamberardino MA, Barke A, Korwisi B, Baranowski AP, Wesselmann U, et al. The IASP classification of chronic pain for ICD-11: chronic secondary visceral pain. *Pain.* (2019) 160:69–76. doi: 10.1097/j.pain.0000000000001362
9. Wehkamp J, Götz M, Herrlinger K, Steurer W, Stange EF. Inflammatory bowel disease: Crohn's disease and ulcerative colitis. *Dtsch Arztebl Int.* (2016) 113:72–82. doi: 10.3238/arztebl.2016.0072
10. Halpin SJ, Ford AC. Prevalence of symptoms meeting criteria for irritable bowel syndrome in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol.* (2012) 107:1474–82. doi: 10.1038/ajg.2012.260
11. Enck P, Aziz Q, Barbara G, Farmer AD, Fukudo S, Mayer EA, et al. Irritable bowel syndrome. *Nat Rev Dis Primers.* (2016) 2:16014. doi: 10.1038/nrdp.2016.14
12. Labanski A, Langhorst J, Engler H, Elsenbruch S. Stress and the brain-gut axis in functional and chronic-inflammatory gastrointestinal diseases: a transdisciplinary challenge. *Psychoneuroendocrinology.* (2020) 111:104501. doi: 10.1016/j.psyneuen.2019.104501
13. Bernstein CN. The brain-gut axis and stress in inflammatory bowel disease. *Gastroenterol Clin North Am.* (2017) 46:839–46. doi: 10.1016/j.gtc.2017.08.006
14. Collins SM. Interrogating the gut-brain axis in the context of inflammatory bowel disease: a translational approach. *Inflamm Bowel Dis.* (2020) 26:493–501. doi: 10.1093/ibd/izaa004
15. Mayer EA, Tillisch K. The brain-gut axis in abdominal pain syndromes. *Annu Rev Med.* (2011) 62:381–96. doi: 10.1146/annurev-med-012309-103958
16. Kregel J, Meeus M, Malfliet A, Dolphens M, Danneels L, Nijs J, et al. Structural and functional brain abnormalities in chronic low back pain: a systematic review. *Semin Arthritis Rheum.* (2015) 45:229–37. doi: 10.1016/j.semarthrit.2015.05.002
17. Jorge LL, Amaro E. Brain imaging in fibromyalgia. *Curr Pain Headache Rep.* (2012) 16:388–98. doi: 10.1007/s11916-012-0284-9
18. Chong CD, Schwedt TJ, Dodick DW. Migraine: what imaging reveals. *Curr Neurol Neurosci Rep.* (2016) 16:19–21. doi: 10.1007/s11910-016-0662-5
19. Cauda F, Palermo S, Costa T, Torta R, Duca S, Vercelli U, et al. Gray matter alterations in chronic pain: a network-oriented meta-analytic approach. *Neuroimage Clin.* (2014) 4:676–86. doi: 10.1016/j.nicl.2014.04.007
20. Mayer EA, Labus J, Aziz Q, Tracey I, Kilpatrick L, Elsenbruch S, et al. Role of brain imaging in disorders of brain-gut interaction: a Rome working team report. *Gut.* (2019) 68:1701–15. doi: 10.1136/gutjnl-2019-318308
21. Kano M, Dupont P, Aziz Q, Fukudo S. Understanding neurogastroenterology from neuroimaging perspective: a comprehensive review of functional and structural brain imaging in functional gastrointestinal disorders. *J Neurogastroenterol Motil.* (2018) 24:512–27. doi: 10.5056/jnm18072
22. Weaver KR, Sherwin LB, Walitt B, Melkus GDE, Henderson WA. Neuroimaging the brain-gut axis in patients with irritable bowel syndrome. *World J Gastrointest Pharmacol Ther.* (2016) 7:320. doi: 10.4292/wjgpt.v7.i2.320
23. Kornelsen J, Wilson A, Labus JS, Witges K, Mayer EA, Bernstein CN. Brain resting-state network alterations associated with Crohn's disease. *Front Neurol.* (2020) 11:48. doi: 10.3389/fneur.2020.00048
24. Bao CH, Liu P, Liu HR, Wu LY, Shi Y, Chen WF, et al. Alterations in brain grey matter structures in patients with Crohn's disease and their correlation with psychological distress. *J Crohns Colitis.* (2015) 9:532–40. doi: 10.1093/ecco-jcc/jjv057
25. Bao C, Liu P, Shi Y, Wu L, Jin X, Zeng X, et al. Differences in brain gray matter volume in patients with Crohn's disease with and without abdominal pain. *Oncotarget.* (2017) 8:93624–32. doi: 10.18632/oncotarget.21161
26. Fan Y, Bao C, Wei Y, Wu J, Zhao Y, Zeng X, et al. Altered functional connectivity of the amygdala in Crohn's disease. *Brain Imaging Behav.* (2019) 14:2097–106. doi: 10.1007/s11682-019-00159-8
27. Agostini A, Benuzzi F, Filippini N, Bertani A, Scarcelli A, Farinelli V, et al. New insights into the brain involvement in patients with Crohn's disease: a voxel-based morphometry study. *Neurogastroenterol Motil.* (2013) 25:147–54. doi: 10.1111/nmo.12017
28. Zikou AK, Kosmidou M, Astrakas LG, Tzarouchi LC, Tsianos E, Argyropoulou MI. Brain involvement in patients with inflammatory bowel disease: a voxel-based morphometry and diffusion tensor imaging study. *Eur Radiol.* (2014) 24:2499–506. doi: 10.1007/s00330-014-3242-6
29. Thomann AK, Schmitgen MM, Kmuche D, Ebert MP, Thomann PA, Szabo K, et al. Exploring joint patterns of brain structure and function in inflammatory bowel diseases using multimodal data fusion. *Neurogastroenterol Motil.* (2021) 33:e14078. doi: 10.1111/nmo.14078
30. Agostini A, Campieri M, Bertani A, Scarcelli A, Ballotta D, Calabrese C, et al. Absence of change in the gray matter volume of patients with ulcerative colitis in remission: a voxel based morphometry study. *Biopsychosoc Med.* (2015) 8:10–3. doi: 10.1186/s13030-014-0028-7
31. Qin HY, Cheng CW, Tang XD, Bian ZX. Impact of psychological stress on irritable bowel syndrome. *World J Gastroentero.* (2014) 20:14126–31. doi: 10.3748/wjg.v20.i39.14126
32. Mawdsley JE, Rampton DS. Psychological stress in IBD: new insights into pathogenic and therapeutic implications. *Gut.* (2005) 54:1481–91. doi: 10.1136/gut.2005.064261
33. Seminowicz DA, Labus JS, Bueller JA, Tillisch K, Naliboff BD, Bushnell MC, et al. Regional gray matter density changes in brains of patients with irritable bowel syndrome. *Gastroenterology.* (2010) 139:48–57. doi: 10.1053/j.gastro.2010.03.049
34. Blankstein U, Chen J, Diamant NE, Davis KD. Altered brain structure in irritable bowel syndrome: potential contributions of pre-existing and disease-driven factors. *Gastroenterology.* (2010) 138:1783–9. doi: 10.1053/j.gastro.2009.12.043
35. Labus JS, Dinov ID, Jiang Z, Ashe-McNalley C, Zamanyan A, Shi Y, et al. Irritable Bowel Syndrome in female patients is associated with alterations in structural brain networks. *Pain.* (2014) 155:137–49. doi: 10.1016/j.pain.2013.09.020
36. Agostini A, Ballotta D, Righi S, Moretti M, Bertani A, Scarcelli A, et al. Stress and brain functional changes in patients with Crohn's disease: a functional magnetic resonance imaging study. *Neurogastroenterol Motil.* (2017) 29:e13108. doi: 10.1111/nmo.13108
37. Hirten RP, Danieletto M, Scheel R, Shervey M, Ji J, Hu L, et al. Longitudinal autonomic nervous system measures correlate with stress and ulcerative colitis disease activity and predict flare. *Inflamm Bowel Dis.* (2020). doi: 10.1093/ibd/izaa323. [Epub ahead of print].
38. Langhorst J, Hofstetter A, Wolfe F, Häuser W. Short-term stress, but not mucosal healing nor depression was predictive for the risk of relapse in patients with ulcerative colitis: a prospective 12-month follow-up study. *Inflamm Bowel Dis.* (2013) 19:2380–6. doi: 10.1097/MIB.0b013e3182a192ba
39. Sweeney L, Moss-Morris R, Czuber-Dochan W, Meade L, Chumbley G, Norton C. Systematic review: psychosocial factors associated with pain in inflammatory bowel disease. *Aliment Pharmacol Ther.* (2018) 47:715–29. doi: 10.1111/apt.14493
40. Rachmilewitz D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. *BMJ.* (1989) 298:82–6. doi: 10.1136/bmj.298.6666.82
41. Langhorst J, Elsenbruch S, Koelzer J, Rueffer A, Michalsen A, Dobos GJ. Noninvasive markers in the assessment of intestinal inflammation in inflammatory bowel diseases: performance of fecal lactoferrin, calprotectin, and PMN-elastase, CRP, and clinical indices. *Am J Gastroenterol.* (2008) 103:162–9. doi: 10.1111/j.1572-0241.2007.01556.x
42. Kucharzik T, Koletzko S, Kannengießer K, Dignaß A. Colitis ulcerosa - diagnostische und therapeutische algorithmen. *Dtsch Arztebl Int.* (2020) 117:564–73. doi: 10.3238/arztebl.2020.0564
43. Lacy BE, Mearin F, Chang L, Chey WD, Lembo AJ, Simren M, et al. Bowel disorders. *Gastroenterology.* (2016) 150:1393–407. doi: 10.1053/j.gastro.2016.02.031

44. Whitehead WE, Palsson O, Jones KR. Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications? *Gastroenterology.* (2002) 122:1140–56. doi: 10.1053/gast.2002.32392
45. López San Román A, Munoz F. Comorbidity in inflammatory bowel disease. *World J Gastroenterol.* (2011) 17:2723–33. doi: 10.3748/wjg.v17.i22.2723
46. Lacourt TE, Houtveen JH, Doornen LJP, Benson S, Grigoleit JS, Cesko E, et al. Biological and psychological predictors of visceral pain sensitivity in healthy premenopausal women. *Eur J Pain.* (2014) 18:567–74. doi: 10.1002/j.1532-2149.2013.00397.x
47. Schoepfer AM, Beglinger C, Straumann A, Trummler M, Renzulli P, Seibold F. Ulcerative colitis: correlation of the rachmilewitz endoscopic activity index with fecal calprotectin, clinical activity, C-reactive protein, and blood leukocytes. *Inflamm Bowel Dis.* (2009) 15:1851–8. doi: 10.1002/ibd.20986
48. Schulz P, Schlotz W. The trier inventory for the assessment of chronic stress (TICS): scale construction, statistical testing, and validation of the scale work overload. *Diagnostica.* (1999) 45:8–19.
49. Petrowski K, Paul S, Albani C, Brähler E. Factor structure and psychometric properties of the trier inventory for chronic stress (TICS) in a representative German sample. *BMC Med Res Methodol.* (2012) 12:42. doi: 10.1186/1471-2288-12-42
50. Icenhour A, Labrenz F, Roderigo T, Benson S, Elsenbruch S. The role of chronic stress in normal visceroception: insights from an experimental visceral pain study in healthy volunteers. *Front Psychiatry.* (2020) 11:107. doi: 10.3389/fpsyt.2020.00107
51. Herrmann-Lingen C, Buss U, Snaith RP. *Hospital Anxiety and Depression Scale–German Version*. Bern: Huber (2005).
52. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* (1983) 67:361–70. doi: 10.1111/j.1600-0447.1983.tb09716.x
53. Salimi-Khorshidi G, Smith SM, Nichols TE. Adjusting the effect of nonstationarity in cluster-based and TFCE inference. *Neuroimage.* (2011) 54:2006–19. doi: 10.1016/j.neuroimage.2010.09.088
54. Smith SM, Nichols TE. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. *Neuroimage.* (2009) 44:83–98. doi: 10.1016/j.neuroimage.2008.03.061
55. Bao CH, Liu P, Liu HR, Wu LY, Jin XM, Wang SY, et al. Differences in regional homogeneity between patients with Crohn's disease with and without abdominal pain revealed by resting-state functional magnetic resonance imaging. *Pain.* (2016) 157:1037–44. doi: 10.1097/j.pain.0000000000000479
56. Neeb L, Bayer A, Bayer KE, Farmer A, Fiebach JB, Siegmund B, et al. Transcranial direct current stimulation in inflammatory bowel disease patients modifies resting-state functional connectivity: a RCT. *Brain Stimul.* (2019) 12:978–80. doi: 10.1016/j.brs.2019.03.001
57. Rubio A, Pellissier S, Van Oudenhove L, Ly HG, Dupont P, Tack J, et al. Brain responses to uncertainty about upcoming rectal discomfort in quiescent Crohn's disease - a fMRI study. *Neurogastroenterol Motil.* (2016) 28:1419–32. doi: 10.1111/nmo.12844
58. Leone M, Proietti Cecchini A, Mea E, Tullo V, Curone M, Bussone G. Neuroimaging and pain: a window on the autonomic nervous system. *Neurol Sci.* (2006) 27:134–7. doi: 10.1007/s10072-006-0588-9
59. Pellissier S, Dantzer C, Canini F, Mathieu N, Bonaz B. Psychological adjustment and autonomic disturbances in inflammatory bowel diseases and irritable bowel syndrome. *Psychoneuroendocrinology.* (2010) 35:653–62. doi: 10.1016/j.psyneuen.2009.10.004
60. Pellissier S, Dantzer C, Mondillon L, Trocme C, Gauchez AS, Ducros V, et al. Relationship between vagal tone, cortisol, TNF-alpha, epinephrine and negative affects in Crohn's disease and irritable bowel syndrome. *PLoS ONE.* (2014) 9:e105328. doi: 10.1371/journal.pone.0105328
61. Schmid J, Langhorst J, Gaß F, Theysohn N, Benson S, Engler H, et al. Placebo analgesia in patients with functional and organic abdominal pain: a fMRI study in IBS, UC and healthy volunteers. *Gut.* (2015) 64:418–27. doi: 10.1136/gutjnl-2013-306648
62. Huang JS, Terrones L, Simmons AN, Kaye W, Strigo I. Pilot study of functional magnetic resonance imaging responses to somatic pain stimuli in youth with functional and inflammatory gastrointestinal disease. *J Pediatr Gastroenterol Nutr.* (2016) 63:500–7. doi: 10.1097/MPG.0000000000001390
63. Turkiewicz J, Bhatt RR, Wang H, Vora P, Krause B, Sauk JS, et al. Altered brain structural connectivity in patients with longstanding gut inflammation is correlated with psychological symptoms and disease duration. *Neuroimage Clinical.* (2021) 30:102613. doi: 10.1016/j.nicl.2021.102613
64. Mayer EA, Berman S, Suyenobu B, Labus J, Mandelkern MA, Naliboff BD, et al. Differences in brain responses to visceral pain between patients with irritable bowel syndrome and ulcerative colitis. *Pain.* (2005) 115:398–409. doi: 10.1016/j.pain.2005.03.023
65. Hong JY, Labus JS, Jiang Z, Ashe-Mcnalley C, Dinov I, Gupta A, et al. Regional neuroplastic brain changes in patients with chronic inflammatory and non-inflammatory visceral pain. *PLoS ONE.* (2014) 9:e84564. doi: 10.1371/journal.pone.0084564
66. Spiller R, Major G. IBS and IBD—separate entities or on a spectrum? *Nat Rev Gastroenterol Hepatol.* (2016) 13:613–21. doi: 10.1038/nrgastro.2016.141
67. Quigley EM. Overlapping irritable bowel syndrome and inflammatory bowel disease: less to this than meets the eye? *Ther Adv Gastroenterol.* (2016) 9:199–212. doi: 10.1177/1756283X15621230
68. Li J, Yuan B, Li G, Lu X, Guo Y, Yang Y, et al. Convergent syndromic atrophy of pain and emotional systems in patients with irritable bowel syndrome and depressive symptoms. *Neurosci Lett.* (2020) 723:134865. doi: 10.1016/j.neulet.2020.134865
69. Roderigo T, Benson S, Schols M, Hetkamp M, Schedlowski M, Enck P, et al. Effects of acute psychological stress on placebo and nocebo responses in a clinically relevant model of visceroception. *Pain.* (2017) 158:1489–98. doi: 10.1097/j.pain.0000000000000940
70. Elsenbruch S, Rosenberger C, Bingel U, Forsting M, Schedlowski M, Gizewski ER. Patients with irritable bowel syndrome have altered emotional modulation of neural responses to visceral stimuli. *Gastroenterology.* (2010) 139:1310–9. doi: 10.1053/j.gastro.2010.06.054
71. O'malley D, Quigley EMM, Dinan TG, Cryan JF. Do interactions between stress and immune responses lead to symptom exacerbations in irritable bowel syndrome? *Brain Behav Immun.* (2011) 25:1333–41. doi: 10.1016/j.bbi.2011.04.009
72. Moloney RD, O'Mahony SM, Dinan TG, Cryan JF. Stress-induced visceral pain: toward animal models of irritable-bowel syndrome and associated comorbidities. *Front Psychiatry.* (2015) 6:15. doi: 10.3389/fpsyt.2015.00015
73. Soares RL. Irritable bowel syndrome: a clinical review. *World J Gastroenterol.* (2014) 20:12144–60. doi: 10.3748/wjg.v20.i34.12144
74. McCombie AM, Mulder RT, Gearry RB. Psychotherapy for inflammatory bowel disease: a review and update. *J Crohns Colitis.* (2013) 7:935–49. doi: 10.1016/j.crohns.2013.02.004
75. Langhorst J, Schols M, Cinar Z, Eilert R, Kofink K, Paul A, et al. Comprehensive lifestyle-modification in patients with ulcerative colitis-a randomized controlled trial. *J Clin Med.* (2020) 9:3087. doi: 10.3390/jcm9103087
76. Engler H, Elsenbruch S, Rebernik L, Köcke J, Cramer H, Schöls M, et al. Stress burden and neuroendocrine regulation of cytokine production in patients with ulcerative colitis in remission. *Psychoneuroendocrinology.* (2018) 98:101–7. doi: 10.1016/j.psyneuen.2018.08.009

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2021 Öhlmann, Koenen, Labrenz, Engler, Theysohn, Langhorst and Elsenbruch. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Neurology

REVIEW
published: 03 January 2022
doi: 10.3389/fneur.2021.734821

Brain Imaging Biomarkers for Chronic Pain

Zhengwu Zhang[1], *Jennifer S. Gewandter*[2] *and Paul Geha*[3,4,5]*

[1] Department of Statistics and Operations Research, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States, [2] Anesthesiology and Perioperative Medicine, School of Medicine and Dentistry, University of Rochester, Rochester, NY, United States, [3] Department of Psychiatry, School of Medicine and Dentistry, University of Rochester, Rochester, NY, United States, [4] Department of Neurology, School of Medicine and Dentistry, University of Rochester, Rochester, NY, United States, [5] Del Monte Neuroscience Institute, University of Rochester, Rochester, NY, United States

The prevalence of chronic pain has reached epidemic levels. In addition to personal suffering chronic pain is associated with psychiatric and medical co-morbidities, notably substance misuse, and a huge a societal cost amounting to hundreds of billions of dollars annually in medical cost, lost wages, and productivity. Chronic pain does not have a cure or quantitative diagnostic or prognostic tools. In this manuscript we provide evidence that this situation is about to change. We first start by summarizing our current understanding of the role of the brain in the pathogenesis of chronic pain. We particularly focus on the concept of learning in the emergence of chronic pain, and the implication of the limbic brain circuitry and dopaminergic signaling, which underly emotional learning and decision making, in this process. Next, we summarize data from our labs and from other groups on the latest brain imaging findings in different chronic pain conditions focusing on results with significant potential for translation into clinical applications. The gaps in the study of chronic pain and brain imaging are highlighted in throughout the overview. Finally, we conclude by discussing the costs and benefits of using brain biomarkers of chronic pain and compare to other potential markers.

Keywords: chronic pain, neuroimaging, limbic brain, diagnosis, prognosis, biomarkers

OPEN ACCESS

Edited by:
Susanne Becker,
University of Zurich, Switzerland

Reviewed by:
Scott Holmes,
Boston Children's Hospital,
United States
Landrew Sevel,
Vanderbilt University Medical Center,
United States
Choongwan Woo,
Sungkyunkwan University,
South Korea

***Correspondence:**
Paul Geha
paul_geha@urmc.rochester.edu

Specialty section:
This article was submitted to Applied Neuroimaging, a section of the journal Frontiers in Neurology

Received: *01 July 2021*
Accepted: *08 December 2021*
Published: *03 January 2022*

Citation:
Zhang Z, Gewandter JS and Geha P (2022) Brain Imaging Biomarkers for Chronic Pain. Front. Neurol. 12:734821. doi: 10.3389/fneur.2021.734821

INTRODUCTION

Chronic pain affects more than 20% of the US adult population (1) and is more prevalent in women than in men (2). Unfortunately, chronic pain does not have a cure or quantitative diagnostic or prognostic tools. Objective measures of disease and response to treatment are necessary for rational and quantitative medical decision making (3). The advent of functional magnetic resonance brain imaging (fMRI) (4) has given a boost to the efforts of understanding the brain neurophysiology of acute and chronic pain as fMRI, along with other techniques such as electroencephalography (EEG), are being intensely applied to the study of various clinical pain populations. These efforts have opened the door for the development of quantitative brain measures of diagnosis, prognosis, and treatment of the disease (5, 6). Here we provide an overview of recent studies advancing potential biomarkers of chronic pain considering our current understanding of the neural pathogenesis of the condition. We discuss the emerging role of the brain limbic system (7) in the pathophysiology of chronic pain and how its role in affective learning and memory can help us develop biologically plausible brain biomarkers for chronic pain. We also touch on the potential economic benefits of brain biomarkers of chronic pain in the context of the staggering cost that this disease is annually engendering (8).

THE BURDEN OF CHRONIC PAIN

Chronic pain is one of the most common reasons adults seek medical care (9). It is also one of the most common causes of disability (10–12), and is associated with major comorbidities like obesity (13) and mental health problems (14) such as depression (15), alcohol (16, 17) and opioid misuse (18). It is estimated that > 50 million American adults live with chronic pain (1) with a staggering annual cost reaching $500–600 billion dollars (19). Low back-pain (LBP) is one of the most prevalent clinical pain conditions (11), with an annual cost reaching $100 billion dollars (20). Osteoarthritis, the most common form of arthritis, affects more than 32.5 million adults in the United States (US), with total annual arthritis-attributable medical care expenditures and earning losses of > $300 billion dollars (21). Inadequately controlled osteoarthritis pain is the primary reason for total joint replacement (22), and available first line analgesic treatments have no (e.g., paracetamol) to small effects (e.g., NSAIDs) over placebo (23). The problem of chronic pain is expected to worsen in the coming decades because the population is getting older. The number of individuals aged above 60 years old is expected to triple by 2050 (24) and age is a major risk factor for developing chronic pain. It is estimated that 50–70% of people over the age of 65 report at least some persistent pain (25–27), and the prevalence of severe pain is higher in the elderly (28). Older adults suffering from low-back pain, for example, are more disabled than their healthy peers (29–31), are more predisposed to frailty (32, 33), and tend to be undertreated (34–36) because of increased difficulty of diagnosis (37) and increased propensity to side effects from analgesics [e.g., non-steroidal anti-inflammatory drugs causing kidney injury (38, 39) or opioids causing increased falls (40, 41)].

Associated with this "population-level pain crisis" is a crisis of opioid analgesic dependence and opioid analgesic overdose death as 450,000 people died from overdoses involving prescription and illicit opioids between 1999 and 2019 in the US (42). These crises are partly a reflection of major gaps in the understanding of the mechanisms of nociception (43), acute, and chronic pain (44) despite significant recent advances (3, 6). Unfortunately, novel pharmacologic treatments for pain have not emerged for some time (44). Together this data indicates that chronic pain is a huge individual and societal burden necessitating further research into mechanism guided novel diagnostic, prognostic, and therapeutic approaches.

DIAGNOSTIC AND PROGNOSTIC TOOLS FOR CHRONIC PAIN

Chronic pain remains a clinical diagnosis based primarily on subjective reports of pain intensity and pain localization (45). Currently, "there are no biomarkers for pain accepted by the US Food and Drug Administration (FDA) or the European Medicines Agency for use in clinical trials (46)." This is a major hurdle in the care of patients suffering from chronic pain because the absence of objective and quantitative tools to diagnose disease, like glucose for diabetes or blood pressure for hypertension, and to measure disease progression or response to treatment, precludes rationale medical decision making. In 1971, the Framingham study identified systolic hypertension as a determinant of long-term cardiovascular risk (47); since then, the reduction of cardiovascular risk by reducing blood pressure (48) and the calculation of risk scores incorporating other objective measures such as cholesterol levels or body mass index (47) have been a major fixture of successful preventive medicine. Instead, most, if not all, the current approaches to treating chronic pain are based on a "trial and error strategy." This has led to the sad state of affair summarized in the Burden of Chronic Pain section. Hence, the need for objective and quantitative tools to assist clinicians in medical decision making when treating chronic pain patients and to be used as targets or surrogate endpoints in development of new analgesics cannot be more over-emphasized. In addition to the need for quantification in medicine, a mechanism-based approach is critical for treatments and preventions to be impactful (43).

PAIN PERCEPTION AND THE BRAIN: HOW MUCH DO WE KNOW?

The lack of understanding of how nociceptive input to the brain gives rise to the conscious perception of pain is a significant knowledge gap in the science of pain (49). It constitutes an obstacle to the discovery of brain biomarkers for chronic pain because the neurophysiology of conscious pain perception is still unknown and consequently the pathophysiology of how this process turns chronic becomes harder to decipher. Unlike touch or vision, which arise because of activity in specific brain tissues (50), pain has very scarce and hard to detect specialized neurons. In addition, the activation of nociceptive input to the brain is not always sufficient or necessary to elicit painful perceptions. This is supported by phenomena such as offset analgesia (51) and the thermal grill illusion (52) suggesting that pain may arise as a result of a pattern of non-nociceptive afferent activations rather than labeled lines of nociceptors (53). Early attempts at identifying a "pain specific" brain tissue in the primary and secondary somatosensory areas (SI and SII) or insula seemed futile (54). Although a more recent cortical stimulation study in humans identified neurons selectively eliciting pain in the posterior insula/SII and adjacent parietal operculum pain responses were very scarce occurring only in 1.4% of all stimulations. The advent of brain imaging (structural and functional magnetic resonance imaging) in the past three decades saw a flurry of studies examining the brain activity associated with acute and chronic pain (55–57). All the same, the physiology of how pain perception arises from nociceptive input is still poorly understood (58). An ensemble of a relatively large number of brain areas are frequently seen to significantly activate in response to acute pain when activity is measured using fMRI (55, 59, 60). An activation likelihood estimation based meta-analysis of acute noxious stimulation fMRI studies showed clusters of activity in the thalamus, basal ganglia, SI, SII, insula/inferior parietal lobule, anterior cingulate cortex (ACC), superior temporal gyrus, and middle and superior frontal gyri,

and cerebellum (60). A sub-group of these brain areas (i.e., thalamus, SI, SII, insula and ACC) were dubbed as the "pain matrix" (59) as they are seen in more than 80% of studies of acute pain in healthy subjects (55). However, there is no clear evidence to date that any of these activations are specific to pain perception because the same brain areas observed during painful stimulations are as active during the perception of other salient stimuli in the environment like touch or visual stimuli (61–63), or during negative affective experiences (63), or during salient sensory stimulation in individuals with congenital insensitivity to pain (64). Efforts using novel methods not relying on the general linear model (65) but on the interaction of various brain areas (e.g., functional connectivity) (66) and machine learning (67) are underway to identify specific neural signatures of pain perception (**Figure 1**). However, the interpretability of such approaches remains limited and has not, to date, significantly advanced our understanding of the physiology of pain perception. Together, the knowledge we accumulated to date about nociceptive processing and pain perception in the brain still cannot explain the neurophysiology of how the former leads to the latter. This unknown is not specific to the perception of pain as it is also unclear how perception of other complex stimuli carrying an incentive salience comparable to pain such as food give rise to feelings of pleasure (i.e., food liking) (70) or flavor constructs (71). This unknown did not however prevent the discovery of reproducible patterns of brain activity and structure changes in chronic pain patients which, although far from explaining the complete picture of the neurophysiology of pain, are nevertheless able to track clinical pain and/or response to treatment. These findings will be discussed below.

BEYOND SENSORY PERCEPTION: CHRONIC PAIN AND AVERSIVE LEARNING A CONCEPTUALIZATION IN BRIEF

Pain is a sensory and affective experience (72, 73) and engages the limbic brain (7)-in addition to, and part of the "pain matrix or connectome" discussed in the previous section-composed of but not limited to the amygdala, hippocampus, striatum, anterior insula, and prefrontal cortex (60, 63, 67). The limbic system overlaps with the learning circuitry in the brain which integrates motivations and memories to guide behavior (50). As described by Melzack and Casey pain "…becomes overwhelming, demands immediate attention, and disrupts ongoing behavior and thought" (72). To complete the picture this "overwhelming" experience leads to new learning and memory formation with the most likely explanation being to avoid such experiences in the future (74). That nociceptive signals from the periphery eliciting pain lead to learning in animals (75, 76) offers an adaptive advantage is obvious, because animals need to navigate the environment seeking food while at the same time avoiding harm from being attacked or from physical injury (e.g., fall). While the persistence of pain beyond the time needed for healing might be construed as maladaptive recent evidence point to the protective effect of central sensitization in avoiding predation (77). Besides, persistence of pain is thought to be the inevitable consequence of the protective effects of pain as the evolutionary cost of having a hypersensitive nociceptive system protecting animals from injury outweighs the cost of living in chronic pain (78). In both scenarios, the persistence of pain entails ongoing learning as the continuous barrage of afferent nociceptive input entrains the limbic brain and updates memories and associations. Pre-clinical evidence shows in fact that disrupting learning by blocking hippocampal neurogenesis prevents the development of pain behavior in rodent models of inflammatory and neuropathic chronic pain (79). In addition, there is good evidence that persistent pain is associated with new learning (80–82) and altered memories (83) and decision making (84–87). Therefore, the physiological properties of the limbic brain and its plastic response to ongoing pain, which can be measured with multi-modal brain imaging, will directly contribute to the risk of developing chronic pain and the experience of chronic pain, respectively. It stands to reason therefore that diagnostic and prognostic biomarkers of chronic pain should directly involve that circuitry (88, 89). This presents a specificity challenge to the identification of brain biomarkers for chronic pain because the brain circuitry underlying emotions (i.e., limbic) and learning mediates also several other normal and pathological behaviors and traits such as normal memory formation (90) and addiction related learning (91), among others.

The increased likelihood of observing limbic brain areas tracking spontaneous pain (without any outside stimulation) intensity in clinical populations compared to acute pain (elicited by a noxious stimulus) is in fact a distinguishing feature of brain activity collected when chronic pain patients report their spontaneous pain online in the scanner (49, 92–94). Significant evidence exists now showing that activity and functional connectivity in the nucleus accumbens (NAc) and medial prefrontal cortex (mPFC) track chronic low-back pain (CLBP) intensity (95–100). NAc activity tracks also the change in neuropathic pain of patients with post-herpetic neuralgia after treatment (101), is correlated to the number of peripatellar tender sites in knee arthritis patients (102), and shows increased activation during migraine attacks (103). Consistent with fMRI findings, a decrease in μ-opioid binding potential in the NAc have been demonstrated by positron emission tomography (PET) studies across several chronic pain conditions (104–107), indicating either increased binding or decreased baseline levels of internal opioids.

The ventral striatum (including the NAc)-mPFC is the brain network that encodes value of nearly all reward types on a common scale (108). In addition, the accumbens' function is best described as a limbic-motor interface translating motivations into actions (109). Accordingly, healthy pain whether external (e.g., a hot stove) or internal (e.g., belly ache) is a major stimulus requiring the engagement of valuational and motivational circuitry to decide the next step (e.g., moving away from the stimulus or seeking help) (110). Considering this understanding of the role of NAc-mPFC in valuation and motivation under normal conditions the plasticity observed in chronic pain patients emphasizes the valuational and motivational disruptions as key phenotypic expressions of chronic pain consistent with the described clinical picture (111). How this confluence affects the

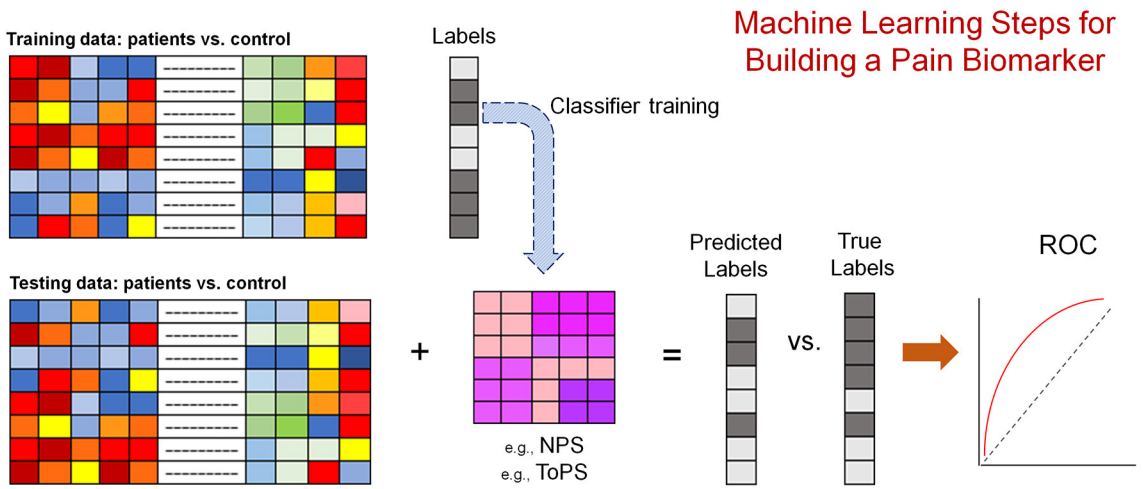


FIGURE 1 | Schematic depiction of the approach used by many papers aimed at developing pain biomarkers. The modality used (i.e., training and testing data) can be the beta maps of the general linear model fit in response to a stimulus [e.g., painful heat (67)], or the connectivity matrix of resting brain activity or structural information [e.g., volume (68, 69)]. Labels (i.e., patient or control) is one example of predictions. Pain intensity is often used as a predicted measure. The most rigorous approach is to keep training and testing data totally separate. However, a lot of the published works out there have used k-fold cross validation approaches.

validity of NAc-mPFC based biomarkers in chronic pain has not been explicitly studied and must be investigated in the future. However, existing evidence strongly suggests for example that the valuation signal of acute pain experienced by chronic pain patients is largely different and opposite from the valuation signal of the same stimulus experienced by healthy subjects (96, 112). As such, the NAc activity drops in patients with chronic pain relative to controls during an acute thermal heat pain offset with a large effect size (Cohen's-d >>1) (96) suggesting that signals during acute pain might be readily distinguishable from signals experienced in the context of clinical pain.

In addition to NAc and mPFC, amygdala and hippocampus-both major nodes of the limbic brain (7)-have been directly implicated in chronic pain conditions. Hence, amygdala functional connectivity is consistently altered in migraine patients (113–115). Amygdala volume and shape on the other hand are altered in CLBP patients (116, 117). Hippocampal morphology is also changed in chronic pain; CLBP and complex regional pain syndrome patients exhibit decreased hippocampal volume (81) although this finding is not consistent between studies (100). Interestingly, Berger et al. (83) reported that hippocampal morphology predicted pain memory bias in CLBP patients as 77% of the patients exaggerated remembered daily pain. Nociceptive information reaches the limbic brain areas via the spinothalamic-cortical (118), spino-parabrachial-thalmic-cortical (119), spino-parabrachial-amygdala (120) nociceptive projections. A parsimonious model of nociceptive processing would therefore posit that nociceptive information reaching hippocampus and amygdala mediate memory formation and feeds to the NAc and mPFC (74, 76, 121) to guide value based decision making and motor behavior (108, 122). In addition, both the amygdala and the mPFC project to brainstem centers (110) like the periaqueductal gray (PAG) and modulate descending pathways regulating noxious input at the dorsal horn of the spinal cord (110). Given the known anatomy to date, chronic pain can therefore arise either as a result of persistent input from the periphery secondary to injury or inflammation (123) or as a result of gain in the system as the limbic circuitry amplify afferent signals or from the interplay between these two factors (49).

BRAIN BIOMARKERS OF CHRONIC PAIN

The FDA-NIH Biomarker Working Group (124) defines a biomarker as "a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, or physiologic characteristics are types of biomarkers. A biomarker is not an assessment of how individual feels, functions, or survives." The definition implies that, in the case of chronic pain, measures of brain structure or brain activity would be potential biomarkers of disease whereas subjective reports of ongoing pain or elicited pain cannot be biomarkers. This definition does however introduce a logical conundrum into the search for biomarkers for chronic pain and other chronic conditions where subjective report is still the gold-standard like major depressive or anxiety disorders: how can biomarkers be objective if they are derived based on the subjective report of patients to start with? One solution is to rely on big data. Assuming there are objective biomarkers to predict pain pathology and the subjective reported pain intensity is centered around the corresponding pathology level with noise. The problem of identifying important variables with noisily observed responses has been well-studied in statistics, and many famous methods have been developed (125), including LASSO (126) and Elastic Net (127). Theoretical studies have shown that under some regularity conditions, the selected features converge to the true feature as the sample of size goes to infinity (128, 129). With recent advancement

in deep learning and convolutional neural networks, automatic feature/biomarker learning becomes possible. However, these methods require large amount of data. For example, in a recently published article, we have shown that a complex model such as a neural network can have much better performance if trained with more brain data (130). Another approach to solving the logical conundrum of biomarker discovery is to test biomarkers in animal models of chronic pain. The same brain activity or structure measure can be obtained in animals confirmed to have an injury (e.g., the spared nerve injury model) and the biomarker then validated in classifying individuals with disease or measuring the extent of pain behavior. Mansour et al. (131) have demonstrated for example that a global measure of disruption of functional connectivity (132, 133) measure correlated to reports of clinical pain intensity in three different types of chronic pain patients (chronic low-back pain, complex regional pain syndrome and knee osteoarthritis) and was also reproducible in a spared nerve injury model of chronic pain in rodents as the disrupted connectivity measure correlated to measures of mechanical allodynia. This approach has the limitation that no subjective reports of pain can be obtained from animals.

Several non-invasive modalities measuring brain structure and activity have been used in the past three decades in pain research (55) and could potentially be used to discover and validate brain-based biomarkers of chronic pain. These modalities include structural and functional magnetic resonance imaging (fMRI), electroencephalography (EEG), magnetoencephalography (MEG), and more recently functional near infrared spectroscopy (fNIRS). While EEG and MEG offer the best temporal resolution, their spatial resolution is limited compared to fMRI. In addition, the location accuracy of EEG, MEG, and fNIRS techniques deteriorates with increasing distance from the scalp, and hence activity in deeper brain structures such as thalamus, striatum or insula, which are important in pain perception (55, 59, 93), might be hard to measure. In contrast, EEG and fNIRS data collection devices are mobile and relatively cheap potentially offering clinicians easy and affordable tools to use.

Diagnostic Brain Biomarkers

A diagnostic biomarker is "used to detect or confirm presence of a disease or condition of interest or to identify individuals with a subtype of the disease" (124). A review (134) of EEG patterns in patients with chronic pain reported increased theta and alpha power compared to controls but the results are very diverse, and no other EEG studies have validated these findings yet. Interestingly, one of the earliest EEG studies (135) reported *increased* theta power with active treatment but not with placebo and an inverse correlation between change in theta power and change in clinical pain intensity suggesting that the diagnostic EEG patterns of chronic pain patients might be intrinsic and not correctable with analgesia. More recent EEG and MEG studies used machine learning approaches (**Figure 1**) (136) to discriminate between chronic pain patients and healthy controls (137–140). Some of these studies propose thalamo-cortical dysrhythmia (141) as an underlying pathophysiology of various chronic pain conditions although this dysrhythmia is not specific to chronic pain but is also observed in several other chronic neurologic conditions like chronic tinnitus and depression (137).

Early and consistent findings of altered brain connectivity measured with blood oxygen level dependent (BOLD) (4) fMRI in chronic pain patients (142, 143) suggested a large-scale functional reorganization with biomarker(s) potential. Altered insula to default mode connectivity in chronic pain patients is a notable reproducible finding across studies (96, 97, 144–147), although generalizability of this finding has not been formally tested within one study using separate training and testing data sets. As multivariate data analysis approaches gained traction into the field of brain imaging (148), several potential diagnostic biomarkers were advanced for chronic pain where brain derived classifiers are used to discriminate patients from controls (149) (**Figure 1**). Both Ung et al. (68), and Labus et al. (69), used multivariate data analysis and validation on held-out samples to identify morphological signatures of chronic pain; their approaches achieved a classification accuracy of 70–76%. Ung et al. (68), used gray matter density derived with voxel morphometry (150) in patients with CLBP, and Labus et al. (69) used cortical thickness derived with FreeSurfer (151) in patients with irritable bowel syndrome, as features to build their predictive models. Mano et al. (152), used brain connectivity (adjacency matrices) and support vector machine to discriminate CLBP patients from healthy controls studied at different sites and achieved an accuracy of 68%. The added contribution of this study was the testing of the predictive model on a previously unseen independent data set rather than on held-out samples only. The authors characterized further brain network changes in CLBP and observed significant modular (153) reorganization of bilateral somatosensory motor cortices in the patients' groups, although how the reorganization of these brain areas contributed to their predictive models was not clear. Lopez-Sola et al. (154) used brain response to painful and non-painful stimuli and the neurologic pain signature (67) weighted pattern of activity to derive a classifier for fibromyalgia patients whose diagnosis relies on testing for hyperalgesia. Authors reported a high sensitivity and specificity (>90%) in discriminating between patients and healthy controls using an out-of-sample validation approach. However, the absence of control chronic pain populations precluded the generalization of these findings to other conditions. An observation common to these studies is the identification of highly distributive predictive brain patterns involving all four lobes of the brain and the cerebellum. In keeping with the thalamo-cortical dysrhythmia theory of chronic pain (155), Tu et al. (156) discovered that CLBP patients dwell longer in a state of increased connectivity between the sub-cortical (including the thalamus) and somatosensory networks and validated their finding using an independent data set. Notably, the dwell time in that hyperconnected state was correlated to pain severity (156).

More recently, Lee et al. (157) built a brain connectivity-based predictive model of tonic pain intensity from fMRI data collected in healthy subjects receiving capsaicin on their

tongue, which they dubbed the tonic pain signature (ToPS). Like other multivariate predictive patterns, ToPS was highly distributed across all brain subnetworks with the strongest connections being those between sub-networks, particularly the connections between the somato-motor and fronto-parietal networks. After extensive and rigorous model validations in healthy subjects authors used ToPS to predict clinical pain intensity of sub-acute and chronic low-back pain patients using fMRI data collected at rest and data collected when patients were continuously rating their low-back pain intensity (i.e., task-based data) in the scanner (152, 158). The ToPS predictive performance on the clinical data was mixed. While ToPS' brain response was highly correlated to ratings of SBP intensity using data collected during pain intensity ratings, the correlation was flat when ToPS was obtained from data collected at rest. In contrast, ToPS did not significantly predict ratings of CLBP intensity obtained from data collected during intensity ratings but significantly predicted CLBP intensity when using imaging data obtained at rest. Notably, ToPS response discriminated between patients and healthy controls in two additional and separate brain imaging data sets with an AUC of 73 and 71%, respectively. Lee et al., reported also that ToPS performed better (correlation coefficient-r = 0.48) at predicting low-back pain intensity than models trained on the SBP clinical datasets ($r = 0.36$), but the difference was not statistically significant and the sample size for the clinical validation data sets was relatively smaller ($n = 35$) than the healthy control data sets used to validate ToPS. Besides, ToPS performed better in predicting CLBP pain intensity than the model trained on 17 CLBP patients using the same approach to generate ToPS. As the authors note, ToPS will need to be tested across laboratories and clinical data collected from different pain conditions for further validation before being considered for translational applications.

Cross-sectional studies cannot differentiate causal from consequential brain patterns predictive of chronic pain; therefore, observed diagnostic patterns of chronic pain obtained using cross-sectional approaches are a mixture of both predisposing neural features to chronic pain and plastic changes resulting from living in chronic pain. This highlights the importance of longitudinal studies of the transition from acute to chronic pain where the distinction between causal and consequential brain patterns predictive of chronic pain becomes possible. We have recently identified a neural signature for CLBP that has the potential to become a diagnostic biomarker for this condition (100). Using a combination of a longitudinal design where SBP patients were scanned before and after pain "chronification" or remission and cross sectional cohorts of CLBP studied at different sites, we observed loss of amplitude in the slow-5 (0.01–0.027 Hz) (159) frequency band of NAc activity in CLBP patients. Importantly, the loss of slow-5 was not observed at baseline in SBP patients even if patients are stratified by long-term risk but developed only in SBPp patients after ∼1 year of persistent pain. In addition, the loss of slow-5 amplitude was validated in a separate data set pooled from two different sites and discriminated between CLBP patients and healthy controls (AUC > 0.72) from yet another 2 studies **(Figure 2)**. Hence, this change in frequency content of NAc activity was absent during the early phase of sub-acute pain, developed as pain became chronic and was highly reproducible across datasets collected at different sites. As we discussed previously the NAc is a hot spot in the pathophysiology of chronic pain as several previous studies pointed to its role in tracking the intensity of pain (95, 96, 98, 101, 158, 160). In addition, pre-clinical data provides neurophysiologic evidence corroborating the role of NAc in chronic pain. Using optogenetic activations, Lee et al. showed that prelimbic (equivalent to mPFC in humans) projections to the NAc in rodents can gate incoming afferent nociceptive input in rodents' models of chronic pain (161). When studied in rodents, acute to chronic pain transition is characterized by decreased dopaminergic signaling between the ventral tegmental area and the NAc, and plastic changes in the cellular structure of medium spiny neurons of the NAc shell (162). Available PET studies of chronic pain patients examining dopamine signaling also suggest the association of chronic pain with a hypodopaminergic state (163–165). The critical involvement of the brain valuation system (108, 166, 167) (e.g., NAc, mPFC) in the plasticity associated with chronic pain is consistent with the often observed disruption of cognitive processes mediated by these brain circuities in chronic pain populations. Chronic pain patients exhibit for example anhedonia (168, 169), disrupted satiety signals (168), and impaired emotional decision making (84, 85, 87). These behavioral impairments indicate in turn that the reproducible changes in the valuation circuitry of patients are biologically explainable and plausible (170) biomarkers of chronic pain.

Prognostic Brain Biomarkers

A prognostic biomarker is "used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest" (124).

To date only a handful of studies used fMRI to identify prognostic biomarkers for the transition from acute to chronic pain. Baliki et al. (158) observed that the volume of the NAc measured using voxel-based morphometry shrank in size only in sub-acute low-back pain patients (SBP) (duration 6–12 weeks) who transitioned to chronic pain (SBPp) compared to those who did not (SBPr) and to healthy controls. They also showed that the magnitude of NAc-mPFC functional connectivity is increased in SBPp patients compared to SBPr patients both at baseline and at 1 year follow-up. In an independent (i.e., never "seen" before") cohort they validated their finding with an area under the curve (AUC) equal to 0.81 when using NAc-mPFC to classify SBPp vs. SBPr at follow-up. Using an expanded sample from the same study they later demonstrated that the morphological properties of the limbic brain predicted the risk of transition from sub-acute to chronic pain (117). They observed that limbic brain white matter connections centered on the dorso-medial and ventro-medial prefrontal cortex, amygdala and hippocampus as well as a smaller volume of the latter two structures constituted independent risk factors for the transition from sub-acute to chronic low-back pain. Combining candidate risk gene single nucleotide polymorphism with the functional and structural properties of the limbic brain in a path analysis allowed them

to predict 60% of the variance of the outcome after a sub-acute bout of low-back pain (117). Consistent with these findings we have recently reported using a similar longitudinal design, studying SBP patients at baseline and after transition into chronic pain, that a significantly smaller volume of the NAc in at risk SBPp patients compared to healthy controls predates CLBP; in addition, we corroborated Vachon et al. findings that the volume of amygdala at baseline predicts the risk of transition to CLBP. The volume of NAc was *smaller* in SBPp patients than in healthy controls both at baseline and at follow-up and *smaller* in a cross-sectional cohort of CLBP patients. In contrast, the volume of the amygdala was *larger* at baseline in SBPr patients than in both SBPp patients and healthy controls (**Figure 2**). This observation suggests that while NAc morphology is a biomarker of risk of pain "chronification," the morphology of the amygdala is a biomarker of resilience to persisting pain because it was not different from the healthy controls in the at-risk group (i.e., SBPp patients). Mansour et al. reported another potential structural biomarker for resilience to low-back pain chronification using diffusion weighed imaging (DWI) (171). Using fractional anisotropy (FA) measures of white matter diffusion they found that FA values in the superior longitudinal fasciculus and the internal capsule were increased in resilient SBPr patients compared to SBPp patients and healthy controls at baseline when pain was still sub-acute (6–12 weeks duration) and discriminated between SBPp and SBPr patients in an independent cohort an AUC = 0.81. DWI based biomarkers carry a strong potential for translation into clinical applications because they can be easily obtained on hospital scanners in a relatively short period of time (15 min), and have good to excellent test-retest reliability for both intra- and inter-sites repeated measures (172, 173). High reliability is an important and desirable characteristic of biomarkers as it helps in their widespread deployment and generalizability (174). Notably, functional imaging measures that are often considered for biomarkers (131, 157, 158) have lower reliability than DWI measures especially across sites (175–177). A common clinical scenario where DWI of the brain can be added to the work-up would be in patients with low-back pain preparing for spine surgery. The DWI data would then serve to predict the probability of remission or persistence of pain after spine surgery for example where up to 40% of patients report persistent pain post-operatively (178). The DWI scan can be added to the spinal imaging work-up obtained in preparation for surgery and could serve as a quantitative risk assessment to help clinicians and patients make an informed decision about the procedure's outcome. This of course will depend on completing large, and preferably multi-center, clinical trials where DWI brain measures are used to build and validate predictive models of prognosis (e.g., back-pain intensity, or disability) after spine surgery (179).

METHODS OF DETECTION AND CLINICAL CONTEXT OF USE

The candidate biomarkers we discussed are measured using magnetic resonance imaging (MRI). The approach leverages the ability of MRI to detect a wide range of brain tissue (white and gray matter) and neuronal activity signals in a relatively short data acquisition time and the widespread availability of MRI scanners in medical centers. Blood oxygen level dependent (BOLD) signal is used to measure brain activity and connectivity (4, 180), T1w/T2w weighted images are used to measure subcortical volumes and shapes, and cortical thickness (151, 181), and diffusion weighted imaging (DWI) to measure white matter structure and connectivity (182, 183). These measures can be obtained in a relatively short time 30–60 min, can now be analyzed either online or outsourced easily to biomarker analysis companies in partnership with NIH (184), are non-invasive and low-risk, and require no contrast injection.

In addition to the clinical and economic need that brain biomarkers for chronic pain address in our society they also would be a tremendous help in alleviating discrimination and care inequities in non-communicative patients like new born babies, in patients with communication disabilities, in groups suffering from social bias (185, 186) and in patients where currently available diagnostic tests cannot identify any pathological abnormalities (187) [e.g., a majority of chronic low-back pain patients (188) and patients diagnosed with fibromyalgia (189, 190)]. Rigorously validated brain imaging biomarkers would therefore improve access to treatment and social resources in patients' groups that have been suffering from marginalization in pain treatment (191). Several recent reviews in major pain and neuroscience journals supports the pursuit of brain biomarkers of chronic pain (58, 174, 192–195). Nevertheless, the use of brain biomarkers in an actual clinical scenarios of pain management remain scarce. Harris et al. (196), showed that treatment with pregabalin but not placebo altered insula chemistry and connectivity in patients with fibromyalgia but neither treatment was accompanied by a significant change in clinical pain rating. Most recently, Ashar et al. used fMRI as "an objective correlate of treatment effects" in a clinical trial (NCT0394148) testing pain reprocessing therapy vs. placebo in patients with CLBP (197) and reported decreased anterior middle cingulate cortex activity in response to evoked clinical pain and increased anterior insula to somatosensory cortex connectivity with pain reprocessing therapy more than with placebo treatment. In addition, Reckzeigel et al. (198) recently used brain biomarkers to assess the risk of transition from sub-acute to chronic pain in sub-acute low-back pain patients entering a pharmacological clinical trial (NCT01951105) aimed at preventing the transition to CLBP. The brain based pre-trial risk assessment served to enrich their sample with patients whose risk of recovery was $< 60\%$. FMRI was also used to examine objective correlates of treatment effects where authors observed a treatment by sex interaction on the magnitude of NAc-mPFC (198). These are pioneering studies in the field and set the stage for steering the approach to measures in pain treatment clinical trial in a very promising and exciting new direction.

One criticism for using MRI biomarkers is cost, which varies between \$500 and \$1,000 for 30 min of brain MRI scanning. To date there are no cost benefit analysis studies to offer guidance on the economic benefits of brain-based biomarkers for chronic

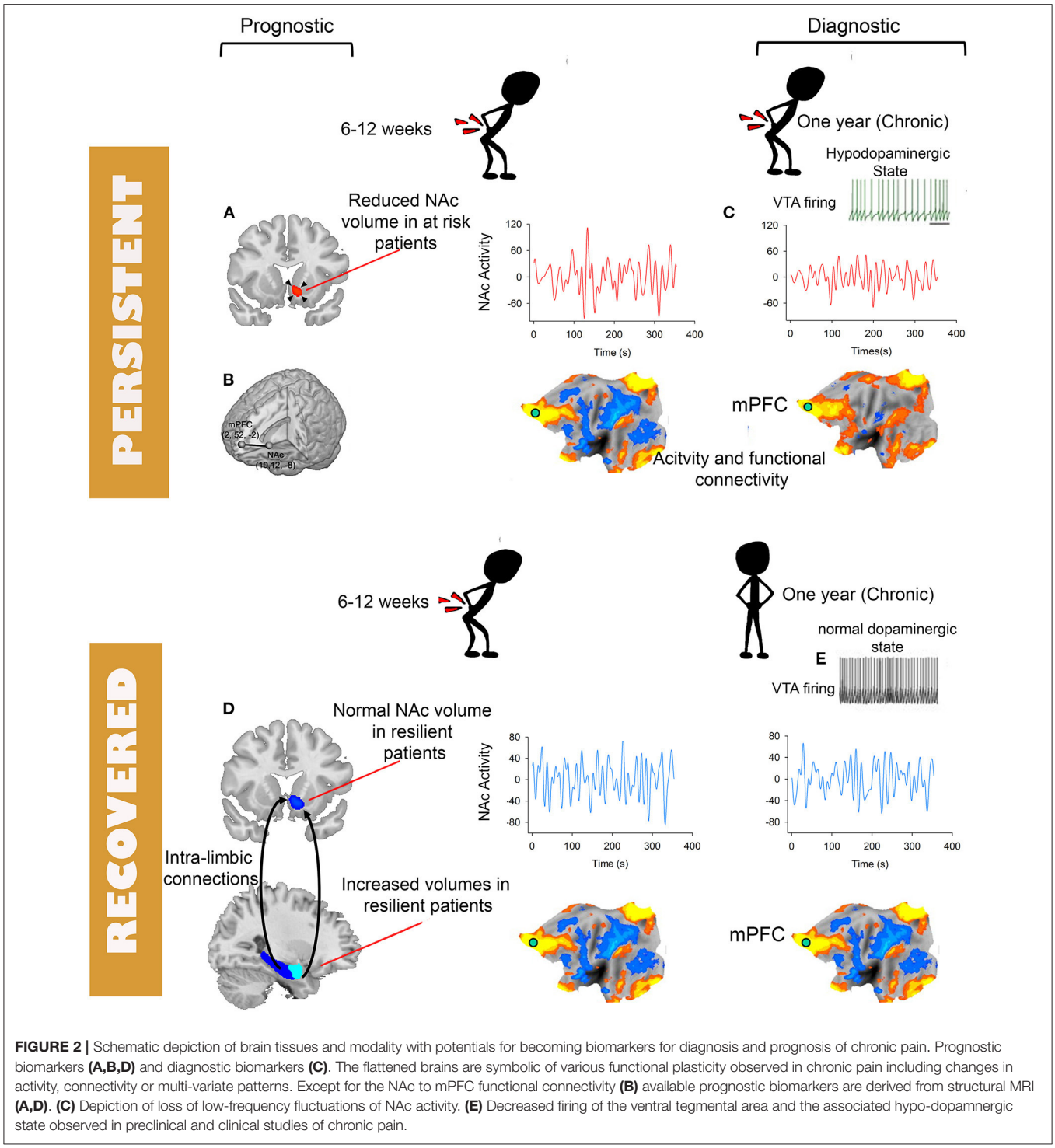


FIGURE 2 | Schematic depiction of brain tissues and modality with potentials for becoming biomarkers for diagnosis and prognosis of chronic pain. Prognostic biomarkers **(A,B,D)** and diagnostic biomarkers **(C)**. The flattened brains are symbolic of various functional plasticity observed in chronic pain including changes in activity, connectivity or multi-variate patterns. Except for the NAc to mPFC functional connectivity **(B)** available prognostic biomarkers are derived from structural MRI **(A,D)**. **(C)** Depiction of loss of low-frequency fluctuations of NAc activity. **(E)** Decreased firing of the ventral tegmental area and the associated hypo-dopamnergic state observed in preclinical and clinical studies of chronic pain.

pain. Such analysis will depend on the clinical context of use and is beyond the scope of this review. We will present, however, an example of the savings that could be achieved should a prognostic brain biomarker for spine surgery success be translated into clinical use. The literature suggests that spine surgery fails to improve CLBP pain or disability 40% of the time (178). The 2017 Medicare reimbursement rate for a lumbar fusion surgery was at $25,261 in 2017 (199). The estimated utilization rate of lumbar fusion per 1,000 beneficiaries per year was at 20.8 (199). Therefore, the total cost of failed spinal fusions would be 0.4 x 20.8 x $25,261 = $210,172 per 1,000 beneficiaries per year. Assuming a brain-based biomarker can predict success of the surgery with a 90% sensitivity and 66% specificity (**Figure 3**), the number of patients undergoing surgery will be reduced by

32%, which can save 0.32×20.8 × $25,261 - 20.8 × $1,000 = $147,337, per 1,000 beneficiary per year, where 20.8 × $1,000 is MRI related cost. This is an underestimation of the saving because the subsequent medical cost that the patients who fail the surgery will incur throughout their life is not considered. While this benefit comes at the risk of leaving out a small number of patients without surgery, who would have otherwise benefited if they had the surgery because they fall in the false negative range, it is an example of how such tools could be used to help both clinicians and patients gauge the risk of success and failure and help them come to a decision. MRI biomarkers can also provide novel standardized measures of endpoints for phase II and III clinical trials (200–202), which rely mostly on subjective pain ratings, and novel targets for reverse translational animal studies for drug developments (161, 201, 203). For example, a standardized volumetric, shape or activity measure [e.g., hippocampus (117), NAc (203)] would provide a quantitative and reliable tool for clinical pain prognosis/diagnosis. In addition, a diagnostic biomarker of chronic pain can be used as a surrogate endpoint in clinical trials to test if they are changed by analgesia and to help make medical related decision making (e.g., spine surgery). On the other hand, prognostic brain biomarkers can help identify high risk patients for chronic pain in clinical trials and hence decrease sample size requirements by targeting specifically these patients.

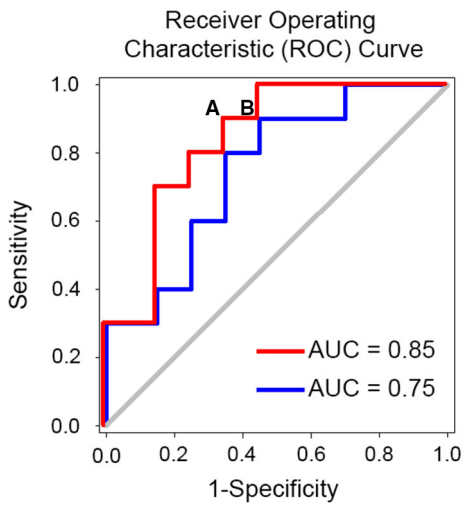


FIGURE 3 | Example of simulated receiver operating characteristic curve (ROC) and identification of optimal cut-off point for decision. An optimal cut off for predicting the success of spine surgery would minimize the false negative rate (i.e., patients who would benefit from the surgery but end up not having it) and minimize the false positive rate (FPR) (i.e., patients who would not have the surgery and end up having it). Note that the false positive rate is equal to 1-specificity and is depicted on the x-axis in the figure. If we consider point **(A)** on the red curve, we will have a biomarker with 90% sensitivity and 34% FPR or 66% specificity. Given that 60% of patients undergoing spine surgery are expected to benefit from it our theoretical biomarker will miss 10% of these patients and hence 6 patients for each 100 patients. Also, given an expected 40% failure rate we expect that ∼26 patients will not undergo the surgery anymore. In total, 32 patients who would otherwise undergo surgery without a biomarker-based work-up end up triaged to the no surgery options. If instead we consider point **(B)**, we will have a biomarker with 90% sensitivity and 45% FPR. Following the same calculation 28 patients who would otherwise undergo surgery without a biomarker-based work-up end up triaged to the no surgery options. Abbreviation: AUC, area under the curve.

COMPARISON TO OTHER PAIN (BIO-) MARKERS

Brain MRI based biomarkers offer the advantage of being part of the *specific* pathogenic process leading to chronic pain (46, 58, 174), the nervous tissue including the brain being the biological substrate of chronic pain independently from any subjective psychological reports. Once validated, brain MRI based biomarkers are therefore more amenable to reverse translation to animal research, and hence novel analgesic targets development, than quantitative sensory testing (QST) or psychosocial phenotyping (204), which depend on subjective patient reports, are unobtainable in animals. Furthermore, the direct access of brain imaging techniques to brain structure and physiology of patients' brain tissue relative to other approaches lends it more potential for specificity. For example, when different types of chronic pain patients report their stimulus-free spontaneous pain in the magnet they show different corresponding functional maps (92). Similarly, altered brain networks in chronic pain patients differ between different clinical pain syndromes (99, 114, 144). In contrast, no QST profile is specific to a given clinical pain condition (204). In addition, studies using QST to differentiate pain patients from healthy controls (205, 206) or using QST for prognostic profiling of pain patients (207) are still conflicting. Recent data has also shown that chronic pain and disability can be reduced with no associated change in QST profiles (208), and QST profiles can improve with treatment without a significant change in spontaneous subjective clinical pain (196). However, some evidence suggests that QST can predict response to chronic pain treatments (209). Compared to other biological markers of clinical pain such as genetic profiling, MRI based biomarkers have seen a faster progress (5, 174, 210, 211) and are closer to adoption in clinical trials (145, 191, 198, 212). As such progress in identifying reproducible diagnostic or prognostic genetic polymorphism for chronic pain has been limited so far to rare causes of chronic pain such as gain of function mutations of the sodium channel causing inherited erythromelalgia (213). Although more common chronic pain conditions like chronic low back pain or migraine headaches have a significant heritability (214, 215) a gene-based diagnostic biomarker, for example, is difficult to establish because these conditions are polygenic (216) hence requiring very large sample sizes for replicability, which, to date, remains limited (5, 210). The availability of large data banks with genetic information such as the UKBioBank (https://www.ukbiobank.ac.uk/) will hopefully accelerate the development of genetic biomarkers for chronic pain (217). In contrast, brain MRI based biomarkers might be more expensive than QST, psychosocial assessments, or genetic testing, and their analysis in remote medical centers might necessitate outsourcing. Regardless, the development of all these (bio)-markers of chronic pain are not mutually exclusive and will hopefully be combined to better predict outcomes.

CONCLUSION

The use of brain imaging to discover biomarker for chronic pain has a reached an exciting period as we inch closer to translate experimental findings into clinical use. The accumulation of neuroimaging repositories will tremendously help with this effort, emphasizing the need for pain scientists to share their data to allow biomarker validations across sites. Other brain imaging approaches targeting glial physiology in humans (218) and imaging of animal models of chronic pain (131, 219–221) will also help in further developing biomarkers for chronic pain and in invasively studying their sub-components.

AUTHOR CONTRIBUTIONS

PG and ZZ drafted the brain imaging sections of the manuscript. JG drafted the sections on non-imaging biomarkers. All authors edited the final version.

FUNDING

This work was supported by grants from National Institute on Drug Abuse K08DA037525, National Institute of Neurologic Disorders and Stroke R21NS1188162, Yale University Department of Psychiatry, and University of Rochester Department of Psychiatry.

REFERENCES

1. Dahlhamer J, Lucas J, Zelaya C, Nahin R, Mackey S, Debar L, et al. Prevalence of chronic pain and high-impact chronic pain among adults - United States, 2016. *MMWR Morb Mortal Wkly Rep.* (2018) 67:1001–6. doi: 10.15585/mmwr.mm6736a2
2. Mogil JS. Sex differences in pain and pain inhibition: multiple explanations of a controversial phenomenon. *Nat Rev Neurosci.* (2012) 13:859–66. doi: 10.1038/nrn3360
3. Davis KD, Aghaeepour N, Ahn AH, Angst MS, Borsook D, Brenton A, et al. Discovery and validation of biomarkers to aid the development of safe and effective pain therapeutics: challenges and opportunities. *Nat Rev Neurol.* (2020) 16:381–400. doi: 10.1038/s41582-020-0362-2
4. Ogawa S, Lee TM, Nayak AS, Glynn P. Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. *Magn Reson Med.* (1990) 14:68–78. doi: 10.1002/mrm.1910140108
5. Tracey I, Woolf CJ, Andrews NA. Composite pain biomarker signatures for objective assessment and effective treatment. *Neuron.* (2019) 101:783–800. doi: 10.1016/j.neuron.2019.02.019
6. Van Der Miesen MM, Lindquist MA, Wager TD. Neuroimaging-based biomarkers for pain: state of the field and current directions. *Pain Rep.* (2019) 4:e751. doi: 10.1097/PR9.0000000000000751
7. Catani M, Dell'acqua F, Thiebaut De Schotten M. A revised limbic system model for memory, emotion and behaviour. *Neurosci Biobehav Rev.* (2013) 37:1724–37. doi: 10.1016/j.neubiorev.2013.07.001
8. Gaskin DJ, Richard P. The economic costs of pain in the United States. *J Pain.* (2012) 13:715–24. doi: 10.1016/j.jpain.2012.03.009
9. Schappert SM, Burt CW. Ambulatory care visits to physician offices, hospital outpatient departments, and emergency departments: United States, 2001-02. *Vital Health Stat.* (2006) 13:1–66. Available online at: https://www.cdc.gov/nchs/data/series/sr_13/sr13_159.pdf
10. Hoy D, March L, Brooks P, Blyth F, Woolf A, Bain C, et al. The global burden of low back pain: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis.* (2014) 73:968–74. doi: 10.1136/annrheumdis-2013-204428
11. Hartvigsen J, Hancock MJ, Kongsted A, Louw Q, Ferreira ML, Genevay S, et al. What low back pain is and why we need to pay attention. *Lancet.* (2018) 391:2356–67. doi: 10.1016/S0140-6736(18)30480-X
12. Pitcher MH, Von Korff M, Bushnell MC, Porter L. Prevalence and profile of high-impact chronic pain in the United States. *J Pain.* (2019) 20:146–60. doi: 10.1016/j.jpain.2018.07.006
13. Okifuji A, Hare BD. The association between chronic pain and obesity. *J Pain Res.* (2015) 8:399–408. doi: 10.2147/JPR.S55598
14. Knaster P, Karlsson H, Estlander AM, Kalso E. Psychiatric disorders as assessed with SCID in chronic pain patients: the anxiety disorders precede the onset of pain. *Gen Hosp Psychiatry.* (2012) 34:46–52. doi: 10.1016/j.genhosppsych.2011.09.004
15. Chopra K, Arora V. An intricate relationship between pain and depression: clinical correlates, coactivation factors and therapeutic targets. *Expert Opin Ther Targets.* (2014) 18:159–76. doi: 10.1517/14728222.2014.855720
16. Brennan PL, Schutte KK, Moos RH. Pain and use of alcohol to manage pain: prevalence and 3-year outcomes among older problem and non-problem drinkers. *Addiction.* (2005) 100:777–86. doi: 10.1111/j.1360-0443.2005.01074.x
17. Riley JL, King C. Self-report of alcohol use for pain in a multi-ethnic community sample. *J Pain.* (2009) 10:944–52. doi: 10.1016/j.jpain.2009.03.005
18. Volkow ND, Mclellan AT. Opioid abuse in chronic pain–misconceptions and mitigation strategies. *N Engl J Med.* (2016) 374:1253–63. doi: 10.1056/NEJMra1507771
19. Institute of Medicine US Committee on Advancing Pain Research, Care, Education. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. Washington, DC: National Academies Press (2011).
20. Katz JN. Lumbar disc disorders and low-back pain: socioeconomic factors and consequences. *J.Bone Joint Surg Am.* (2006) 88:21–24. doi: 10.2106/00004623-200604002-00005
21. Murphy LB, Cisternas MG, Pasta DJ, Helmick CG, Yelin EH. Medical expenditures and earnings losses among US adults with arthritis in 2013. *Arthritis Care Res.* (2018) 70:869–76. doi: 10.1002/acr.23425
22. Dieppe P, Lim K, Lohmander S. Who should have knee joint replacement surgery for osteoarthritis? *Int J Rheum Dis.* (2011) 14:175–80. doi: 10.1111/j.1756-185X.2011.01611.x
23. Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, et al. OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis Cartilage.* (2010) 18:476–99. doi: 10.1016/j.joca.2010.01.013
24. United Nations. Department of Economic and Social Affairs. Population Division. *World Population Ageing 2009*. New York, NY: United Nations, Dept. of Economic and Social Affairs, Population Division (2010).
25. Tsang A, Von Korff M, Lee S, Alonso J, Karam E, Angermeyer MC, et al. Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. *J Pain.* (2008) 9:883–91. doi: 10.1016/j.jpain.2008.05.005
26. Mccarthy LH, Bigal ME, Katz M, Derby C, Lipton RB. Chronic pain and obesity in elderly people: results from the Einstein aging study. *J Am Geriatr Soc.* (2009) 57:115–9. doi: 10.1111/j.1532-5415.2008.02089.x
27. Fayaz A, Croft P, Langford RM, Donaldson LJ, Jones GT. Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. *BMJ Open.* (2016) 6:e010364. doi: 10.1136/bmjopen-2015-010364
28. Nahin RL. Estimates of pain prevalence and severity in adults: United States, 2012. *J Pain.* (2015) 16:769–80. doi: 10.1016/j.jpain.2015.05.002
29. Meyer T, Cooper J, Raspe H. Disabling low back pain and depressive symptoms in the community-dwelling elderly: a prospective study. *Spine.* (2007) 32:2380–6. doi: 10.1097/BRS.0b013e3181557955
30. Rudy TE, Weiner DK, Lieber SJ, Slaboda J, Boston JR. The impact of chronic low back pain on older adults: a comparative study of patients and controls. *Pain.* (2007) 131:293–301. doi: 10.1016/j.pain.2007.01.012

31. Knauer SR, Freburger JK, Carey TS. Chronic low back pain among older adults: a population-based perspective. *J Aging Health.* (2010) 22:1213–34. doi: 10.1177/0898264310374111
32. Coyle PC, Sions JM, Velasco T, Hicks GE. Older adults with chronic low back pain: a clinical population vulnerable to frailty? *J Frailty Aging.* (2015) 4:188–90. doi: 10.14283/jfa.2015.75
33. Cedraschi C, Luthy C, Allaz AF, Herrmann FR, Ludwig C. Low back pain and health-related quality of life in community-dwelling older adults. *Eur Spine J.* (2016) 25:2822–32. doi: 10.1007/s00586-016-4483-7
34. Podichetty VK, Mazanec DJ, Biscup RS. Chronic non-malignant musculoskeletal pain in older adults: clinical issues and opioid intervention. *Postgrad Med J.* (2003) 79:627–33. doi: 10.1136/pmj.79.937.627
35. Wong AY, Karppinen J, Samartzis D. Low back pain in older adults: risk factors, management options and future directions. *Scoliosis Spinal Disord.* (2017) 12:14. doi: 10.1186/s13013-017-0121-3
36. Schneider J, Algharably E, Budnick A, Wenzel A, Drager D, Kreutz R. Deficits in pain medication in older adults with chronic pain receiving home care: A cross-sectional study in Germany. *PLoS ONE.* (2020) 15:e0229229. doi: 10.1371/journal.pone.0229229
37. Cayea D, Perera S, Weiner DK. Chronic low back pain in older adults: What physicians know, what they think they know, and what they should be taught. *J Am Geriatr Soc.* (2006) 54:1772–7. doi: 10.1111/j.1532-5415.2006.00883.x
38. American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older P. Pharmacological management of persistent pain in older persons. *J Am Geriatr Soc.* (2009) 57:1331–46. doi: 10.1111/j.1532-5415.2009.02376.x
39. Nash DM, Markle-Reid M, Brimble KS, Mcarthur E, Roshanov PS, Fink JC, et al. Nonsteroidal anti-inflammatory drug use and risk of acute kidney injury and hyperkalemia in older adults: a population-based study. *Nephrol Dial Transplant.* (2019) 34:1145–54. doi: 10.1093/ndt/gfz062
40. Shorr RI, Griffin MR, Daugherty JR, Ray WA. Opioid analgesics and the risk of hip fracture in the elderly: codeine and propoxyphene. *J Gerontol.* (1992) 47:M111–5. doi: 10.1093/geronj/47.4.M111
41. Saunders KW, Dunn KM, Merrill JO, Sullivan M, Weisner C, Braden JB, et al. Relationship of opioid use and dosage levels to fractures in older chronic pain patients. *J Gen Intern Med.* (2010) 25:310–5. doi: 10.1007/s11606-009-1218-z
42. WONDER. *Wide-ranging online data for epidemiologic research (WONDER).* Atlanta, GA: CDC, National Center for Health Statistics (2020).
43. Vardeh D, Mannion RJ, Woolf CJ. Toward a Mechanism-Based Approach to Pain Diagnosis. *J Pain.* (2016) 17:T50–69. doi: 10.1016/j.jpain.2016.03.001
44. Federal Pain Research Strategy. *The Interagency Pain Research Coordinating Committee.* FPRS research recommendations (2018).
45. Maher C, Underwood M, Buchbinder R. Non-specific low back pain. *Lancet.* (2017) 389:736–47. doi: 10.1016/S0140-6736(16)30970-9
46. Smith SM, Dworkin RH, Turk DC, Baron R, Polydefkis M, Tracey I, et al. The potential role of sensory testing, skin biopsy, and functional brain imaging as biomarkers in chronic pain clinical trials: IMMPACT considerations. *J Pain.* (2017) 18:757–77. doi: 10.1016/j.jpain.2017.02.429
47. Mahmood SS, Levy D, Vasan RS, Wang TJ. The Framingham Heart Study and the epidemiology of cardiovascular disease: a historical perspective. *Lancet.* (2014) 383:999–1008. doi: 10.1016/S0140-6736(13)61752-3
48. Fuchs FD, Whelton PK. High blood pressure and cardiovascular disease. *Hypertension.* (2020) 75:285–92. doi: 10.1161/HYPERTENSIONAHA.119.14240
49. Baliki MN, Apkarian AV. Nociception, pain, negative moods, behavior selection. *Neuron.* (2015) 87:474–91. doi: 10.1016/j.neuron.2015.06.005
50. Mesulam MM. *Principles of behavioral and cognitive neurology*. New York, NY: Oxford University Press (2000).
51. Grill JD, Coghill RC. Transient analgesia evoked by noxious stimulus offset. *J Neurophysiol.* (2002) 87:2205–8. doi: 10.1152/jn.00730.2001
52. Craig AD, Bushnell MC. The thermal grill illusion: unmasking the burn of cold pain. *Science.* (1994) 265:252–5. doi: 10.1126/science.8023144
53. Prescott SA, Ma Q, De Koninck Y. Normal and abnormal coding of somatosensory stimuli causing pain. *Nat Neurosci.* (2014) 17:183–91. doi: 10.1038/nn.3629
54. Penfield W, Faulk ME. The insula; further observations on its function. *Brain.* (1955) 78:445–70. doi: 10.1093/brain/78.4.445
55. Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. *Eur J Pain.* (2005) 9:463–84. doi: 10.1016/j.ejpain.2004.11.001
56. Bushnell MC, Ceko M, Low LA. Cognitive and emotional control of pain and its disruption in chronic pain. *Nat Rev Neurosci.* (2013) 14:502–11. doi: 10.1038/nrn3516
57. Kuner R, Flor H. Structural plasticity and reorganisation in chronic pain. *Nat Rev Neurosci.* (2016) 18:20–30. doi: 10.1038/nrn.2016.162
58. Mouraux A, Iannetti GD. The search for pain biomarkers in the human brain. *Brain.* (2018) 141:3290–307. doi: 10.1093/brain/awy281
59. Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. *Neuron.* (2007) 55:377–91. doi: 10.1016/j.neuron.2007.07.012
60. Jensen KB, Regenbogen C, Ohse MC, Frasnelli J, Freiherr J, Lundstrom JN. Brain activations during pain: a neuroimaging meta-analysis of patients with pain and healthy controls. *Pain.* (2016) 157:1279–86. doi: 10.1097/j.pain.0000000000000517
61. Baliki MN, Geha PY, Apkarian AV. Parsing pain perception between nociceptive representation and magnitude estimation. *J Neurophysiol.* (2009) 101:875–87. doi: 10.1152/jn.91100.2008
62. Legrain V, Iannetti GD, Plaghki L, Mouraux A. The pain matrix reloaded: a salience detection system for the body. *Prog Neurobiol.* (2011) 93:111–24. doi: 10.1016/j.pneurobio.2010.10.005
63. Shackman AJ, Salomons TV, Slagter HA, Fox AS, Winter JJ, Davidson RJ. The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nat Rev Neurosci.* (2011) 12:154–67. doi: 10.1038/nrn2994
64. Salomons TV, Iannetti GD, Liang M, Wood JN. The "Pain Matrix" in pain-free individuals. *JAMA Neurol.* (2016) 73:755–6. doi: 10.1001/jamaneurol.2016.0653
65. Friston KJ, Holmes AP, Worsley KJ, Poline JB, Frith CD, Frackowiak RS. Statistic parametric maps in functional imaging: A general linear approach. *Hum.Brain Mapp.* (1994) 2:189–210. doi: 10.1002/hbm.460020402
66. Kucyi A, Davis KD. The dynamic pain connectome. *Trends Neurosci.* (2015) 38:86–95. doi: 10.1016/j.tins.2014.11.006
67. Wager TD, Atlas LY, Lindquist MA, Roy M, Woo CW, Kross E. An fMRI-based neurologic signature of physical pain. *N Engl J Med.* (2013) 368:1388–97. doi: 10.1056/NEJMoa1204471
68. Ung H, Brown JE, Johnson KA, Younger J, Hush J, Mackey S. Multivariate classification of structural MRI data detects chronic low back pain. *Cereb Cortex.* (2014) 24:1037–44. doi: 10.1093/cercor/bhs378
69. Labus JS, Van Horn JD, Gupta A, Alaverdyan M, Torgerson C, Ashe-Mcnalley C, et al. Multivariate morphological brain signatures predict patients with chronic abdominal pain from healthy control subjects. *Pain.* (2015) 156:1545–54. doi: 10.1097/j.pain.0000000000000196
70. Berridge KC, Kringelbach ML. Pleasure systems in the brain. *Neuron.* (2015) 86:646–64. doi: 10.1016/j.neuron.2015.02.018
71. Small DM, Green BG. A proposed model of a flavor modality. *Sci Stud Read.* (2012) 16:504–25. doi: 10.1037/e512592013-002
72. Melzack R, Casey K. Sensory, motivational, and central contol determinants of pain. In Kenshalo DR, editor. *The Skin Senses*. Springfield: Charles C. Thomas (1968).
73. Price DD. Psychological and neural mechanisms of the affective dimension of pain. *Science.* (2000) 288:1769–72. doi: 10.1126/science.288.5472.1769
74. Seymour B. Pain: a precision signal for reinforcement learning and control. *Neuron.* (2019) 101:1029–41. doi: 10.1016/j.neuron.2019.01.055
75. Balleine BW, O'doherty JP. Human and rodent homologies in action control: corticostriatal determinants of goal-directed and habitual action. *Neuropsychopharmacology.* (2010) 35:48–69. doi: 10.1038/npp.2009.131
76. Ledoux JE. Coming to terms with fear. *Proc Natl Acad Sci USA.* (2014) 111:2871–8. doi: 10.1073/pnas.1400335111
77. Crook RJ, Dickson K, Hanlon RT, Walters ET. Nociceptive sensitization reduces predation risk. *Curr Biol.* (2014) 24:1121–5. doi: 10.1016/j.cub.2014.03.043
78. Nesse RM, Schulkin J. An evolutionary medicine perspective on pain and its disorders. *Philos Trans R Soc Lond B Biol Sci.* (2019) 374:20190288. doi: 10.1098/rstb.2019.0288
79. Apkarian AV, Mutso AA, Centeno MV, Kan L, Wu M, Levinstein M, et al. Role of adult hippocampal neurogenesis in persistent pain. *Pain.* (2016) 157:418–28. doi: 10.1097/j.pain.0000000000000332

80. Ji G, Sun H, Fu Y, Li Z, Pais-Vieira M, Galhardo V, et al. Cognitive impairment in pain through amygdala-driven prefrontal cortical deactivation. *J Neurosci.* (2010) 30:5451–64. doi: 10.1523/JNEUROSCI.0225-10.2010
81. Mutso AA, Radzicki D, Baliki MN, Huang L, Banisadr G, Centeno MV, et al. Abnormalities in hippocampal functioning with persistent pain. *J Neurosci.* (2012) 32:5747–56. doi: 10.1523/JNEUROSCI.0587-12.2012
82. Liu Y, Zhou LJ, Wang J, Li D, Ren WJ, Peng J, et al. TNF-alpha differentially regulates synaptic plasticity in the hippocampus and spinal cord by microglia-dependent mechanisms after peripheral nerve injury. *J Neurosci.* (2017) 37:871–81. doi: 10.1523/JNEUROSCI.2235-16.2016
83. Berger SE, Vachon-Presseau E, Abdullah TB, Baria AT, Schnitzer TJ, Apkarian AV. Hippocampal morphology mediates biased memories of chronic pain. *Neuroimage.* (2018) 166:86–98. doi: 10.1016/j.neuroimage.2017.10.030
84. Apkarian AV, Sosa Y, Krauss BR, Thomas PS, Fredrickson BE, Levy RE, et al. Chronic pain patients are impaired on an emotional decision-making task. *Pain.* (2004) 108:129–36. doi: 10.1016/j.pain.2003.12.015
85. Verdejo-Garcia A, Lopez-Torrecillas F, Calandre EP, Delgado-Rodriguez A, Bechara A. Executive function and decision-making in women with fibromyalgia. *Arch Clin Neuropsychol.* (2009) 24:113–22. doi: 10.1093/arclin/acp014
86. Walteros C, Sanchez-Navarro JP, Munoz MA, Martinez-Selva JM, Chialvo D, Montoya P. Altered associative learning and emotional decision making in fibromyalgia. *J Psychosom Res.* (2011) 70:294–301. doi: 10.1016/j.jpsychores.2010.07.013
87. Tamburin S, Maier A, Schiff S, Lauriola MF, Di Rosa E, Zanette G, et al. Cognition and emotional decision-making in chronic low back pain: an ERPs study during Iowa gambling task. *Front Psychol.* (2014) 5:1350. doi: 10.3389/fpsyg.2014.01350
88. Apkarian AV. Pain perception in relation to emotional learning. *Curr Opin Neurobiol.* (2008) 18:464–8. doi: 10.1016/j.conb.2008.09.012
89. Mansour AR, Farmer MA, Baliki MN, Apkarian AV. Chronic pain: the role of learning and brain plasticity. *Restor Neurol Neurosci.* (2014) 32:129–39. doi: 10.3233/RNN-139003
90. Squire LR. Memory systems of the brain: a brief history and current perspective. *Neurobiol Learn Mem.* (2004) 82:171–7. doi: 10.1016/j.nlm.2004.06.005
91. Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. *Lancet Psychiatry*. (2016) 3:760–73. doi: 10.1016/S2215-0366(16)00104-8
92. Apkarian AV, Baliki MN, Geha PY. Towards a theory of chronic pain. *Prog.Neurobiol.* (2009) 87:81–97. doi: 10.1016/j.pneurobio.2008.09.018
93. Borsook D, Linnman C, Faria V, Strassman AM, Becerra L, Elman I. Reward deficiency and anti-reward in pain chronification. *Neurosci Biobehav Rev.* (2016) 68:282–97. doi: 10.1016/j.neubiorev.2016.05.033
94. Dossantos MF, Moura BS, Dasilva AF. Reward circuitry plasticity in pain perception and modulation. *Front Pharmacol.* (2017) 8:790. doi: 10.3389/fphar.2017.00790
95. Baliki MN, Chialvo DR, Geha PY, Levy RM, Harden RN, Parrish TB, et al. Chronic pain and the emotional brain: specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. *J Neurosci.* (2006) 26:12165–73. doi: 10.1523/JNEUROSCI.3576-06.2006
96. Baliki MN, Geha PY, Fields HL, Apkarian AV. Predicting value of pain and analgesia: nucleus accumbens response to noxious stimuli changes in the presence of chronic pain. *Neuron.* (2010) 66:149–60. doi: 10.1016/j.neuron.2010.03.002
97. Baliki MN, Baria AT, Apkarian AV. The cortical rhythms of chronic back pain. *J Neurosci.* (2011) 31:13981–90. doi: 10.1523/JNEUROSCI.1984-11.2011
98. Hashmi JA, Baliki MN, Huang L, Baria AT, Torbey S, Hermann KM, et al. Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits. *Brain.* (2013) 136:2751–68. doi: 10.1093/brain/awt211
99. Tu Y, Jung M, Gollub RL, Napadow V, Gerber J, Ortiz A, et al. Abnormal medial prefrontal cortex functional connectivity and its association with clinical symptoms in chronic low back pain. *Pain.* (2019) 160:1308–18. doi: 10.1097/j.pain.0000000000001507
100. Makary MM, Polosecki P, Cecchi GA, Dearaujo IE, Barron DS, Constable TR, et al. Loss of nucleus accumbens low-frequency fluctuations is a signature of chronic pain. *Proc Nat Acad Sci USA.* (2020) 2019:18682. doi: 10.1073/pnas.1918682117
101. Geha PY, Baliki MN, Chialvo DR, Harden RN, Paice JA, Apkarian AV. Brain activity for spontaneous pain of postherpetic neuralgia and its modulation by lidocaine patch therapy. *Pain.* (2007) 128:88–100. doi: 10.1016/j.pain.2006.09.014
102. Pujol J, Martinez-Vilavella G, Llorente-Onaindia J, Harrison BJ, Lopez-Sola M, Lopez-Ruiz M, et al. Brain imaging of pain sensitization in patients with knee osteoarthritis. *Pain.* (2017) 158:1831–8. doi: 10.1097/j.pain.0000000000000985
103. Sprenger T, Borsook D. Migraine changes the brain: neuroimaging makes its mark. *Curr Opin Neurol.* (2012) 25:252–62. doi: 10.1097/WCO.0b013e3283532ca3
104. Harris RE, Clauw DJ, Scott DJ, Mclean SA, Gracely RH, Zubieta JK. Decreased central mu-opioid receptor availability in fibromyalgia. *J Neurosci.* (2007) 27:10000–6. doi: 10.1523/JNEUROSCI.2849-07.2007
105. Maarrawi J, Peyron R, Mertens P, Costes N, Magnin M, Sindou M, et al. Differential brain opioid receptor availability in central and peripheral neuropathic pain. *Pain.* (2007) 127:183–94. doi: 10.1016/j.pain.2006.10.013
106. Nusbaum F, Redoute J, Le BD, Volckmann P, Simon F, Hannoun S, et al. Chronic low-back pain modulation is enhanced by hypnotic analgesic suggestion by recruiting an emotional network: a PET imaging study. *Int J Clin Exp Hypn.* (2011) 59:27–44. doi: 10.1080/00207144.2011.522874
107. Dossantos MF, Martikainen IK, Nascimento TD, Love TM, Deboer MD, Maslowski EC, et al. Reduced basal ganglia mu-opioid receptor availability in trigeminal neuropathic pain: A pilot study. *Mol Pain.* (2012) 8:74. doi: 10.1186/1744-8069-8-74
108. Levy DJ, Glimcher PW. The root of all value: a neural common currency for choice. *Curr Opin Neurobiol.* (2012) 22:1027–38. doi: 10.1016/j.conb.2012.06.001
109. Mogenson GJ, Jones DL, Yim CY. From motivation to action: functional interface between the limbic system and the motor system. *Prog Neurobiol.* (1980) 14:69–97. doi: 10.1016/0301-0082(80)90018-0
110. Fields H. State-dependent opioid control of pain. *Nat Rev Neurosci.* (2004) 5:565–75. doi: 10.1038/nrn1431
111. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. *Psychol Bull.* (2007) 133:581–624. doi: 10.1037/0033-2909.133.4.581
112. Loggia ML, Berna C, Kim J, Cahalan CM, Gollub RL, Wasan AD, et al. Disrupted brain circuitry for pain-related reward/punishment in fibromyalgia. *Arthritis Rheumatol.* (2014) 66:203–12. doi: 10.1002/art.38191
113. Hadjikhani N, Ward N, Boshyan J, Napadow V, Maeda Y, Truini A, et al. The missing link: enhanced functional connectivity between amygdala and visceroceptive cortex in migraine. *Cephalalgia.* (2013) 33:1264–8. doi: 10.1177/0333102413490344
114. Chen Z, Chen X, Liu M, Dong Z, Ma L, Yu S. Altered functional connectivity of amygdala underlying the neuromechanism of migraine pathogenesis. *J Headache Pain.* (2017) 18:7. doi: 10.1186/s10194-017-0722-5
115. Huang X, Zhang D, Wang P, Mao C, Miao Z, Liu C, et al. Altered amygdala effective connectivity in migraine without aura: evidence from resting-state fMRI with Granger causality analysis. *J Headache Pain.* (2021) 22:25. doi: 10.1186/s10194-021-01240-8
116. Mao CP, Yang HJ. Smaller amygdala volumes in patients with chronic low back pain compared with healthy control individuals. *J Pain.* (2015) 16:1366–76. doi: 10.1016/j.jpain.2015.08.012
117. Vachon-Presseau E, Tetreault P, Petre B, Huang L, Berger SE, Torbey S, et al. Corticolimbic anatomical characteristics predetermine risk for chronic pain. *Brain.* (2016) 139:1958–70. doi: 10.1093/brain/aww100
118. Mcmahon SB. *Wall and Melzack's Textbook of Pain*. Philadelphia, PA: Elsevier/Saunders (2013).
119. Klop EM, Mouton LJ, Hulsebosch R, Boers J, Holstege G. In cat four times as many lamina I neurons project to the parabrachial nuclei and twice as many to the periaqueductal gray as to the thalamus. *Neuroscience.* (2005) 134:189–97. doi: 10.1016/j.neuroscience.2005.03.035

120. Gauriau C, Bernard JF. Pain pathways and parabrachial circuits in the rat. *Exp Physiol.* (2002) 87:251–8. doi: 10.1113/eph8702357
121. Floresco SB. The nucleus accumbens: an interface between cognition, emotion, and action. *Annu Rev Psychol.* (2015) 66:25–52. doi: 10.1146/annurev-psych-010213-115159
122. Neugebauer V. Amygdala pain mechanisms. *Handb Exp Pharmacol.* (2015) 227:261–84. doi: 10.1007/978-3-662-46450-2_13
123. Ji RR, Chamessian A, Zhang YQ. Pain regulation by non-neuronal cells and inflammation. *Science.* (2016) 354:572–7. doi: 10.1126/science.aaf8924
124. FDA-NIH, Biomarker Working Group. *BEST (Biomarkers, EndpointS, and other Tools) Resource*. (Silver Spring, MD) (2016).
125. Guyon I, Elisseeff A. An introduction to variable and feature selection. *J Mach Learn Res.* (2003) 3:1157–82. doi: 10.1162/153244303322753616
126. Tibshirani R. Regression shrinkage and selection via the Lasso. *J R Statistical Soc Series B-Methodol.* (1996) 58:267–88. doi: 10.1111/j.2517-6161.1996.tb02080.x
127. Zou H, Hastie T. Regularization and variable selection via the elastic net. *J R Statist Soc Series B.* (2005) 67:301–20. doi: 10.1111/j.1467-9868.2005.00503.x
128. Knight K, Fu WJ. Asymptotics for lasso-type estimators. *Ann Stat.* (2000) 28:1356–78. doi: 10.1214/aos/1015957397
129. Zhao P, Yu B. On model selection consistency of Lasso. *J Mach Learn Res.* (2006) 7:2541–63.
130. Liu M, Zhang Z, Dunson DB. Graph auto-encoding brain networks with applications to analyzing large-scale brain imaging datasets. *Neuroimage.* (2021) 245:118750. doi: 10.1016/j.neuroimage.2021.118750
131. Mansour A, Baria AT, Tetreault P, Vachon-Presseau E, Chang PC, Huang L, et al. Global disruption of degree rank order: a hallmark of chronic pain. *Sci Rep.* (2016) 6:34853. doi: 10.1038/srep34853
132. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson.Med.* (1995) 34:537–41. doi: 10.1002/mrm.1910340409
133. Achard S, Delon-Martin C, Vertes PE, Renard F, Schenck M, Schneider F, et al. Hubs of brain functional networks are radically reorganized in comatose patients. *Proc Natl Acad Sci USA.* (2012) 109:20608–13. doi: 10.1073/pnas.1208933109
134. Pinheiro ES, De Queiros FC, Montoya P, Santos CL, Do Nascimento MA, Ito CH, et al. Electroencephalographic patterns in chronic pain: a systematic review of the literature. *PLoS ONE.* (2016) 11:e0149085. doi: 10.1371/journal.pone.0149085
135. Graversen C, Olesen SS, Olesen AE, Steimle K, Farina D, Wilder-Smith OH, et al. The analgesic effect of pregabalin in patients with chronic pain is reflected by changes in pharmaco-EEG spectral indices. *Br J Clin Pharmacol.* (2012) 73:363–72. doi: 10.1111/j.1365-2125.2011.04104.x
136. Cortes C, Vapnik V. Support-vector networks. *Mach Learn.* (1995) 20:273–97. doi: 10.1007/BF00994018
137. Vanneste S, Song JJ, De Ridder D. Thalamocortical dysrhythmia detected by machine learning. *Nat Commun.* (2018) 9:1103. doi: 10.1038/s41467-018-02820-0
138. Vuckovic A, Gallardo VJF, Jarjees M, Fraser M, Purcell M. Prediction of central neuropathic pain in spinal cord injury based on EEG classifier. *Clin Neurophysiol.* (2018) 129:1605–17. doi: 10.1016/j.clinph.2018.04.750
139. Dinh ST, Nickel MM, Tiemann L, May ES, Heitmann H, Hohn VD, et al. Brain dysfunction in chronic pain patients assessed by resting-state electroencephalography. *Pain.* (2019) 160:2751. doi: 10.1101/595470
140. Levitt J, Edhi MM, Thorpe RV, Leung JW, Michishita M, Koyama S, et al. Pain phenotypes classified by machine learning using electroencephalography features. *Neuroimage.* (2020) 223:117256. doi: 10.1016/j.neuroimage.2020.117256
141. Schulman JJ, Ramirez RR, Zonenshayn M, Ribary U, Llinas R. Thalamocortical dysrhythmia syndrome: MEG imaging of neuropathic pain. *Thalamus Relat Syst.* (2005) 3:33–9. doi: 10.1017/S1472928805000063
142. Baliki MN, Geha PY, Apkarian AV, Chialvo DR. Beyond feeling: chronic pain hurts the brain, disrupting the default-mode network dynamics. *J Neurosci.* (2008) 28:1398–403. doi: 10.1523/JNEUROSCI.4123-07.2008
143. Kucyi A, Moayedi M, Weissman-Fogel I, Goldberg MB, Freeman BV, Tenenbaum HC, et al. Enhanced medial prefrontal-default mode network functional connectivity in chronic pain and its association with pain rumination. *J Neurosci.* (2014) 34:3969–75. doi: 10.1523/JNEUROSCI.5055-13.2014
144. Napadow V, Lacount L, Park K, As-Sanie S, Clauw DJ, Harris RE. Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity. *Arthritis Rheum.* (2010) 62:2545–55. doi: 10.1002/art.27497
145. Napadow V, Kim J, Clauw DJ, Harris RE. Decreased intrinsic brain connectivity is associated with reduced clinical pain in fibromyalgia. *Arthritis Rheum.* (2012) 64:2398–403. doi: 10.1002/art.34412
146. Hsiao FJ, Wang SJ, Lin YY, Fuh JL, Ko YC, Wang PN, et al. Altered insula-default mode network connectivity in fibromyalgia: a resting-state magnetoencephalographic study. *J Headache Pain.* (2017) 18:89. doi: 10.1186/s10194-017-0799-x
147. Cottam WJ, Iwabuchi SJ, Drabek MM, Reckziegel D, Auer DP. Altered connectivity of the right anterior insula drives the pain connectome changes in chronic knee osteoarthritis. *Pain.* (2018) 159:929–38. doi: 10.1097/j.pain.0000000000001209
148. Haxby JV, Gobbini MI, Furey ML, Ishai A, Schouten JL, Pietrini P. Distributed and overlapping representations of faces and objects in ventral temporal cortex. *Science.* (2001) 293:2425–30. doi: 10.1126/science.1063736
149. Pereira F, Mitchell T, Botvinick M. Machine learning classifiers and fMRI: a tutorial overview. *Neuroimage.* (2009) 45:S199–209. doi: 10.1016/j.neuroimage.2008.11.007
150. Ashburner J, Friston KJ. Voxel-based morphometry–the methods. *Neuroimage.* (2000) 11:805–21. doi: 10.1006/nimg.2000.0582
151. Fischl B. FreeSurfer. *Neuroimage.* (2012) 62:774–781. doi: 10.1016/j.neuroimage.2012.01.021
152. Mano H, Kotecha G, Leibnitz K, Matsubara T, Sprenger C, Nakae A, et al. Classification and characterisation of brain network changes in chronic back pain: A multicenter study. *Wellcome Open Res.* (2018) 3:19. doi: 10.12688/wellcomeopenres.14069.2
153. Rubinov M, Sporns O. Complex network measures of brain connectivity: uses and interpretations. *Neuroimage.* (2010) 52:1059–69. doi: 10.1016/j.neuroimage.2009.10.003
154. Lopez-Sola M, Woo CW, Pujol J, Deus J, Harrison BJ, Monfort J, et al. Towards a neurophysiological signature for fibromyalgia. *Pain.* (2017) 158:34–47. doi: 10.1097/j.pain.0000000000000707
155. Jones EG. Thalamocortical dysrhythmia and chronic pain. *Pain.* (2010) 150:4–5. doi: 10.1016/j.pain.2010.03.022
156. Tu Y, Fu Z, Mao C, Falahpour M, Gollub RL, Park J, et al. Distinct thalamocortical network dynamics are associated with the pathophysiology of chronic low back pain. *Nat Commun.* (2020) 11:3948. doi: 10.1038/s41467-020-17788-z
157. Lee JJ, Kim HJ, Ceko M, Park BY, Lee SA, Park H, et al. A neuroimaging biomarker for sustained experimental and clinical pain. *Nat Med.* (2021) 27:174–82. doi: 10.1038/s41591-020-1142-7
158. Baliki MN, Petre B, Torbey S, Herrmann KM, Huang L, Schnitzer TJ, et al. Corticostriatal functional connectivity predicts transition to chronic back pain. *Nat Neurosci.* (2012) 15:1117–9. doi: 10.1038/nn.3153
159. Gohel SR, Biswal BB. Functional integration between brain regions at rest occurs in multiple-frequency bands. *Brain Connect.* (2015) 5:23–34. doi: 10.1089/brain.2013.0210
160. Woo CW, Roy M, Buhle JT, Wager TD. Distinct brain systems mediate the effects of nociceptive input and self-regulation on pain. *PLoS Biol.* (2015) 13:e1002036. doi: 10.1371/journal.pbio.1002036
161. Lee M, Manders TR, Eberle SE, Su C, D'amour J, Yang R, et al. Activation of corticostriatal circuitry relieves chronic neuropathic pain. *J Neurosci.* (2015) 35:5247–59. doi: 10.1523/JNEUROSCI.3494-14.2015
162. Ren W, Centeno MV, Berger S, Wu Y, Na X, Liu X, et al. The indirect pathway of the nucleus accumbens shell amplifies neuropathic pain. *Nat Neurosci.* (2016) 19:220–2. doi: 10.1038/nn.4199
163. Jaaskelainen SK, Rinne JO, Forssell H, Tenovuo O, Kaasinen V, Sonninen P, et al. Role of the dopaminergic system in chronic pain – a fluorodopa-PET study. *Pain.* (2001) 90:257–60. doi: 10.1016/S0304-3959(00)00409-7
164. Hagelberg N, Forssell H, Aalto S, Rinne JO, Scheinin H, Taiminen T, et al. Altered dopamine D2 receptor binding in atypical facial pain. *Pain.* (2003) 106:43–8. doi: 10.1016/S0304-3959(03)00275-6

165. Hagelberg N, Forssell H, Rinne JO, Scheinin H, Taiminen T, Aalto S, et al. Striatal dopamine D1 and D2 receptors in burning mouth syndrome. *Pain.* (2003) 101:149–54. doi: 10.1016/S0304-3959(02)00323-8
166. Kuhn S, Gallinat J. The neural correlates of subjective pleasantness. *Neuroimage.* (2012) 61:289–94. doi: 10.1016/j.neuroimage.2012.02.065
167. Salamone JD, Correa M. The mysterious motivational functions of mesolimbic dopamine. *Neuron.* (2012) 76:470–85. doi: 10.1016/j.neuron.2012.10.021
168. Geha P, Dearaujo I, Green B, Small DM. Decreased food pleasure and disrupted satiety signals in chronic low back pain. *Pain.* (2014) 155:712–22. doi: 10.1016/j.pain.2013.12.027
169. Garland EL, Trostheim M, Eikemo M, Ernst G, Leknes S. Anhedonia in chronic pain and prescription opioid misuse. *Psychol Med.* (2019) 2019:1–12. doi: 10.31234/osf.io/ghrdb
170. Woo CW, Chang LJ, Lindquist MA, Wager TD. Building better biomarkers: brain models in translational neuroimaging. *Nat Neurosci.* (2017) 20:365–77. doi: 10.1038/nn.4478
171. Mansour AR, Baliki MN, Huang L, Torbey S, Herrmann KM, Schnitzer TJ, et al. Brain white matter structural properties predict transition to chronic pain. *Pain.* (2013) 154:2160–8. doi: 10.1016/j.pain.2013.06.044
172. Vollmar C, O'muircheartaigh J, Barker GJ, Symms MR, Thompson P, Kumari V, et al. Identical, but not the same: intra-site and inter-site reproducibility of fractional anisotropy measures on two 3.0T scanners. *Neuroimage.* (2010) 51:1384–94. doi: 10.1016/j.neuroimage.2010.03.046
173. Venkatraman VK, Gonzalez CE, Landman B, Goh J, Reiter DA, An Y, et al. Region of interest correction factors improve reliability of diffusion imaging measures within and across scanners and field strengths. *Neuroimage.* (2015) 119:406–16. doi: 10.1016/j.neuroimage.2015.06.078
174. Woo CW, Wager TD. Neuroimaging-based biomarker discovery and validation. *Pain.* (2015) 156:1379–81. doi: 10.1097/j.pain.0000000000000223
175. Braun U, Plichta MM, Esslinger C, Sauer C, Haddad L, Grimm O, et al. Test-retest reliability of resting-state connectivity network characteristics using fMRI and graph theoretical measures. *Neuroimage.* (2012) 59:1404–12. doi: 10.1016/j.neuroimage.2011.08.044
176. Birn RM, Molloy EK, Patriat R, Parker T, Meier TB, Kirk GR, et al. The effect of scan length on the reliability of resting-state fMRI connectivity estimates. *Neuroimage.* (2013) 83:550–8. doi: 10.1016/j.neuroimage.2013.05.099
177. Noble S, Scheinost D, Finn ES, Shen X, Papademetris X, Mcewen SC, et al. Multisite reliability of MR-based functional connectivity. *Neuroimage.* (2017) 146:959–70. doi: 10.1016/j.neuroimage.2016.10.020
178. Thomson S. Failed back surgery syndrome - definition, epidemiology and demographics. *Br J Pain.* (2013) 7:56–9. doi: 10.1177/2049463713479096
179. De Silva T, Vedula SS, Perdomo-Pantoja A, Vijayan R, Doerr SA, Uneri A, et al. SpineCloud: image analytics for predictive modeling of spine surgery outcomes. *J Med Imaging (Bellingham).* (2020) 7:031502. doi: 10.1117/12.2566372
180. De Luca M, Beckmann CF, De Stefano N, Matthews PM, Smith SM. fMRI resting state networks define distinct modes of long-distance interactions in the human brain 1. *Neuroimage.* (2006) 29:1359–67. doi: 10.1016/j.neuroimage.2005.08.035
181. Patenaude B, Smith SM, Kennedy DN, Jenkinson M. A Bayesian model of shape and appearance for subcortical brain segmentation. *Neuroimage.* (2011) 56:907–22. doi: 10.1016/j.neuroimage.2011.02.046
182. Beaulieu C. The basis of anisotropic water diffusion in the nervous system - a technical review. *NMR Biomed.* (2002) 15:435–55. doi: 10.1002/nbm.782
183. Behrens TE, Johansen-Berg H, Woolrich MW, Smith SM, Wheeler-Kingshott CA, Boulby PA, et al. Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. *Nat.Neurosci.* (2003) 6:750–7. doi: 10.1038/nn1075
184. Wholley D. The biomarkers consortium. *Nat Rev Drug Discov.* (2014) 13:791–2. doi: 10.1038/nrd4439
185. Hoffman KM, Trawalter S, Axt JR, Oliver MN. Racial bias in pain assessment and treatment recommendations, and false beliefs about biological differences between blacks and whites. *Proc Natl Acad Sci USA.* (2016) 113:4296–301. doi: 10.1073/pnas.1516047113
186. Craig KD, Holmes C, Hudspith M, Moor G, Moosa-Mitha M, Varcoe C, et al. Pain in persons who are marginalized by social conditions. *Pain.* (2020) 161:261–5. doi: 10.1097/j.pain.0000000000001719
187. Pustilnik AC. Legal evidence of subjective states: a brain-based model of chronic pain increases accuracy and fairness in law. *Harv Rev Psychiatry.* (2017) 25:279–88. doi: 10.1097/HRP.0000000000000175
188. Balague F, Mannion AF, Pellise F, Cedraschi C. Non-specific low back pain. *Lancet.* (2012) 379:482–91. doi: 10.1016/S0140-6736(11)60610-7
189. Clauw DJ. Fibromyalgia: a clinical review. *JAMA.* (2014) 311:1547–55. doi: 10.1001/jama.2014.3266
190. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Hauser W, Katz RL, et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. *Semin Arthritis Rheum.* (2016) 46:319–29. doi: 10.1016/j.semarthrit.2016.08.012
191. Davis KD, Flor H, Greely HT, Iannetti GD, Mackey S, Ploner M, et al. Brain imaging tests for chronic pain: medical, legal and ethical issues and recommendations. *Nat Rev Neurol.* (2017) 13:624–38. doi: 10.1038/nrneurol.2017.122
192. Borsook D, Becerra L, Hargreaves R. Biomarkers for chronic pain and analgesia. Part. 2: how, where, and what to look for using functional imaging. *Discov Med.* (2011) 11:209–19.
193. Boissoneault J, Sevel L, Letzen J, Robinson M, Staud R. Biomarkers for musculoskeletal pain conditions: use of brain imaging and machine learning. *Curr Rheumatol Rep.* (2017) 19:5. doi: 10.1007/s11926-017-0629-9
194. Mackey S, Greely HT, Martucci KT. Neuroimaging-based pain biomarkers: definitions, clinical and research applications, and evaluation frameworks to achieve personalized pain medicine. *Pain Rep.* (2019) 4:e762. doi: 10.1097/PR9.0000000000000762
195. Pfannmoller J, Lotze M. Review on biomarkers in the resting-state networks of chronic pain patients. *Brain Cogn.* (2019) 131:4–9. doi: 10.1016/j.bandc.2018.06.005
196. Harris RE, Napadow V, Huggins JP, Pauer L, Kim J, Hampson J, et al. Pregabalin rectifies aberrant brain chemistry, connectivity, and functional response in chronic pain patients. *Anesthesiology.* (2013) 119:1453–64. doi: 10.1097/ALN.0000000000000017
197. Ashar YK, Clark J, Gunning FM, Goldin P, Gross JJ, Wager TD. Brain markers predicting response to cognitive-behavioral therapy for social anxiety disorder: an independent replication of Whitfield-Gabrieli et al. 2015. *Transl Psychiatry.* (2021) 11:260. doi: 10.1038/s41398-021-01366-y
198. Reckziegel D, Tetreault P, Ghantous M, Wakaizumi K, Petre B, Huang L, et al. Sex-specific pharmacotherapy for back pain: a proof-of-concept randomized trial. *Pain Ther.* (2021) 10:1375–400. doi: 10.1007/s40122-021-00297-2
199. Lopez CD, Boddapati V, Lombardi JM, Lee NJ, Saifi C, Dyrszka MD, et al. Recent trends in medicare utilization and reimbursement for lumbar spine fusion and discectomy procedures. *Spine J.* (2020) 20:1586–94. doi: 10.1016/j.spinee.2020.05.558
200. Wanigasekera V, Lee MC, Rogers R, Kong Y, Leknes S, Andersson J, et al. Baseline reward circuitry activity and trait reward responsiveness predict expression of opioid analgesia in healthy subjects. *Proc Natl Acad Sci USA.* (2012) 109:17705–10. doi: 10.1073/pnas.1120201109
201. Borsook D, Becerra L, Fava M. Use of functional imaging across clinical phases in CNS drug development. *Transl Psychiatry.* (2013) 3:e282. doi: 10.1038/tp.2013.43
202. Wanigasekera V, Mezue M, Andersson J, Kong Y, Tracey I. Disambiguating pharmacodynamic efficacy from behavior with neuroimaging: implications for analgesic drug development. *Anesthesiology.* (2016) 124:159–68. doi: 10.1097/ALN.0000000000000924
203. Becerra L, Navratilova E, Porreca F, Borsook D. Analogous responses in the nucleus accumbens and cingulate cortex to pain onset (aversion) and offset (relief) in rats and humans. *J Neurophysiol.* (2013) 110:1221–6. doi: 10.1152/jn.00284.2013
204. Edwards RR, Dworkin RH, Turk DC, Angst MS, Dionne R, Freeman R, et al. Patient phenotyping in clinical trials of chronic pain treatments: IMMPACT recommendations. *Pain.* (2016) 157:1851–71. doi: 10.1097/j.pain.0000000000000602
205. Roussel NA, Nijs J, Meeus M, Mylius V, Fayt C, Oostendorp R. Central sensitization and altered central pain processing in chronic low back pain: fact or myth? *Clin J Pain.* (2013) 29:625–38. doi: 10.1097/AJP.0b013e31826f9a71
206. Goubert D, Danneels L, Graven-Nielsen T, Descheemaeker F, Meeus M. Differences in pain processing between patients with chronic low back

pain, recurrent low back pain, and fibromyalgia. *Pain Physician.* (2017) 20:307–18. doi: 10.36076/ppj.2017.318
207. Marcuzzi A, Dean CM, Wrigley PJ, Chakiath RJ, Hush JM. Prognostic value of quantitative sensory testing in low back pain: a systematic review of the literature. *J Pain Res.* (2016) 9:599–607. doi: 10.2147/JPR.S115659
208. Palsson TS, Christensen SWM, De Martino E, Graven-Nielsen T. Pain and disability in low back pain can be reduced despite no significant improvements in mechanistic pain biomarkers. *Clin J Pain.* (2021) 37:330–8. doi: 10.1097/AJP.0000000000000927
209. Forstenpointner J, Otto J, Baron R. Individualized neuropathic pain therapy based on phenotyping: are we there yet? *Pain.* (2018) 159:569–75. doi: 10.1097/j.pain.0000000000001088
210. Vlaeyen JWS, Maher CG, Wiech K, Van Zundert J, Meloto CB, Diatchenko L, et al. Low back pain. *Nat Rev Dis Primers.* (2018) 4:52. doi: 10.1038/s41572-018-0052-1
211. Sadraee A, Paulus M, Ekhtiari H. fMRI as an outcome measure in clinical trials: A systematic review in clinicaltrials.gov. *medRxiv.* (2019) 2019:19002972. doi: 10.1101/19002972
212. Tetreault P, Mansour A, Vachon-Presseau E, Schnitzer TJ, Apkarian AV, Baliki MN. Brain connectivity predicts placebo response across chronic pain clinical trials. *PLoS Biol.* (2016) 14:e1002570. doi: 10.1371/journal.pbio.1002570
213. Drenth JP, Waxman SG. Mutations in sodium-channel gene SCN9A cause a spectrum of human genetic pain disorders. *J Clin Invest.* (2007) 117:3603–9. doi: 10.1172/JCI33297
214. Ferreira PH, Beckenkamp P, Maher CG, Hopper JL, Ferreira ML. Nature or nurture in low back pain? Results of a systematic review of studies based on twin samples. *Eur J Pain.* (2013) 17:957–71. doi: 10.1002/j.1532-2149.2012.00277.x
215. De Boer I, Van Den Maagdenberg, AMJM, Terwindt GM. Advance in genetics of migraine. *Curr Opin Neurol.* (2019) 32:413–21. doi: 10.1097/WCO.0000000000000687
216. Gormley P, Kurki MI, Hiekkala ME, Veerapen K, Häppöl,ä P, Mitchell AA, et al. Common variant burden contributes to the familial aggregation of migraine in 1,589 families. *Neuron.* (2018) 98:743–53.e744. doi: 10.1016/j.neuron.2018.04.014
217. Johnston KJA, Ward J, Ray PR, Adams MJ, Mcintosh AM, Smith BH, et al. Sex-stratified genome-wide association study of multisite chronic pain in UK Biobank. *PLoS Genet.* (2021) 17:e1009428. doi: 10.1371/journal.pgen.1009428
218. Loggia ML, Chonde DB, Akeju O, Arabasz G, Catana C, Edwards RR, et al. Evidence for brain glial activation in chronic pain patients. *Brain.* (2015) 138:604–15. doi: 10.1093/brain/awu377
219. Borsook D, Becerra L. CNS animal fMRI in pain and analgesia. *Neurosci Biobehav Rev.* (2011) 35:1125–43. doi: 10.1016/j.neubiorev.2010.11.005
220. Chang PC, Pollema-Mays SL, Centeno MV, Procissi D, Contini M, Baria AT, et al. Role of nucleus accumbens in neuropathic pain: linked multi-scale evidence in the rat transitioning to neuropathic pain. *Pain.* (2014) 155:1128–39. doi: 10.1016/j.pain.2014.02.019
221. Chang PC, Centeno MV, Procissi D, Baria A, Apkarian AV. Brain activity for tactile allodynia: a longitudinal awake rat functional magnetic resonance imaging study tracking emergence of neuropathic pain. *Pain.* (2017) 158:488–97. doi: 10.1097/j.pain.0000000000000788

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Zhang, Gewandter and Geha. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Neurology

ORIGINAL RESEARCH
published: 10 January 2022
doi: 10.3389/fneur.2021.695187

Gamma Band Oscillations Reflect Sensory and Affective Dimensions of Pain

Yuanyuan Lyu[1,2], Francesca Zidda[1], Stefan T. Radev[1], Hongcai Liu[1], Xiaoli Guo[2], Shanbao Tong[2], Herta Flor[1] and Jamila Andoh[1,3]**

[1] Department of Cognitive and Clinical Neuroscience, Medical Faculty Mannheim, Central Institute of Mental Health, Heidelberg University, Mannheim, Germany, [2] School of Biomedical Engineering, Shanghai Jiao Tong University, Shanghai, China, [3] Department of Psychiatry and Psychotherapy, Medical Faculty Mannheim, Central Institute of Mental Health, University of Heidelberg, Mannheim, Germany

Pain is a multidimensional process, which can be modulated by emotions; however, the mechanisms underlying this modulation are unknown. We used pictures with different emotional valence (negative, positive, and neutral) as primes and applied electrical painful stimuli as targets to healthy participants. We assessed pain intensity and unpleasantness ratings and recorded electroencephalograms (EEGs). We found that pain unpleasantness and not pain intensity ratings were modulated by emotion, with increased ratings for negative and decreased ratings for positive pictures. We also found two consecutive gamma band oscillations (GBOs) related to pain processing from time frequency analyses of the EEG signals. The early GBO had a cortical distribution contralateral to the painful stimulus and its amplitude was positively correlated with intensity and unpleasantness ratings, but not with prime valence. The late GBO had a centroparietal distribution and its amplitude was larger for negative compared to neutral and positive pictures. The emotional modulation effect (negative vs. positive) of the late GBO amplitude was positively correlated with pain unpleasantness. The early GBO might reflect the overall pain perception, possibly involving the thalamocortical circuit, while the late GBO might be related to the affective dimension of pain and top-down-related processes.

Keywords: emotional valence, pain, self-reported pain ratings, gamma band oscillations (GBOs), priming

OPEN ACCESS

Edited by:
Flavia Di Pietro, Curtin University, Australia

Reviewed by:
Andy Schumann, University Hospital Jena, Germany
Thomas Weiss, Friedrich Schiller University Jena, Germany

****Correspondence:***
Yuanyuan Lyu
lvyuanyuanoo@gmail.com
Jamila Andoh
jamila.andoh@zi-mannheim.de

Specialty section:
This article was submitted to Applied Neuroimaging, a section of the journal Frontiers in Neurology

Received: *14 April 2021*
Accepted: *07 December 2021*
Published: *10 January 2022*

Citation:
Lyu Y, Zidda F, Radev ST, Liu H, Guo X, Tong S, Flor H and Andoh J (2022) Gamma Band Oscillations Reflect Sensory and Affective Dimensions of Pain. Front. Neurol. 12:695187. doi: 10.3389/fneur.2021.695187

INTRODUCTION

Pain is an unpleasant sensory and emotional experience associated with potential or actual tissue damage or described in such terms. From this definition, it emerges that pain contains both a sensory-discriminative and an affective-motivational dimension (1, 2). The sensory-discriminative dimension refers to the intensity quality of pain, whereas the affective-motivational dimension reflects the unpleasantness of a painful experience and the associated tendency to avoid it (3–5). Although pain intensity and unpleasantness ratings are known to be highly correlated, experimental manipulations using various modalities (visual, auditory, and olfactory) showed a differential modulation of the two dimensions. For instance, pleasant compared with unpleasant odors could decrease pain unpleasantness but had little effect on pain intensity (6, 7). Listening to pleasant music, however, reduced both pain intensity and unpleasantness (8). In all these studies, presentations of emotional material and painful stimulation occurred simultaneously. Additionally, these studies

used a relatively long trial duration (>6 s), which might introduce cognitive confounds to the emotional modulation of pain such as attentional processes. Thus, a special experimental paradigm, such as prime-target presentation, might be useful to reduce those attentional or cognitive factors on emotional modulation of pain.

Cortical oscillations, which can be extracted by frequency domain analysis from scalp electroencephalogram (EEG) signal, reflect synchronization of neuronal ensembles (9). Recently, a focus was put on the cortical oscillations related to pain (10), such as the lower bands, like alpha (8–13 Hz), beta (14–30 Hz), and also higher gamma band oscillations (GBOs) (30–100 Hz). For instance, the amplitude of GBO has been shown to be closely coupled with the perceived pain intensity, rather than the actual stimulus intensity (11–14), suggesting that GBO could reflect the sensory-discriminative dimension of pain. However, it remains controversial whether GBO also carries information about the affective dimension of pain perception and thus changes in emotional valence could also affect GBO (15–19).

In this study, we investigated the influence of emotional valence on pain perception using both pain rating and cortical oscillatory measures. We presented pictures of various types of emotional valence (negative, neutral, and positive) as primes and then applied painful electrical stimuli to healthy participants. Changes in pain perception were assessed using pain intensity and unpleasantness ratings. Based on previous literature, we expected that emotional valence would modulate pain ratings such that negative pictures would increase pain perception compared with positive pictures (20). For cortical oscillations, we expected that the amplitude of GBO would be positively correlated with pain ratings and would be also modulated by emotional valence, especially for the negative one. Finally, we expected a positive correlation between normalized pain ratings (i.e., negative vs. neutral and negative vs. positive) and normalized GBO amplitude (i.e., negative vs. neutral and negative vs. positive).

MATERIALS AND METHODS

Participants

A total of 21 healthy subjects (age: 23.5 ± 2.6 years, 11 females) participated in this study. Participants were all right-handed (mean score of the sample = +95.6), as assessed using the Edinburgh Handedness Inventory (21) and had no history of mental or neurological disorders. The participants were informed about the purpose and the methods used in this study and gave signed informed consent. This study was approved by the Ethics Committee of the Medical Faculty Mannheim of Heidelberg University.

Experimental Procedure

The participants sat in a comfortable chair in front of a monitor and the distance between the eyes and the monitor was ∼50 cm. Before each trial, a fixation cross was presented in the center of a gray background for a randomized duration between 1,200 and 2,400 ms denoting the intertrial interval (**Figure 1**). Following the first fixation cross, a prime picture was displayed for 200 ms and was then replaced by a second fixation cross. After 200 ms, a painful electrical stimulus was applied at the left forearm by a bar electrode. After 1,000 ms from the onset of electrical stimulation, the participants were asked to perform ratings on the two consecutive visual analog scales (VASs): the first VAS related to the intensity of the pain (i.e., how intense was the painful stimulus?) ranging from no pain to most intense pain imaginable and the second VAS was used to rate the unpleasantness of pain (i.e., how unpleasant was the stimulus?) and ranged from not at all unpleasant to most unpleasant pain imaginable. The participants were asked to rate pain intensity and pain unpleasantness with the mean of a keyboard. They pressed the left and right arrow keys to adjust their ratings and then pressed the space bar to confirm. The prime pictures contained emotions of different valence (negative, neutral, or positive) and were taken from the International Affective Picture System (22)[1]. The pictures were selected based on normative ratings on the dimensions of affective valence (negative: 2.17 ± 0.36, neutral: 5.22 ± 0.55, and positive: 7.40 ± 0.40) and arousal (negative: 5.74 ± 0.51, neutral: 4.27 ± 0.59, and positive: 4.83 ± 0.73) and the rating scale ranged from 1 to 9, with 1 representing low pleasure and low arousal and 9 representing high pleasure and high arousal (23). We converted the rating scales to 0–100 for analysis. Although the arousal ratings of valence were different, we analyzed the results for a subset of stimuli with comparable arousal to show that arousal is not the main contributor to the present results (see the discussion). The three valence conditions were randomly presented over trials for each participant and consisted of 40 pictures each and each picture was only presented one time, i.e., 120 trials in total (40 × 3).

The electrical stimuli were generated by a constant stimulator (Digitimer® DS7A, Hertfordshire, UK). The Digitimer sends a square wave of 1 ms duration to a bar electrode attached to the right forearm of a participant. The intensity of the stimulus is determined by the voltage and duration of the square waves. For each participant, we measured the intensity of stimulus corresponding to the perception threshold, pain threshold, and pain tolerance three times before the experiment, respectively. For example, we increased the stimulation intensity until the participant perceived pain to determine the pain threshold. To make the electrical stimulus painful but tolerable, the chosen intensity was defined as mean pain threshold plus 80% of the difference between mean pain tolerance and mean pain threshold. To make sure the calculated intensity was robust and elicited reliable sensations before the experiment started, we tested the calculated intensity by asking participants to rate how

[1]Picture numbers were: neutral (1,390, 1,903, 2,025, 2,032, 2,235, 2,372, 2,487, 2,514, 2,521, 5,900, 6,000, 7,011, 7,013, 7,018, 7,021, 7,033, 7,042, 7,044, 7,057, 7,058, 7,077, 7,081, 7,096, 7,137, 7,140, 7,183, 7,184, 7,188, 7,237, 7,248, 7,249, 7,513, 7,550, 7,560, 7,620, 7,632, 7,820, 7,830, 9,150, and 9,468); positive (1,410, 2,035, 2,045, 2,050, 2,057, 2,070, 2,150, 2,274, 2,311, 2,340, 2,352, 1,440, 2,360, 2,395, 2,550, 2,660, 4,640, 4,641, 5,220, 5,480, 5,825, 5,830, 1,463, 7,230, 7,260, 7,270, 7,330, 7,470, 8,120, 8,461, 8,496, 8,501, 8,502, 1,510, 8,540, 1,630, 1,710, 1,721, 1,750, and 1,999); and negative (2,301, 2,352, 2,710, 2,800, 2,900, 2,981, 3,016, 3,017, 3,051, 3,059, 3,061, 3,064, 3,168, 3,181, 3,185, 3,220, 3,225, 3,301, 3,550, 6,022, 6,213, 6,243, 6,415, 6,520, 6,560, 6,563, 9,040, 9,043, 9,075, 9,140, 9,181, 9,185, 9,253, 9,265, 9,332, 9,405, 9,571, 9,635, 9,800, and 9,902).

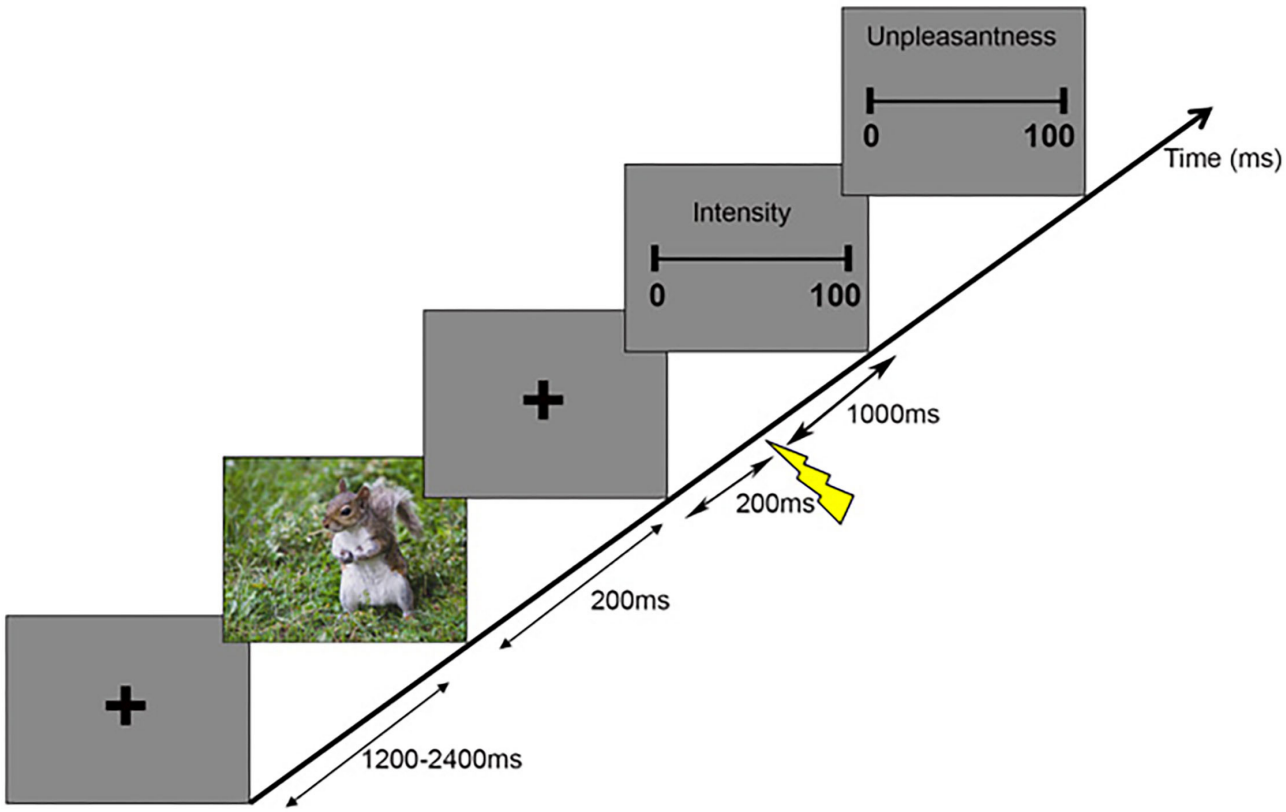


FIGURE 1 | Schematic representation of the experimental paradigm. Each trial began with a fixation cross with a variable duration between 1,200 and 2,400 ms, followed by a picture lasting 200 ms. Then, another fixation cross was presented for 1,200 ms, during which painful stimuli were applied at a frequency of 3–7 Hz starting 200 ms after the prime picture. Then, two consecutive scales appeared, where participants indicated the intensity and unpleasantness of the perceived painful stimuli.

painful was the stimuli perceived on the VAS, analogous to the one used for the pain intensity ratings. When the stimuli were not perceived as painful (i.e., with ratings inferior to 7/10), the intensity was increased until participants rated the stimuli with 7 or 8/10 on the VAS.

EEG Acquisition and Analysis

The EEG signals were amplified by the BrainAmp amplifiers (BrainProducts GmbH, Munich, Germany, UK) and collected with BrainVision Recorder software, sampled at 1,000 Hz, and filtered online between 0.016 and 250 Hz. EEG was recorded using a 64-channel actiCAP with active Ag/silver chloride (AgCl) electrodes. Electrode positions on the cap were following the standard 10–10 system. Two more electrodes were used to record vertical and horizontal electro-oculograms to detect eye movements and blinks. The ground electrode was placed at AFz and the reference electrode was placed at FCz. Electrode impedance was kept at <20 kΩ, as suggested by the manufacturer. The active electrodes used here were demonstrated to be insensitive to moderate levels of impedance (<50 kΩ) when compared to passive electrodes for measurements such as EEG spectra (24).

Electroencephalogram data were preprocessed using EEGLAB version 15.3.6 (25). Data were first filtered using a 1-Hz high-pass filter and then interpolated the bad channels (percentage: $2.71 \pm 2.06\%$). The filtered data were re-referenced to an average reference except for the eye electrodes and segmented in epochs from 1 s before to 2 s after the onset of the prime picture. Epochs with motion artifacts (i.e., 26.19 ± 17.19 epochs out of 120 epochs, i.e., $21.83 \pm 14.33\%$) were rejected by visual inspection and the behavioral data of the rejected epochs were also excluded. After motion artifact rejection, there were 30.71 ± 6.05 negative epochs, 30.90 ± 6.67 neutral trials, and 32.14 ± 5.75 positive epochs per subject. The numbers of epochs showed no significant difference along with valence [$F_{(2,40)} = 1.707$, $p = 0.194$]. Independent component analysis was applied to the clean epoched data and components representing artifactual non-brain activity were rejected, i.e., eye movements, cardiac activity, powerline noise (50 Hz), and electrical stimulation artifacts. Then, the preprocessed epochs were assigned to the three conditions based on the picture valence (negative, neutral, and positive).

Event-related spectral perturbation (ERSP) analyses (26) were performed using the newtimef() function in EEGLAB. Morlet

wavelets transformation was applied to each single EEG epoch with a sliding window. The window had a length of 1,115 points (1,115 ms) and was shifted in a step of 1 data point (1 ms). The frequency range was from 3 to 100 Hz with a resolution of 1 Hz. The cycles of wavelets increased linearly from 3 cycles at the lowest frequency (3 Hz) to 20 cycles at the highest (100 Hz) to achieve a good trade-off between the time and frequency resolutions (27). The time-frequency transformed data were averaged across trials for each condition and each subject. The ERSP amplitude was calculated as 10 × log10 transformed multiples of amplitude change with respect to the baseline. The baseline was defined for each trial before averaging across trials, as the 442 time points before the prime pictures. Global grand averaged ERSPs were obtained by averaging ERSPs across all the prime pictures and all the participants. After visual inspection, we found two prominent GBOs with increased amplitude after the painful electrical stimulus in the stimulation in the following time-frequency windows and regions, i.e., (1) the early GBO, 420–500 ms, 35–70 Hz, right centroparietal area (FCz, FC2, FC4, Cz, C2, C4, CPz, CP2, CP4, Pz, P2, and P4) and (2) the late GBO, 500–660 ms, 60–95 Hz, middle centroparietal area (C3, C1, Cz, C2, C4, CP3, CP1, CPz, CP2, CP4, P3, P1, Pz, P2, and P4). For further analysis, the amplitude of each GBO was calculated by averaging the ERSP amplitudes across the above window and region for each participant and each prime valence.

We then determined the total GBO, defined by both phase-locked and non-phase-locked components. Meanwhile, the intertrial coherence (ITC) (25), also known as an event-related phase-locking value, was calculated for each GBO.

We also assessed the induced GBO defined as the non-phase-locked component of GBOs. For this purpose, we removed the ERSP signal from the EEG segments and calculated the induced ERSP using the same parameters as the one we used for the total ERSP. Then, we extracted the early- and late-induced GBO from the same time-frequency channel window for later statistical analysis.

Statistical Analysis

Pain ratings and GBOs were inspected for normality using the Shapiro–Wilk test (see **Supplementary Table S1**).

Half of the variables were normally distributed (Shapiro–Wilk test, $p > 0.05$). Additionally, measures of skewness and kurtosis were used to evaluate deviation from normality. Absolute skewness values for all the variables were < 2, which is considered acceptable in order to prove normal distribution (28–31).

We also recalculated statistics using non-parametric test equivalents (software R package version 1.3.1093) (see **Supplementary Table S5**).

The pain ratings (intensity (INT) and unpleasantness (UNP)) and ERSP values in different time-frequency windows were analyzed using the one-way repeated measures ANOVA with prime valence (negative, neutral, and positive) as a within-subject factor. The one-way repeated measures ANOVA are considered fairly robust to deviations from normality as long as the levels of the within-subjects factor are similarly skewed. We, therefore, first used Mauchly's test of sphericity to test the assumption of sphericity and then used the Greenhouse–Geisser correction for the results when the sphericity assumption was not met. *Post-hoc* tests were corrected for multiple comparisons using the Bonferroni corrections.

To test whether the early and late GBOs shared the same characteristics of phase-locking activity, ITC values were analyzed using a 2 × 3 repeated measures ANOVA, taking prime valence (negative, neutral, and positive), and GBO (early and late) as within-subject factors. As the normative ratings of arousal differed between the negative and positive pictures, we selected for this study [$F_{(2,117)} = 58.04$, $p < 0.001$] and we introduced arousal as a covariate in all the ANOVAs.

We also examined the relationship between the pain intensity and unpleasantness ratings and ERSPs using Spearman's rank correlation coefficient.

We also assessed the effects of habituation on the prime category as follows: for each prime valence, we divided the total number of trials ($n = 40$) by 4, resulting in 4 time points (10 trials per time point). We then carried out 3 × 4 repeated measured ANOVAs with time points and valence as within-subject factors on pain intensity and pain unpleasantness.

To quantify the emotional modulation effect, we carried out a normalization procedure on the pain ratings and GBO amplitude as follows:

Pain ratings (i.e., INT and UNP) were normalized by dividing them between negative and neutral prime valence [INT (neg/neu) and UNP (neg/neu)] and between negative and positive prime valence [(INT (neg/pos) and UNP (neg/pos)]. Then, we carried out correlation analyses between the normalized pain ratings and the normalized GBO amplitudes.

For GBO, since their amplitude was in the log domain, normalization was performed by subtracting GBO amplitude between the neutral and the negative prime valence [GBO (neg-neu)] and between the positive and the negative prime valence [GBO (neg-pos)]. Then, we carried out correlation analyses between the normalized pain ratings and the normalized GBO amplitudes.

Outliers were detected using the interquartile range (IQR), defined as the upper quartile minus the lower quartile. Values outside the range of the lower quartile-−1.5 × IQR to the upper quartile + 1.5 × IQR were excluded from all the analyses. The significance level was set at $p < 0.05$. All the data are presented as means ± SD.

RESULTS

Pain Intensity and Unpleasantness Ratings

Pain intensity ratings were comparable across valence conditions [$F_{(2,40)} = 0.843$, $p = 0.371$, negative: 31.49 ± 18.31, neutral: 31.70 ± 16.28, and positive: 30.41 ± 17.39]. In contrast, there was a main effect of prime valence on pain unpleasantness ratings [$F_{(2,40)} = 9.579$, $p = 0.006$].

Post-hoc tests indicated that pain unpleasantness ratings were significantly higher for the negative (36.62 ± 19.11) than the neutral (32.15 ± 18.24, $p = 0.001$) and the positive (29.68 ± 18.52, $p = 0.002$) prime valence (for raw data, see **Supplementary Table S2**). In addition, pain unpleasantness ratings were significantly higher for the neutral

than for the positive ($p = 0.023$) prime valence (as shown in **Figure 2A**, **Supplementary Table S3** for mean pain ratings across prime valence).

We also found a positive correlation between the pain intensity and unpleasantness ratings (rho = 0.851, $p < 0.001$, $n = 19$, outliers: participants 3 and 8) (as shown in **Figure 2B**).

When excluding two outliers, the ANOVA results reported above led to similar results [i.e., $F_{(2,36)} = 1.83$, $p = 0.192$ for pain intensity ratings and $F_{(2,36)} = 7.84$, $p < 0.001$ for pain unpleasantness ratings].

For pain intensity ratings (INT), there was a trend toward significance for a main effect of time [$F_{(3,60)} = 2.734$, $p = 0.051$], but no interaction between time and valence [$F_{(6,120)} = 0.564$, $p = 0.670$]. For pain unpleasantness ratings (UNP), there was no main effect of time [$F_{(3,60)} = 2.182$, $p = 0.100$] and no interaction between time and valence [$F_{(6,120)} = 0.925$, $p = 0.444$] (refer to **Supplementary Table S4** for the ratings calculated for each time point and for each valence).

Total GBOs

Figure 3A shows the event-related spectral perturbation as CP2 for all the subjects. After visual inspection, we found two prominent GBOs following the painful electrical stimuli. An early GBO (35–70 Hz) appeared in 20–100 ms after the electrical stimulus, centrally distributed in the hemisphere contralateral to the location of the stimulus application (**Figure 3B**). The late GBO, in a higher gamma band (60–95 Hz), appeared in 100–260 ms after the electrical stimuli, with a centroparietal distribution (**Figure 3C**).

The early GBO ∼ 150–300 ms poststimulus mainly reflects the initial visual process of prime stimuli, which occurs before the pain stimuli and is, therefore, not related to emotion modulation of pain.

The amplitude of the early GBO was comparable across prime valences [$F_{(2,40)} = 2.099$, $p = 0.162$, negative: 0.60 ± 0.51 dB, neutral: 0.45 ± 0.57 dB, positive: 0.53 ± 0.59 dB] (as shown in **Figure 3D**). In addition, the mean amplitude of the early GBO across valence conditions was positively correlated with the mean pain intensity rating across valence conditions (**Figure 4A**; rho = 0.608, $p = 0.009$, $n = 18$, outliers: participants 3, 6, and 8) and with the mean pain unpleasantness rating across valence conditions (**Figure 4B**; rho = 0.558, $p = 0.015$, $n = 19$, outliers: participants 3 and 6). Because the amplitude of the early GBO was not significantly different between the prime valences and, therefore, did not show any emotional modulation, we did not assess possible associations between the standardized amplitude of the early GBO and standardized measures of pain ratings, i.e., pain intensity (neg/neu or neg/pos).

The amplitude of the late GBO revealed a main effect of prime valence [$F_{(2,40)} = 6.151$, $p = 0.022$; **Figure 3E**]. *Post-hoc* tests indicated that the amplitude of the late GBO for the negative prime valence (0.66 ± 0.52 dB) was larger than that for the neutral (0.45 ± 0.44 dB, $p = 0.027$) and positive (0.50 ± 0.48 dB, $p = 0.046$) prime valences. In addition, the amplitude of the late GBO was comparable between neutral and positive prime valences ($p = 1.00$). However, unlike the early GBO, the mean amplitude of the late GBO across valence conditions was not significantly correlated with the mean pain intensity ratings (rho = −0.018, $p = 0.943$, $n = 19$, outliers: participants 3 and 8) nor with the mean pain unpleasantness ratings (rho = 0.060, $p = 0.797$, $n = 21$, no outliers).

The correlation analyses showed that there was no relationship between the normalized late GBO (neg-neu) amplitude and UNP (neg/neu) (rho = 0.270, $p = 0.262$, $n = 19$, outliers: participants 5 and 14). However, the normalized late GBO (neg-pos) amplitude was significantly positively correlated

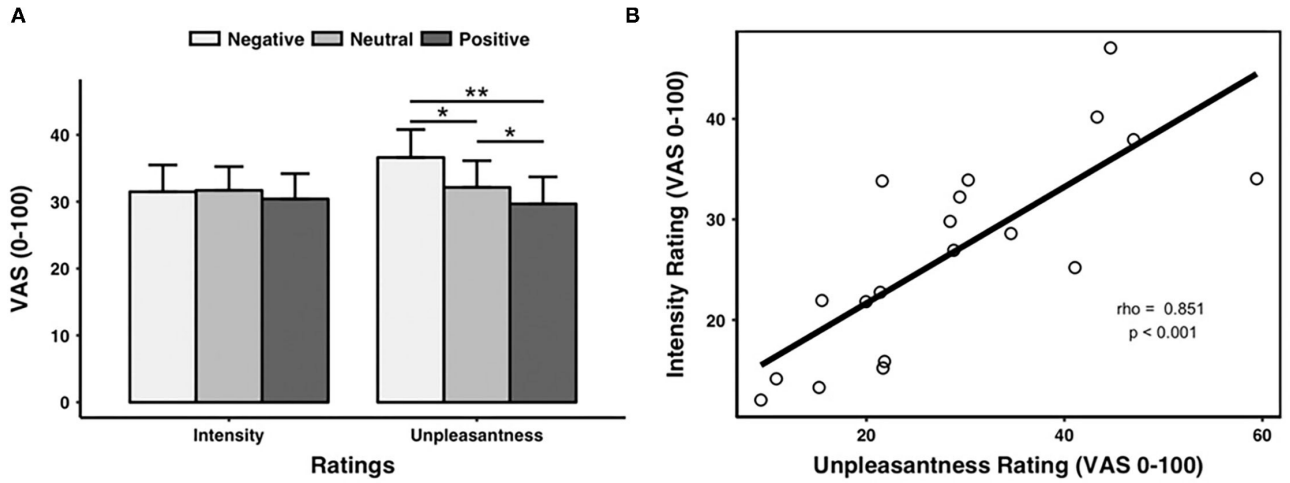


FIGURE 2 | Pain ratings. **(A)** Ratings of pain intensity and unpleasantness for each prime valence (negative, neutral, and positive). The unpleasantness ratings showed a significant main effect of prime valence, while the intensity ratings did not show a significant main effect of prime valence. **(B)** Across all the pictures, the averaged intensity ratings were significantly positively correlated with the averaged unpleasantness ratings. VAS, visual analog scale. *$p < 0.05$, **$p < 0.01$. Error bars stand for SEs.

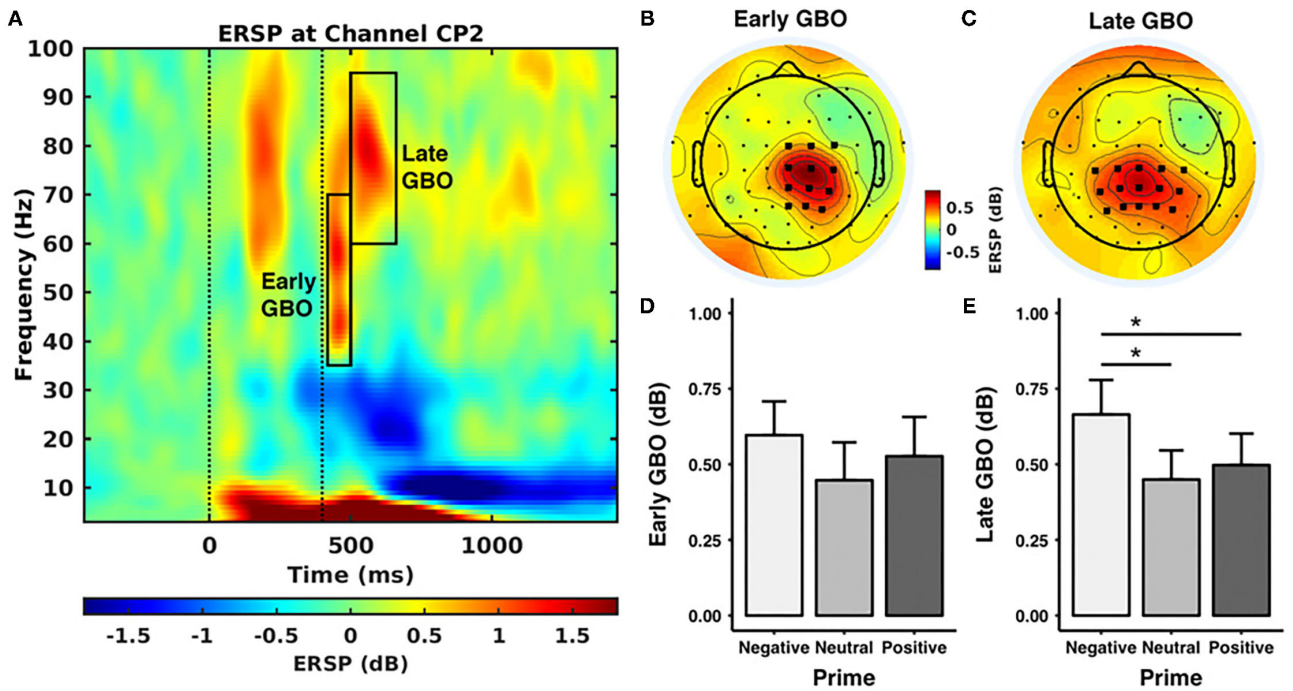


FIGURE 3 | Gamma band oscillations (GBOs). **(A)** Event-related spectral perturbation (ERSP) at CP2 across all the pictures and all the subjects. The first dashed line stands for the onset of the prime stimulus and the second dashed line represents the onset of the electrical stimuli. The black rectangles indicate the time-frequency windows of the early and late GBOs. **(B,C)** The scalp distribution of the early and late GBOs. The early GBO had a central distribution contralateral to the stimulus location and the late GBO had a centroparietal distribution. The bold black dots indicate the regions of interest used in the statistical analyses. **(D,E)** The ERSP value of the GBO for each prime valence. The late GBO showed a significant main effect of prime valence, while the early GBO did not show a significant main effect of prime valence. **p < 0.05.

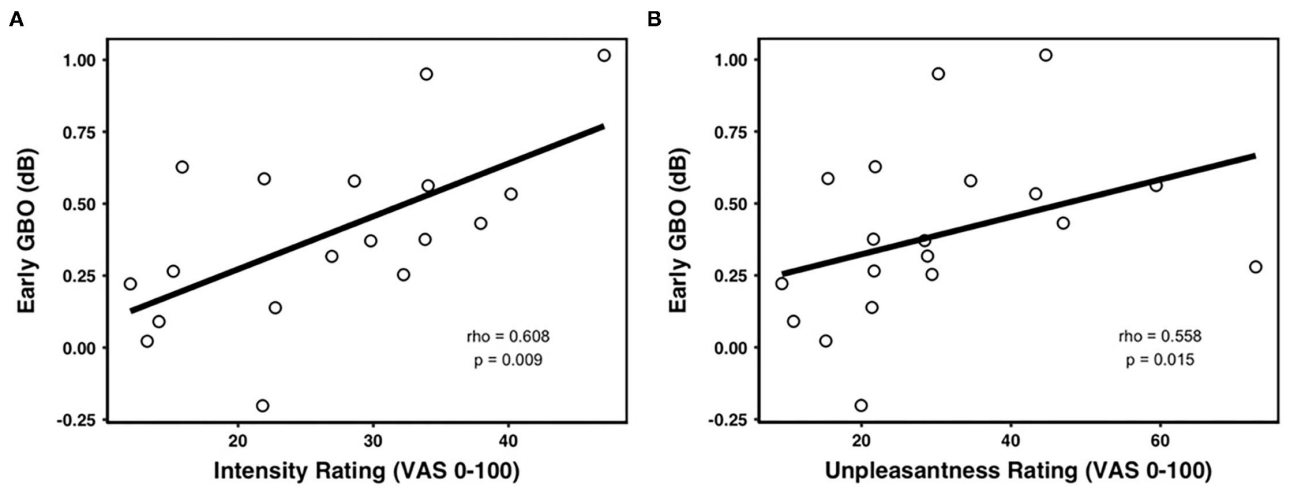


FIGURE 4 | Correlations between the early GBOs and pain ratings. The mean early GBO was significantly positively correlated with **(A)** averaged intensity rating and **(B)** averaged unpleasantness rating across valence.

with UNP (neg/pos) (rho = 0.511, $p = 0.027$, $n = 19$, outliers: participants 5 and 12) (see **Figure 5**).

The non-parametric test results for pain ratings and the early and late GBOs followed the same trend as those reported using the one-way ANOVA (see **Supplementary Table S5**).

Finally, ITC values exhibited a significant main effect of GBO [$F_{(2,40)} = 27.520$, $p < 0.001$] but no significant main effect of prime valence [$F_{(2,40)} = 0.976$, $p = 0.384$] and no interaction between GBO and prime valence [$F_{(2,40)} = 1.544$, $p = 0.226$]. The early GBO (0.23 ± 0.06)

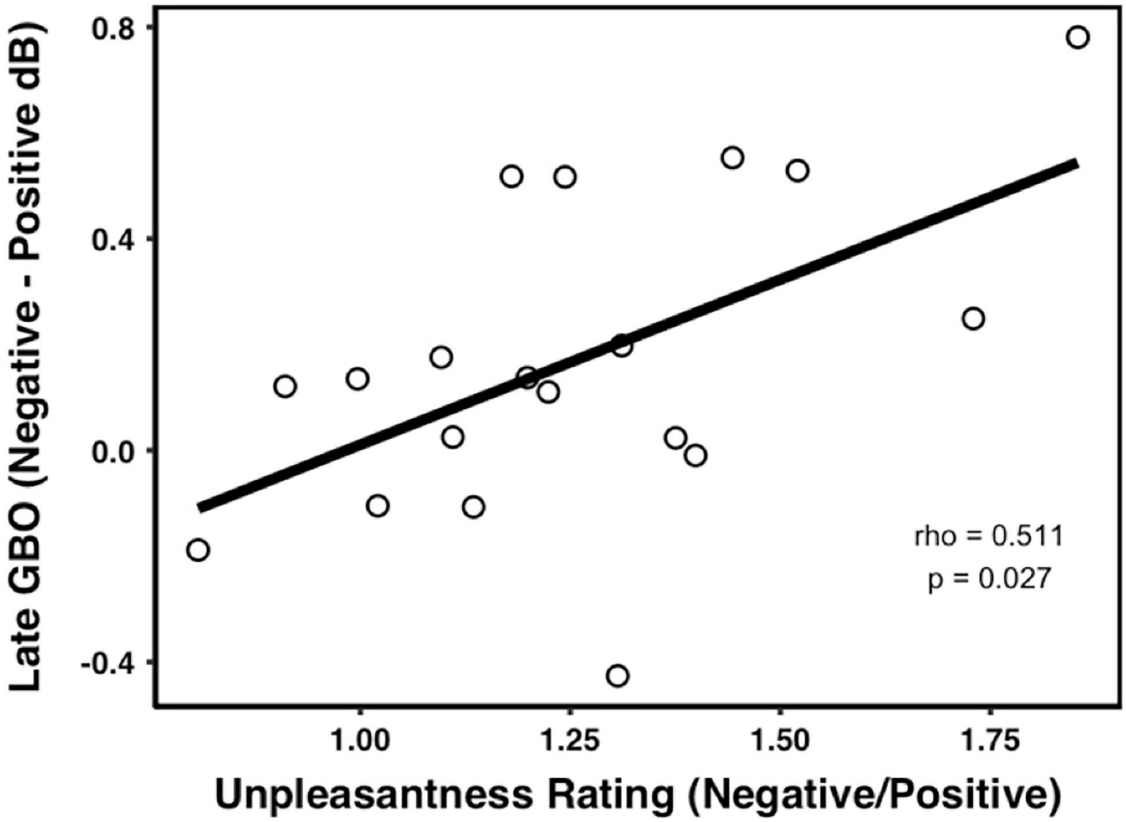


FIGURE 5 | Correlations between the late GBOs and pain ratings. The amplitude of the late GBO was positively correlated with the unpleasantness rating in the negative prime condition compared with the positive prime.

was more phase locked than the late GBO (0.16 ± 0.02) (**Figure 6**).

Induced GBOs

For the induced early GBO amplitude, the ANOVA showed an insignificant main effect of prime valence [$F_{(2,40)} = 1.374$, $p = 0.265$]. Meanwhile, the induced early GBO amplitude was not significantly correlated with neither pain intensity rating (rho = 0.41, $p = 0.63$) nor pain unpleasantness rating (rho = 0.47, $p = 0.19$).

For the induced late GBO amplitude, the ANOVA showed a significant main effect of prime valence [$F_{(2,40)} = 6.547$, $p = 0.003$]. *Post-hoc* analysis showed that the induced late GBO amplitude after negative prime (0.66 ± 0.52 dB) was significantly larger than the one after positive prime (0.44 ± 0.45 dB, $p = 0.035$) and neutral prime (0.50 ± 0.47 dB, $p = 0.019$). The normalized late GBO (neg-pos) amplitude was significantly positively correlated with UNP (neg/pos) (rho = 0.519, $p = 0.024$, $n = 19$, outliers: participants 5 and 12).

DISCUSSION

We investigated how the sensory and affective dimensions of pain were modulated by emotional valence using self-reports of pain and gamma band neural oscillations. Pain ratings showed that emotional valence affected pain unpleasantness, but not pain intensity.

Negative prime pictures increased pain unpleasantness, while positive prime pictures decreased pain unpleasantness. Although there was some habituation of the pain intensity ratings, they stayed in the painful range and did not significantly differ between the valence categories.

Moreover, we identified two consecutive GBOs following painful stimuli. The early GBO correlated with the overall pain intensity and pain unpleasantness ratings and was not influenced by emotional valence. On the other hand, the late GBO in the higher gamma band was modulated by emotional valence, particularly for the negative valence condition.

Only the pain unpleasantness ratings were significantly different across the three prime valences, indicating that the affective rather than the sensory dimension of pain was sensitive to the emotional pictures. The visual stimuli used in the current design were characterized by two dimensions: valence and arousal, but the modulation effect is most likely driven by the dimension of valence. First, in the subset analysis on positive and negative pictures with comparable arousal ratings, the negative pictures elicited significantly larger unpleasantness ratings than positive ones. Second, according to the distraction theory, the

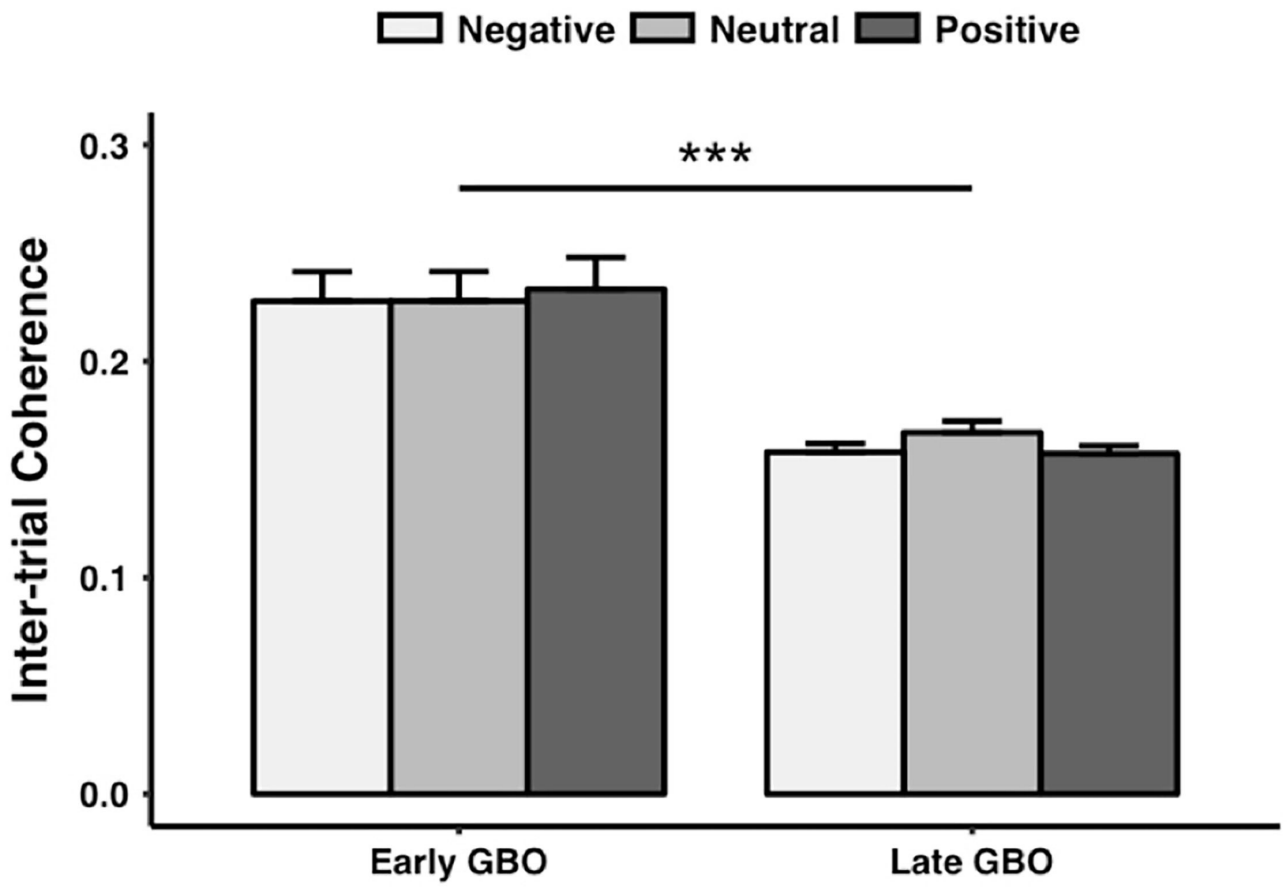


FIGURE 6 | The intertrial coherence of the early GBO was significantly larger than that of the late GBO. ***$p < 0.01$.

pictures with a high arousal rating (positive/negative) would trigger a decrease in pain perception than neural ones, which is not the case in our results (32–34). Our results add a new perspective to the current literature and the experimental design used in this study was intended to optimize the assessment of emotional modulation of pain. On the one hand, the painful stimuli used in this study were delivered without additional concomitant confounds. This may limit the interaction of additional cognitive factors such as attention as concomitant presentation of emotional stimuli with the delivery of painful stimuli was often used in previous studies (6, 17, 20, 35). On the other hand, the assessment of both intensity and unpleasantness pain ratings enabled us to differentiate between sensory and affective dimensions of pain. Indeed, some studies have not assessed both pain unpleasantness and intensity ratings (17, 36, 37) and might have merged the sensory and affective dimensions of pain.

Our findings are in line with the neuroimaging literature highlighting that pain is a multidimensional process, which led to the need to assess both its sensory and affective dimensions (1, 2, 38). Although selective modulation of pain intensity and unpleasantness by cognitive manipulation is widely recognized, the evidence underpinning this separability remains weak (39). In this study, Talbot et al. discuss possible biases in cognitive techniques and statistical methods that could underlie previously found a dissociation between sensory and affective dimensions of pain. Moreover, the authors suggest that cognitive processes might preferentially modulate the affective rather than the sensory dimension of pain. Current literature is still insufficient to provide arguments in favor or against this hypothesis. In this study, however, we used prime pictures to reduce cognitive processing such as attention during picture presentation and reported differential modulation of intensity and unpleasantness dimensions of pain by emotional primes. Further study is needed for manipulating various experimental factors, e.g., prime durations, order of pain ratings to better understand the mechanisms underlying differential regulation of pain intensity and unpleasantness.

With respect to the GBOs, we were able to show two consecutive GBOs following painful stimuli and several dissociations between them: the early GBO had a distribution widespread over the contralateral S1, while the late GBO was widespread over a large centroparietal area in the midline and appeared in a higher gamma band and at later time window. With respect to the behavioral measures, the early GBO encoded the overall perceived pain intensity and unpleasantness, while

the late GBO was modulated by emotional valence. Moreover, the phase-locked value of the early GBO was significantly larger than the late GBO. When we only consider the induced GBO, the correlations between the early GBO and overall pain ratings did not reach a significant level, while modulatory effect and the relationship with unpleasantness rating still hold in the late GBO. Thus, the early and late GBO mainly originate from phase-locked component and non-phase-locked component, respectively, and might be mediated by different mechanisms.

The early GBO is most likely a time-frequency representation of the early complex N20-P30 wave of somatosensory evoked potential (SEP) elicited by the electrical stimulation of the upper limb. The N20-P30 is phase-locked and originates from the contralateral somatosensory cortex (40). A previous study showed that the median nerve SEP contained oscillation components ranging from 30 to 80 Hz (41). Our result showed that the phase-locked component of the early GBO encodes the perceived pain intensity and unpleasantness in the phasic experimental pain condition. Such findings are not surprising, since pain intensity and unpleasantness ratings were highly correlated. The early GBO may reflect the temporal binding of thalamocortical projections (1, 42). Simultaneous recordings from the ventral posterior medial nucleus of the thalamus and corresponding cortical columns showed that the thalamic GBO had a strong phase modulation to the cortical GBO evoked by brief single-whisker deflection in rats (43). Likewise, source analysis of magnetoencephalographic data in humans showed such coherent thalamocortical GBO in the auditory modality (44). Furthermore, our results showed that the early GBO was not significantly modulated by emotional valence.

Unlike previous reports indicating that GBO encodes the perceived pain intensity in a phasic pain condition (11–13, 16), our results showed that the late nonphase-locked GBO did not directly encode the pain perception, but was modulated by emotion valence. The direct comparison of the amplitude of the late GBO among the different prime valence revealed an increased response to negative than positive and neutral prime valence. The role of stimuli valence, especially negative items, has previously been shown to affect GBO in a passive viewing mode (45). Our results indicated that the negative valence from priming visual stimuli could also induce the higher GBO later in the pain perception process and may reflect a top-down modulation. Likewise, an EEG study presenting pain stimuli together with emotional facial expressions also showed an emotional modulation of GBO, in which the authors found facial expression fear elicited increased GBO compared with facial expression angry (17). Since synchrony in the gamma band is related to the communication between cortical areas (46), it can be speculated that the increased late GBO in the centroparietal area may represent upregulated descending pain processing pathway triggered by negative prime. Such a top-down modulation may also contribute to the increased pain unpleasantness rating. Moreover, the emotional modulation effect from negative to positive of the late GBO is significantly correlated to that of pain unpleasantness ratings. Negative affects facilitate avoidance-motivated behavior, while positive affects facilitate approach-motivated behavior (47). As an aversive stimulus, acute pain also triggers avoidance-motivated behavior (48). The late GBO might represent the avoidance-motivated behavior, as negative prime and pain would enhance the effect, while positive prime and pain would counteract the effect. Overall, the late GBO might reveal the emotional modulation in the affective dimension of pain perception.

Finally, our results are in agreement with a serial model of pain perception (49), as the early GBO seems to encode the overall pain intensity and unpleasantness, but the late GBO indicates the emotional modulation in the affective dimension occurs later. The early GBO would be fundamental to the late GBO. Further studies are needed to clarify the mechanisms underlying the GBOs in the emotional modulation of pain.

Limitations

Some limitations need to be addressed in this study. The duration of the presentation of the pictures was relatively short (200 ms) compared with previous studies [2 s for (36) and 6 s for (20, 50)], because we intended to reduce cognitive processing such as attention during picture presentation. Our prime picture duration should, however, have been sufficient, since modulatory effects by emotions have been shown to last up to 700 ms in an event-related potential study (51), which is longer than our prime-target interval (400 ms).

We used a single intensity of stimulation, we therefore cannot preclude the possibility of dependence of priming effects on stimulus intensity (36). Our interpretation is, therefore, limited to a single stimulation intensity.

The electrical stimulation used in this study would inevitably activate the non-nociceptive system, while we targeted the nociceptive system. Our results showed the amplitudes of the early and late GBOs were associated with pain ratings, indicating the brain response following electrical stimulation carries nociceptive information. In future studies, it is better to use laser stimulation or intraepidermal electrical stimulation, which would selectively or largely preferentially activate cutaneous Aδ- and C-fiber nociceptors (52, 53). Alternatively, using non-painful electrical stimulation as a control condition could also work.

The GBO following electrical stimulation might be contaminated by the preceding visual-evoked brain activity. To decrease the potential effect, one could use visual pictures without electrical stimulation as a control condition (17).

Finally, our results showed that the overall early GBO amplitude was significantly correlated with the overall pain intensity and unpleasantness ratings across the emotional valences; thus, in order to dissociate pain intensity and unpleasantness ratings, we carried out partial correlations. The early GBO was not significantly correlated with the pain intensity rating ($p = 0.58$) when the unpleasantness rating was controlled for or the unpleasantness rating ($p = 0.29$) when the intensity rating was controlled for, showing, therefore, that the two pain dimensions strongly interact with each other and that both might contribute to the early GBO.

It is also important to note that the correlation analyses were carried out with outlier extraction. We used an outlier criterion (based on IQR) that resulted in obtaining different outliers

for different analyses. This outcome highlights interindividual variability in experimental pain responses, possibly related to genetic and psychosocial factors [for study (54)].

CONCLUSION

We showed that emotional valence modulated selectively the affective dimension of pain. Moreover, we observed that the early GBO might reflect the overall sensory discriminative and affective dimensions of pain, while the late GBO might reflect the emotional modulation in the affective dimension of pain. Pain perception seems to be composed of serial processes, defined by different temporal dynamics and spatial coding.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Medical Faculty Mannheim of Heidelberg University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SR, FZ, and JA designed the experiments. SR, YL, and HL performed the experiments. YL, FZ, SR, and HL conducted the data analysis. YL and JA prepared figures and tables. YL, FZ, SR, HL, XG, ST, HF, and JA wrote the manuscript. All authors reviewed and approved the final version of the manuscript.

FUNDING

This study was supported by a grant from EFIC Grünenthal (EGG) to JA, a grant from the Deutsche Forschungsgemeinschaft (SFB1158/B07) to HF and JA, and a fellowship by the China Scholarship Council (CSC) to YL and HL.

ACKNOWLEDGMENTS

We thank Dr Daniel Wagner for providing a picture for illustration purposes for **Figure 1**.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.695187/full#supplementary-material

REFERENCES

1. Price DD. Central neural mechanisms that interrelate sensory and affective dimensions of pain. *Mol Interv.* (2002) 2:392. doi: 10.1124/mi.2.6.392
2. Bushnell MC, Ceko M, Low LA. Cognitive and emotional control of pain and its disruption in chronic pain. *Nat Rev Neurosci.* (2013) 14:502–11. doi: 10.1038/nrn3516
3. Melzack R, Casey KL. Sensory, motivational and central control determinants of pain: a new conceptual model. *Skin Senses.* (1968) 1, 423–43.
4. Kerns RD, Turk DC, Rudy TE. The west haven-yale multidimensional pain inventory (WHYMPI). *Pain.* (1985) 23:345–56. doi: 10.1016/0304-3959(85)90004-1
5. Arnold BS, Alpers GW, Süß H, Friedel E, Kosmützky G, Geier A, et al. Affective pain modulation in fibromyalgia, somatoform pain disorder, back pain, and healthy controls. *Europ J Pain.* (2008) 12:329–38. doi: 10.1016/j.ejpain.2007.06.007
6. Villemure C, Bushnell MC. Mood influences supraspinal pain processing separately from attention. *J Neurosci.* (2009) 29:705–15. doi: 10.1523/JNEUROSCI.3822-08.2009
7. Villemure C, Slotnick BM, Bushnell MC. Effects of odors on pain perception: deciphering the roles of emotion and attention. *Pain.* (2003) 106:101–8. doi: 10.1016/S0304-3959(03)00297-5
8. Roy M, Peretz I, Rainville P. Emotional valence contributes to music-induced analgesia. *Pain.* (2008) 134:140–7. doi: 10.1016/j.pain.2007.04.003
9. Pfurtscheller G, Da Silva FL. Event-related EEG/MEG synchronization and desynchronization: basic principles. *Clin Neurophysiol.* (1999) 110:1842–57. doi: 10.1016/S1388-2457(99)00141-8
10. Ploner M, Sorg C, Gross J. Brain rhythms of pain. *Trends Cogn Sci.* (2017) 21:100–10. doi: 10.1016/j.tics.2016.12.001
11. Gross J, Schnitzler A, Timmermann L, Ploner M. Gamma oscillations in human primary somatosensory cortex reflect pain perception. *PLoS Biol.* (2007) 5:e133. doi: 10.1371/journal.pbio.0050133
12. Zhang ZG, Hu L, Hung YS, Mouraux A, Iannetti GD. Gamma-band oscillations in the primary somatosensory cortex–a direct and obligatory correlate of subjective pain intensity. *J Neurosci.* (2012) 32:7429–38. doi: 10.1523/JNEUROSCI.5877-11.2012
13. Schulz E, May ES, Postorino M, Tiemann L, Nickel MM, Witkovsky V, et al. Prefrontal gamma oscillations encode tonic pain in humans. *Cereb Cortex.* (2015) 25:4407–14. doi: 10.1093/cercor/bhv043
14. Nickel MM, May ES, Tiemann L, Schmidt P, Postorino M, Ta Dinh S, et al. Brain oscillations differentially encode noxious stimulus intensity and pain intensity. *Neuroimage.* (2017) 148:141–7. doi: 10.1016/j.neuroimage.2017.01.011
15. Hauck M, Domnick C, Lorenz J, Gerloff C, Engel AK. Top-down and bottom-up modulation of pain-induced oscillations. *Front Hum Neurosci.* (2015) 9:375. doi: 10.3389/fnhum.2015.00375
16. Hauck M, Metzner S, Rohlffs F, Lorenz J, Engel AK. The influence of music and music therapy on pain-induced neuronal oscillations measured by magnetencephalography. *Pain.* (2013) 154:539–47. doi: 10.1016/j.pain.2012.12.016
17. Senkowski D, Kautz J, Hauck M, Zimmermann R, Engel AK. Emotional facial expressions modulate pain-induced beta and gamma oscillations in sensorimotor cortex. *J Neurosci.* (2011) 31:14542–50. doi: 10.1523/JNEUROSCI.6002-10.2011
18. Tiemann L, May ES, Postorino M, Schulz E, Nickel MM, Bingel U, et al. Differential neurophysiological correlates of bottom-up and top-down modulations of pain. *Pain.* (2015) 156:289–96. doi: 10.1097/01.j.pain.0000460309.94442.44
19. Nicolardi V, Valentini E. Commentary: top-down and bottom-up modulation of pain-induced oscillations. *Front Hum Neurosci.* (2016) 10:152. doi: 10.3389/fnhum.2016.00152
20. Kenntner-Mabiala R, Andreatta M, Wieser MJ, Muhlberger A, Pauli P. Distinct effects of attention and affect on pain perception and somatosensory evoked potentials. *Biol Psychol.* (2008) 78:114–22. doi: 10.1016/j.biopsycho.2008.01.007
21. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia.* (1971) 9:97–113. doi: 10.1016/0028-3932(71)90067-4

22. Lang PJ, Bradley MM, Cuthbert BN. *International Affective Picture System (IAPS): Affective Ratings of Pictures and Instruction Manual. Technical Report A-8*. Gainesville, FL: University of Florida (2008).
23. Lang PJ, Bradley MM, Cuthbert BN. *International Affective Picture System (IAPS): Technical Manual and Affective Ratings. NIMH Center for the Study of Emotion and Attention*. Gainesville, FL: The Center for Research in Psychophysiology, University of Florida (1997). p. 39–58.
24. Mathewson KE, Harrison TJ, Kizuk SA. High and dry? Comparing active dry EEG electrodes to active and passive wet electrodes. *Psychophysiology.* (2017) 54:74–82. doi: 10.1111/psyp.12536
25. Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods.* (2004) 134:9–21. doi: 10.1016/j.jneumeth.2003.10.009
26. Makeig S. Auditory event-related dynamics of the EEG spectrum and effects of exposure to tones. *Electroencephalogr Clin Neurophysiol.* (1993) 86:283–93. doi: 10.1016/0013-4694(93)90110-H
27. McLelland D, Lavergne L, VanRullen R. The phase of ongoing EEG oscillations predicts the amplitude of peri-saccadic mislocalization. *Sci Rep.* (2016) 6:29335. doi: 10.1038/srep29335
28. Ghasemi A, Zahediasl S. Normality tests for statistical analysis: a guide for non-statisticians. *Int J Endocrinol Metab.* (2012) 10:486–9. doi: 10.5812/ijem.3505
29. Kim HY. Statistical notes for clinical researchers: assessing normal distribution (2) using skewness and kurtosis. *Restor Dent Endod.* (2013) 38:52–4. doi: 10.5395/rde.2013.38.1.52
30. George D, Mallery P. *SPSS for Windows Step by Step: A Simple Guide and Reference Pearson, Boston 2010*. 10th Edn. Boston, MA: Pearson (2010). p. 56–75.
31. West SG, Finch JF, Curran PJ. *Structural Equation Models With Nonnormal Variables: Problems And Remedies*. In: Hoyle RH, editor. Thousand Oaks: Sage Publications, Inc. (1995). p. 56–75.
32. Buffington AL, Hanlon CA, McKeown M. Acute and persistent pain modulation of attention-related anterior cingulate fMRI activations. *Pain.* (2005) 113:172–84. doi: 10.1016/j.pain.2004.10.006
33. Wiech K, Seymour B, Kalisch R, Stephan KE, Koltzenburg M, Driver J, et al. Modulation of pain processing in hyperalgesia by cognitive demand. *Neuroimage.* (2005) 27:59–69. doi: 10.1016/j.neuroimage.2005.03.044
34. Dunckley P, Aziz Q, Wise RG, Brooks J, Tracey I, Chang L. Attentional modulation of visceral and somatic pain. *Neurogastroenterol Motil.* (2007) 19:569–77. doi: 10.1111/j.1365-2982.2007.00908.x
35. Ring C, Kavussanu M, Willoughby AR. Emotional modulation of pain-related evoked potentials. *Biol Psychol.* (2013) 93:373–6. doi: 10.1016/j.biopsycho.2013.04.006
36. Godinho F, Magnin M, Frot M, Perchet C, Garcia-Larrea L. Emotional modulation of pain: is it the sensation or what we recall? *J Neurosci.* (2006) 26:11454–61. doi: 10.1523/JNEUROSCI.2260-06.2006
37. Roy M, Lebuis A, Peretz I, Rainville P. The modulation of pain by attention and emotion: a dissociation of perceptual and spinal nociceptive processes. *Eur J Pain.* (2011) 15:641 e1–10. doi: 10.1016/j.ejpain.2010.11.013
38. Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. *Neuron.* (2007) 55:377–91. doi: 10.1016/j.neuron.2007.07.012
39. Talbot K, Madden VJ, Jones SL, Moseley GL. The sensory and affective components of pain: are they differentially modifiable dimensions or inseparable aspects of a unitary experience? A systematic review. *Br J Anaesth.* (2019) 123:e263–e72. doi: 10.1016/j.bja.2019.03.033
40. Cruccu G, Aminoff M, Curio G, Guerit J, Kakigi R, Mauguiere F, et al. Recommendations for the clinical use of somatosensory-evoked potentials. *Clin Neurophysiol.* (2008) 119:1705–19. doi: 10.1016/j.clinph.2008.03.016
41. Chen ACN, Herrmann CS. Perception of pain coincides with the spatial expansion of electroencephalographic dynamics in human subjects. *Neurosci Lett.* (2001) 297:183–6. doi: 10.1016/S0304-3940(00)01696-7
42. Bruno RM, Sakmann B. Cortex is driven by weak but synchronously active thalamocortical synapses. *Science.* (2006) 312:1622–7. doi: 10.1126/science.1124593
43. Minlebaev M, Colonnese M, Tsintsadze T, Sirota A, Khazipov R. Early gamma oscillations synchronize developing thalamus and cortex. *Science.* (2011) 334:226–9. doi: 10.1126/science.1210574
44. Ribary U, Ioannides AA, Singh KD, Hasson R, Bolton JP, Lado F, et al. Magnetic field tomography of coherent thalamocortical 40-Hz oscillations in humans. *Proc Natl Acad Sci USA.* (1991) 88:11037–41. doi: 10.1073/pnas.88.24.11037
45. Headley DB, Paré D. In sync: Gamma oscillations and emotional memory. *Front Behav Neurosci.* (2013) 7:170. doi: 10.3389/fnbeh.2013.00170
46. Fries P. A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. *Trends Cogn Sci.* (2005) 9:474–80. doi: 10.1016/j.tics.2005.08.011
47. Cacioppo JT, Berntson GG. Relationship between attitudes and evaluative space: a critical review, with emphasis on the separability of positive and negative substrates. *Psychol Bull.* (1994) 115:401. doi: 10.1037/0033-2909.115.3.401
48. Bromm B, Lorenz J. Neurophysiological evaluation of pain. *Electroencephalogr Clin Neurophysiol.* (1998) 107:227–53. doi: 10.1016/S0013-4694(98)00075-3
49. Price DD. Psychological and neural mechanisms of the affective dimension of pain. *Science.* (2000) 288:1769–72. doi: 10.1126/science.288.5472.1769
50. Kenntner-Mabiala R, Pauli P. Affective modulation of brain potentials to painful and nonpainful stimuli. *Psychophysiology.* (2005) 42:559–67. doi: 10.1111/j.1469-8986.2005.00310.x
51. Aguado L, Dieguez-Risco T, Mendez-Bertolo C, Pozo MA, Hinojosa JA. Priming effects on the N400 in the affective priming paradigm with facial expressions of emotion. *Cogn Affect Behav Neurosci.* (2013) 13:284–96. doi: 10.3758/s13415-012-0137-3
52. Inui K, Tran TD, Hoshiyama M, Kakigi R. Preferential stimulation of Aδ fibers by intra-epidermal needle electrode in humans. *Pain.* (2002) 96:247–52. doi: 10.1016/S0304-3959(01)00453-5
53. Plaghki L, Mouraux A. How do we selectively activate skin nociceptors with a high power infrared laser? Physiology and biophysics of laser stimulation. *Neurophysiol Clin.* (2003) 33:269–77. doi: 10.1016/j.neucli.2003.10.003
54. Fillingim RB. Individual differences in pain: understanding the mosaic that makes pain personal. *Pain.* (2017) 158 (Suppl. 1):S11–8. doi: 10.1097/j.pain.0000000000000775

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Lyu, Zidda, Radev, Liu, Guo, Tong, Flor and Andoh. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Neurology

ORIGINAL RESEARCH
published: 17 February 2022
doi: 10.3389/fneur.2022.792695

Structural and Functional Asymmetry in Precentral and Postcentral Gyrus in Patients With Unilateral Chronic Shoulder Pain

Xiaoya Wei[1†], Guangxia Shi[1†], Jianfeng Tu[1], Hang Zhou[1], Yanshan Duan[1], Chin Kai Lee[1], Xu Wang[2] and Cunzhi Liu[1*]*

[1] International Acupuncture and Moxibustion Innovation Institute, School of Acupuncture-Moxibustion and Tuina, Beijing University of Chinese Medicine, Beijing, China, [2] School of Life Sciences, Beijing University of Chinese Medicine, Beijing, China

OPEN ACCESS

Edited by:
Flavia Di Pietro,
Curtin University, Australia

Reviewed by:
Keerthana Deepti Karunakaran,
Boston Children's Hospital and
Harvard Medical School,
United States
Tommaso Gili,
IMT School for Advanced Studies
Lucca, Italy

***Correspondence:**
Cunzhi Liu
lcz_tg@126.com
Xu Wang
wangx@bucm.edu.cn

[†] These authors have contributed equally to this work

Specialty section:
This article was submitted to Applied Neuroimaging, a section of the journal Frontiers in Neurology

Received: 11 October 2021
Accepted: 13 January 2022
Published: 17 February 2022

Citation:
Wei X, Shi G, Tu J, Zhou H, Duan Y, Lee CK, Wang X and Liu C (2022) Structural and Functional Asymmetry in Precentral and Postcentral Gyrus in Patients With Unilateral Chronic Shoulder Pain. Front. Neurol. 13:792695. doi: 10.3389/fneur.2022.792695

Objective: The purpose of this study was to explore the structural and functional asymmetry of precentral and postcentral gyrus in patients with unilateral chronic shoulder pain (CSP) utilizing MRI.

Patients and Methods: We collected structural and resting-state functional MRI (rs-fMRI) data in 22 left-sided, 15 patients with right-sided CSP, and 24 healthy controls (HCs). Here, we performed the structural asymmetry and seed-based functional connectivity (FC) analyses. We extracted regional cortical thickness and surface area measurements from T1-weighted MRI images, using asymmetry indexes (AIs) to assess asymmetries. We used Data Processing and Analysis for Brain Imaging software for seed-based FC analysis and selected unilateral-precentral and postcentral as the regions of interest. Then, we performed group comparisons of the neuroimaging metrics, and also explored the relationships between brain asymmetry and clinical variables.

Results: We found significant differences in surface area AIs of the precentral among three groups, the AI values were negatively correlated with the visual analog scale score and positively correlated with Constant–Murley scores (CMS) in the left-sided CSP group. Further, FC of left postcentral with cingulate gyrus and left paracentral lobule showed significant group differences; FC of right postcentral with left caudate, left paracentral, and left postcentral were different among groups; FC of right precentral with the cingulate gyrus, precuneus, and left paracentral revealed significant group differences. Besides, there was a positive correlation between right precentral-cingulate gyrus FC and CMS in the right-sided CSP group.

Conclusion: Surface area and FC patterns asymmetry exist in precentral and postcentral gyrus in patients with unilateral CSP. Asymmetry trend is associated with pain severity and shoulder joint function impairment. Brain structural and functional asymmetry may be an important indicator for understanding the potential mechanism of chronic pain.

Keywords: chronic shoulder pain, brain asymmetry, surface area, functional connectivity, precentral gyrus, postcentral gyrus

INTRODUCTION

In a variety of musculoskeletal disorders, chronic shoulder pain (CSP) is ranked third for the number of patients (1). Epidemiological surveys demonstrate that the lifetime prevalence rate of shoulder pain was ranging from 6.7 to 66.7% in the general population (2), and the incidence of chronic shoulder pain was 11% (1). Stiffness, limited motion, and persistent pain are common symptoms in patients (3). It is usually self-limited, resolving in 12–18 months among 40–50% of patients (4), yet the high recurrence rate and slow recovery impact their daily work and life. Due to the different etiologies, such as overload or strain, the affected sides of the shoulder could be different (5). A retrospective analysis revealed that compared with right-sided shoulder pain patients, the left-sided patients had higher scores on the Sickness Impact Profile (6).

According to the concept of homunculus (7), the cortical representation of motor and sensory functions of the shoulder are located in the precentral and postcentral, respectively. The primary motor area of the cerebral cortex is located in the precentral and has the functional characteristics of supporting the movement of the side limbs (8). The primary sensory cortex is located in postcentral, the characteristic of sensory projection is left and right cross (9). Accumulating evidence suggests that many chronic pain-related diseases, including CSP, showed extensive brain function and structural reorganization, such as the primary sensory cortex, primary motor cortex, paracentral, precuneus, cingulate cortex, and caudate (10–12). A study showed that the depth of sulcus in right precentral gyrus decreased in patients with CSP (10). As for patients with chronic neck and shoulder pain, the amplitude of the low-frequency fluctuations (ALFF) of their left precentral, right postcentral, left precuneus, and right cingulate were significantly reduced (11). These findings reflected that the precentral and postcentral gyrus are closely related to the neuropathological changes of CSP. However, these altered brain regions distributed in a wide range of the left or right hemispheres. We hypothesize that one of the most important factors may be the difference in affected sides of CSP.

The asymmetry of the structure and function of the two hemispheres is a distinctive feature of human brain (13). Hemispheric asymmetry changes are related to many mental and neurocognitive diseases, such as schizophrenia (14), autism (15), and obsessive-compulsive disorder (13). Moreover, changes in brain asymmetry have been found in chronic pain diseases. Recently, a chronic low-back pain imaging study (16) found interhemispheric asymmetry in the motor cortex, and cortical motor map of transversus abdominis and multifidus muscles is leftward asymmetric in 40.0% of participants. The asymmetry of the cortex in CSP remains unknown. Therefore, examining the lateralization effects in the cerebral cortex, especially in the precentral and postcentral gyri which are associated with the motor and sensory cortex, may be important for us to further understand the underlying mechanisms of CSP.

Here, this study focuses on assessing the structure and function asymmetry in precentral and postcentral regions in patients with unilateral CSP. We used the asymmetry index (AI) (17, 18) to assess the cerebral cortex thickness and the surface area of the precentral and postcentral regions. Seed-based FC analyses were adopted to evaluate FC patterns based on two pairs of symmetric seeds (left and right precentral and left and right postcentral). Then, we investigated whether left CSP (LCSP), right CSP (RCSP), and healthy controls (HCs) differed in their neuroimaging metrics. In addition, we investigated whether the structural and functional metrics were correlated with the clinical characteristics of pain symptoms.

METHODS

Participants

In this study, 39 patients with unilateral CSP were recruited between December 2016 and July 2017. Moreover, we recruited 26 healthy controls, matching the age and gender of our patients (from March 2017 to December 2018). More details about the recruitment of the CSP and HC participants (19) were described in our previous papers. Briefly, the key inclusion criteria of CSP people were: (1) 45–65 years old; (2) right-handed; (3) shoulder pain duration from 6 weeks to 24 months; (4) visual analog scale (VAS) score between 50 and 100 mm. The key exclusion criteria were: (1) current therapy involving analgesia; (2) abnormal brain structures; and (3) other chronic pain conditions or a history of neuropsychiatric disorders.

This study was conducted in agreement with the Declaration of Helsinki. We collected MRI data from all participants. Before MRI scanning, VAS score (20–22) and Constant–Murley score (CMS) (23) were evaluated by participants. VAS (range 0–100 mm, 0 = no pain, 100 = worst pain) is a commonly used scale to evaluate the intensity of pain. CMS (range, 0–100 points) evaluates shoulder function of the patients. Higher CMS scores indicate better shoulder joint function and mobility.

MRI Acquisition

MRI images were obtained at a Siemens 3.0 T MRI scanner (Skyra, Siemens, Erlangen, Germany) using a standard head coil at the Department of Radiology for Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University. The high-resolution T1 MRI was acquired using gradient echo sequence with the following parameters: repetition time (TR) = 2,300 ms, echo time (TE) = 2.32 ms, flip angle (FA) = 8°, inversion time = 900 ms, field of view (FOV) = 240 × 240 mm, number of slices = 192, voxel size = 0.9375 × 0.9375 × 0.9 mm, and in-plane resolution = 256 × 256. In addition, the resting-state functional MRI (rs-fMRI) was scanned using echo planar imaging (EPI) sequence: TR = 2,000 ms, TE = 30 ms, FOV = 220 × 220 mm, FA = 90°, slice thickness/gap = 3.5/0.6 mm, axial slices = 33, in-plane resolution= 64 × 64, and 240 volumes. We used comfortable foam pads to minimize the head motion and earplugs to reduce noise interference. Before starting the scanning, we instructed participants to keep their eyes closed, stay awake, avoid engaging in any specific thoughts, and keep still.

Image Processing

Using the "recon-all" command implemented in FreeSurfer (http://surfer.nmr.mgh.harvard.edu/, V6.0) to process the

structural MRI data to reconstruct the cortical surface. Mean cortical thickness and surface area were derived for each of the 68 cortical regions of the Desikan-Killiany Atlas (34 per hemisphere). Cortical thickness was estimated for each participant using the distance from the white matter boundary to the corresponding pial surface (24). Cerebral surface area was calculated by mesh generation and surface triangulation. The cortex thickness and surface area of each hemisphere are performed independently.

Furthermore, functional MRI (fMRI) data were processed using the software MATLAB 2013b (MathWorks, Natick, MA, USA) and the toolkit of Data Processing and Analysis for Brain Imaging (DPABI version 5.1, http://www.rfmri.org/dpabi) (25). For each image data of participant, we discarded the first 10 volumes because of signal equilibrium, a total of 230 volumes for each subject were processed with the slice timing, motion correction, spatial smoothing (6-mm FWHM), and spatial normalization to the Montreal Neurological Institute (MNI) space. Then, we re-sampled the data into $3 \times 3 \times 3$ mm^3. Finally, after removing the linear trend, we applied a 0.01–0.08 Hz bandpass filter.

Quality Control

Four participants (two patients and 2 HCs) were excluded from the study on account of excessive head motion (>3 mm in translation or >3.0° in rotation) during the rs-fMRI scanning. As a result, 22 patients with LCSP, 15 patients with RCSP, and 24 HCs were included in further statistical analyses. Furthermore, we extracted the mean framewise displacement (FD) for each participant to measure the extent of head motion (26, 27) and compared them among the three groups. The non-parametric test result showed that there is no significant difference in head motion among the three groups ($H = 4.137$, $p = 0.126$).

Clinical and MRI Statistical Analyses

Demographic and Clinical Characteristics Analyses

We used SPSS statistics 21 software to conduct statistical analyses. Before statistical analyses, we checked the normality of each metric. Age and CMS were normally distributed in each group, whereas pain degree (VAS score) and pain duration were non-normally distributed. We used one-way ANOVA for age, two-sample *t*-test for CMS, and Mann–Whitney *U*-non-parametric tests for VAS and pain duration. As for categorical variables (i.e., gender), we used the chi-square test to evaluate the differences among groups.

Surface-Based Morphometry Analyses

To compare the difference in cortex structural asymmetry of precentral and postcentral regions related to unilateral CSP, AI for each cortical metric is calculated as a widely used formula (28):

$$AI = \frac{(Left - Right)}{(Left + Right)/2}$$

Consequently, a negative AI reflects a rightward asymmetry and a positive AI means that asymmetry is shifted to the left. In the three groups, we used ANOVA or non-parametric tests to compare the difference in asymmetrical changes in cortical surface area and cortical thickness, and then performed the *post-hoc* analysis.

Seed-Based Functional Connectivity Analyses

For the functional analyses, we selected left precentral, right precentral, left postcentral, and right postcentral from the Automated Anatomical Labeling (AAL) atlas (29) as the seeds because AAL is a commonly used atlas in functional space (30–34). We performed Pearson's correlation between each seed region and the whole brain voxel. Then, Fisher's *r*-to-*z* transformation was used to convert each final FC map of individual to *z*-value maps. Among three groups, we used one-way ANOVA analyses to obtain the *F* statistical map. Finally, Gaussian Random Field (GRF) theory multiple comparison correction (35) was used for all maps (voxel-level $p < 0.01$ and cluster-level $p < 0.05$).

Brain Alteration and Clinical Variables Analyses

We extracted FC value between the seed and the region with significant group differences. For normally distributed variables,

TABLE 1 | Demographic and clinical characteristics of patients with chronic shoulder pain (CSP) and healthy control (HC).

Parameter	LCSP patients (n = 22)	RCSP patients (n = 15)	HC (n = 24)	Statistics	*P*-value
Age (year)#	54.18 ± 6.03	54.20 ± 4.81	55.83 ± 4.72	$F = 0.714^a$	0.494
Gender (Male/Female)	11/11	11/4	10/14	$X^2 = 3.795^b$	0.150
Pain duration (months)*	4 (2–24)	5 (1–24)	N/A	$Z = 0.422^c$	0.680
Pain degree (VAS)*	65 (50–100)	60 (55–100)	N/A	$Z = 0.363^c$	0.725
Shoulder function (CMS)#	54.55 ± 13.29	50.47 ± 16.38	N/A	$t = 0.834^d$	0.410

*For continuous variables, we used mean (SD) #if the measurements were normally distributed, and median (minimum to maximum) *if the measurements were not normally distributed.*
[a]*One-way ANOVA.*
[b]*Chi-square test.*
[c]*Non-parametric test: Mann–Whitney U.*
[d]*Two-sample t-test.*
N/A, not applicable; VAS, visual analog scale score, 0–100 mm; CMS, the Constant–Murley score, 0–100 points; LCSP, left chronic shoulder pain; RCSP, right chronic shoulder pain; HC, healthy controls.

Pearson's correlation was used to analyze the correlation between AI and FC values and VAS and CMS. For non-normally-distributed variables, we used Spearman's correlation analysis. The above statistical analysis used SPSS software (significance level is $p < 0.05$).

RESULTS

Participants

Among the three groups, there was no significant difference here in demographic data (age, $F = 0.714$, $p = 0.494$; gender, $X^2 = 3.795$, $p = 0.150$). The pain duration ($Z = 0.422$, $p = 0.680$), VAS ($Z = 0.363$, $p = 0.725$), and CMS ($t = 0.834$, $p = 0.410$) showed no significant differences in patients with LCSP and RCSP. More details are presented in **Table 1**.

Brain Structural Asymmetry

Comparisons among the three groups using ANOVA and non-parametric testing revealed that the precentral region had significantly different brain asymmetry in surface area ($F = 3.958$, $p = 0.024$). According to the *post-hoc* pairwise comparison analyses, there was a significant difference in AI between the LCSP and RCSP groups (ES $= -1.002$, $p = 0.005$), specifically, the LCSP group showed rightward asymmetries (group means AI $= -0.017$), and the RCSP group showed leftward asymmetries (group means AI $= 0.043$) in the precentral surface area (**Table 2**; **Figure 1**). However, we did not find a significant difference in AI of cortical thickness in both the precentral and postcentral regions (**Supplementary Material**).

Brain Functional Asymmetry

When comparing the left postcentral seed-based FC maps among the three groups, two brain regions with significant differences were found, cingulate gyrus and paracentral lobule (voxel-level $p < 0.01$, cluster-level $p < 0.05$, cluster size > 55 voxels; **Table 3**, **Figure 2A**). Otherwise, the caudate, paracentral lobule, and postcentral revealed different FC with the right postcentral seed (voxel-level $p < 0.01$, cluster-level $p < 0.05$, cluster size > 51 voxels; **Table 3**, **Figure 2B**). However, no brain regions showed a significant FC difference with the left precentral seed (**Figure 2C**). For the right precentral seed, FC maps were significantly different in the cingulate gyrus, precuneus, and paracentral lobule (voxel-level $p < 0.01$, clusterlevel $p < 0.05$, cluster size > 47 voxels; **Table 3**, **Figure 2D**).

To rule out the possibility that our results depended on the choice of the atlas, we re-performed seed-based FC analyses using the precentral and postcentral seeds taken from the Desikan-Killiany atlas. We extracted the value of the eight significant regions (**Table 3**) from the FC maps of individuals' based on the Desikan-Killiany atlas and found that the FCs were still significantly different among the three groups (**Table 4**).

Correlation Analysis Results Between AI, FC, and VAS, CMS

Correlation analyses revealed that the AI values of the precentral surface area had a positive correlation with the CMS scores (Pearson's $r = 0.47$, $p = 0.03$) and a negative correlation with the

TABLE 2 | Differences in surface area asymmetry index among left CSP (LCSP), right CSP (RCSP), and HC.

Region	LCSP patients	RCSP patients	HC	Statistics	*P*-value	*Post-hoc* pairwise comparison				
	N = 22	*N* = 15	*N* = 24	X^2/F		LCSP vs. HC	*P*-value	RCSP vs. HC	*P*-value	LCSP vs. RCSP	*P*-value
Postcentral	0.036 (−0.201~0.122)[$]	0.050 ± 0.064	0.051 ± 0.098	$X^2 = 1.461$[a]	0.482	$Z = 0.660$[c]	0.509	−0.012[#]	0.972	$Z = -1.268$[c]	0.213
Precentral	−0.017 ± 0.061	0.043 ± 0.057	0.006 ± 0.068	$F = 3.958$[b]	**0.024***	−0.348[#]	0.245	0.572[#]	0.091	−1.002[#]	**0.005***

We used mean (SD) if the measurements were normally distributed, and the median (minimum to maximum) [$]*if the measurements were not normally distributed.*

[*]*Survives Bonferroni correction.*

[a]*Kruskal–Wallis test.*

[b]*One-way ANOVA.*

[c]*Non-parametric test: Mann–Whitney U.*

[#]*Cohen's d of two-sample t-test.*

LCSP, left chronic shoulder pain; RCSP, right chronic shoulder pain; HC, healthy controls. The bold values indicate the significant results ($p < 0.05$).

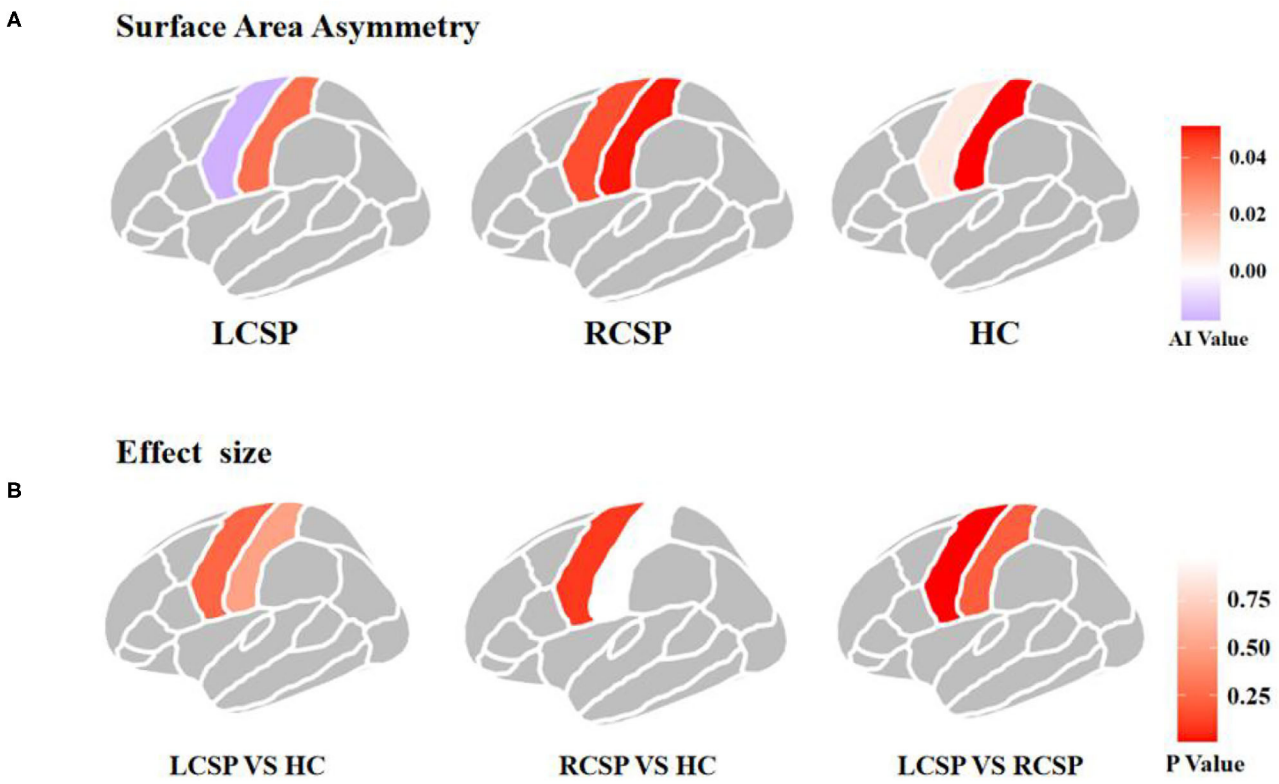


FIGURE 1 | Asymmetry of surface area and effect sizes in the precentral and postcentral gyrus in three groups. **(A)** Asymmetry of surface area in the precentral and postcentral gyrus. Colors indicate the directions of average interhemispheric differences, with red indicating leftward asymmetry, and purple indicating rightward asymmetry. **(B)** Region-wise effect sizes of hemispheric asymmetry. Effect sizes are Cohen's *d* values.

TABLE 3 | Differences in seed-based functional connectivity (FC) among LCSP, RCSP, and HC.

Seed	Connectivity regions	Peak MNI coordinates			Voxels size	*F*-value
		X	Y	Z		
Left postcentral	Cingulate gyrus	9	−3	27	55	10.769
	Left paracentral	−12	−24	63	61	9.264
Right postcentral	Left caudate	−9	−3	15	66	11.093
	Left paracentral	−12	−24	63	99	9.639
	Left postcentral	−48	−27	63	59	9.535
Left precentral	–	–	–	–	–	–
Right precentral	Cingulate gyrus	6	−3	27	102	13.940
	Precuneus	15	−81	30	64	9.876
	Left paracentral	−12	−24	63	61	10.644

MNI, montreal neurological institute; GRF, gaussian random field theory, Voxel p < 0.01, cluster p < 0.05.

VAS scores (Spearman's $r = -0.57$, $p = 0.01$) in the patients with LCSP (**Figures 3A,B**). In addition, there was a significant positive correlation between FC and CMS between the right precentral gyrus and cingulate gyrus ($r = 0.53$, $p = 0.04$) in the RCSP group (**Figure 3C**). Although there was no difference in the cortical area of the postcentral region between the three groups, we still found a positive association between AI of the postcentral surface area and CMS scores (Spearman's $r = 0.46$, $p = 0.03$) in patients with LCSP patients (**Figure 3D**).

DISCUSSION

Based on our hypothesis, we evaluated the structural and functional asymmetry of precentral and postcentral gyrus

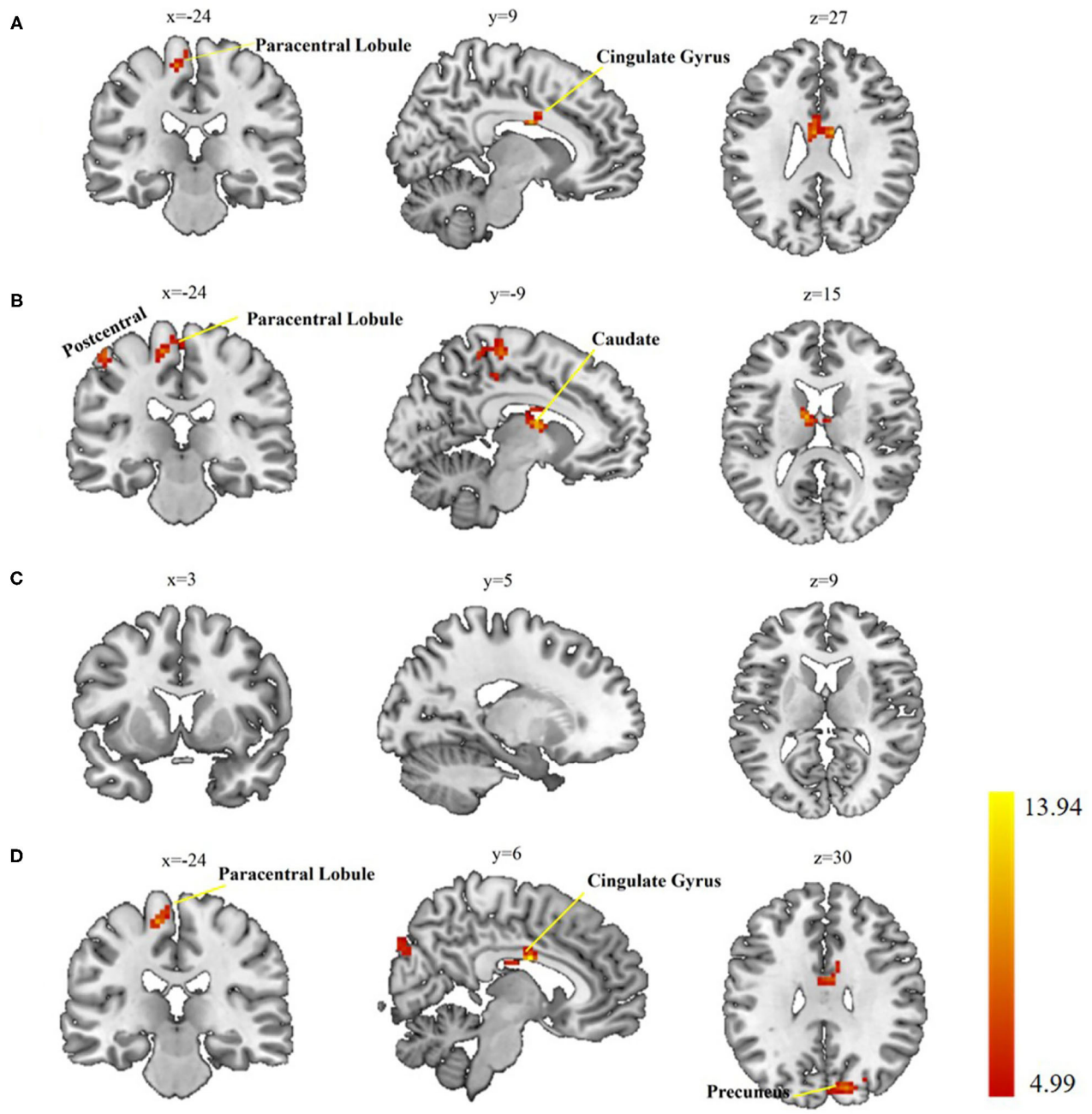


FIGURE 2 | Group differences in seed-based functional connectivity (FC). **(A)** Significant regions based on left postcentral seed; **(B)** significant regions based on right postcentral seed; **(C)** significant regions based left precentral seed; **(D)** significant regions based on right precentral seed. Gaussian Random Field (GRF) theory correction with voxel level $p < 0.01$ and cluster level $p < 0.05$.

in patients with unilateral CSP. For the cortical structural asymmetry analysis, we found significant differences in the surface area of precentral among the left-sided CSP, right-sided CSP, and HC groups. Seed-based FC analyses revealed different connectivity patterns in patients with CSP for two pairs of symmetric seeds (left vs. right precentral, left vs. right postcentral). In addition, we found these structural and functional asymmetry metrics were correlated with clinical parameters. Specifically, AI values of precentral in LCSP had a significant positive correlation with CMS scores and a negative correlation with the VAS scores. Right precentral—cingulate gyrus FC had a significant positive correlation with CMS scores

TABLE 4 | Differences in Desikan-Killiany-seed-based FC among LCSP, RCSP, and HC.

Groups-FC map	Seed	Peak MNI coordinates			*F*-value	*P*
		X	Y	Z		
Left postcentral	Cingulate gyrus	9	−3	27	12.497	<0.001**
	Left paracentral	−12	−24	63	8.396	<0.001**
Right postcentral	Left caudate	−9	−3	15	3.227	0.047*
	Left paracentral	−12	−24	63	9.682	<0.001**
	Left postcentral	−48	−27	63	14.075	<0.001**
Left precentral	–	–	–	–	–	–
Right precentral	Cingulate gyrus	6	−3	27	10.894	<0.001**
	Precuneus	15	−81	30	9.197	<0.001**
	Left paracentral	−12	−24	63	11.746	<0.001**

*$p < 0.05$.
**$p < 0.001$.

in RCSP. Our findings may clarify the neural mechanism of CSP from the perspective of brain asymmetry.

Surface Area Asymmetry of the Precentral Gyrus

A previous meta-analysis (36) has shown that the right precentral gyrus undergoes structural changes in some chronic pain diseases, such as chronic back pain, migraine, or chronic facial pain. Compared with HC, patients with chronic neck pain (CNP) had a smaller cortex in right precentral area, and the study has shown a correlation between the volume changes of the right precentral and degree of neuromuscular control (37). However, these studies only found the chronic pain-related structural changes in the unilateral (i.e., right) precentral gyrus and ignored the possible brain asymmetry substrates. Besides, the affected sides of chronic pain were not considered separately. Interestingly, ANOVA comparing the three groups in the present study showed a significant effect of group, but the *post-hoc* difference was observed only between RCSP and LCSP groups and not between HC and patient groups. Here, the AI of the precentral area had a tendency of rightward asymmetry in the LCSP group, and a tendency of leftward in the RCSP group. The AI of HC was in between. These findings indicate that the precentral areas of the contralateral and ipsilateral to the shoulder pain side are affected asymmetrically. This is consistent with the left-right cross characteristic of sensory/motional projection that the precentral may be more involved to the pain and function of the contralateral shoulder. Our results may further support the lateralization of the brain in pain processing (38–40).

In addition to the precentral gyrus, accumulating evidence has demonstrated that the motor cortical reorganization and asymmetries are associated with many chronic pain diseases (16, 41–43). It was reported that the cortical motor map of 40.0% chronic low-back pain (CLBP) group subjects was leftward asymmetric compared with HC (16). Phantom limb pain (43) patient's motor cortex reorganizes asymmetrically, and the volume of gray matter in the affected hemisphere is reduced. Further studies are needed to investigated the whole motor cortex and reveal the neural asymmetry basis of the CSP or other chronic pain diseases.

Moreover, we found associations of the precentral area's AI with VAS and CMS in LCSP group, indicating that the lower rightward structural asymmetry of precentral may relate to the lower pain degree and better shoulder function (44). However, the VAS and CMS were not correlated with the AI values of the precentral area in RCSP group. We speculate that the difference between the groups could be accounted by different etiologies because the gender proportions and samples in each group were not identical. Particularly, there were only 4 women and 15 sample size in RCSP group. Besides, different potential mechanisms related to handedness may also lead to the observation of such differences. All the participants were right-handed in the present study. Previous study has shown that right-handed patients with left-sided pain had poorer physical functioning than right-sided pain patients (6). Further studies with left-handed participants will be helpful to test this speculation.

FC Pattern Asymmetry of the Precentral and Postcentral Gyrus

Regarding the FC of the right precentral, we found that the connection with the precuneus, cingulate, and left paracentral lobule increased. Our results support previous research, these brain areas play an important role in chronic pain-related diseases (37, 45–47). The cingulate gyrus is related to various cognitive, social, and emotional functioning (45). We speculate that the emotional function of patients with chronic shoulder pain will be affected. However, we cannot confirm this view because the emotional/cognitive ability of patients was not measured in this study. The precuneus is part of a group of areas related to the neurological characteristics of pain (36) and acts as an antinociceptive region (37) and increased FC in the precentral gyrus with the superior parietal cortex in patients with CNP (47). However, in present results, no brain areas with FC were reported with left precentral, it is reasonable to speculate that there may

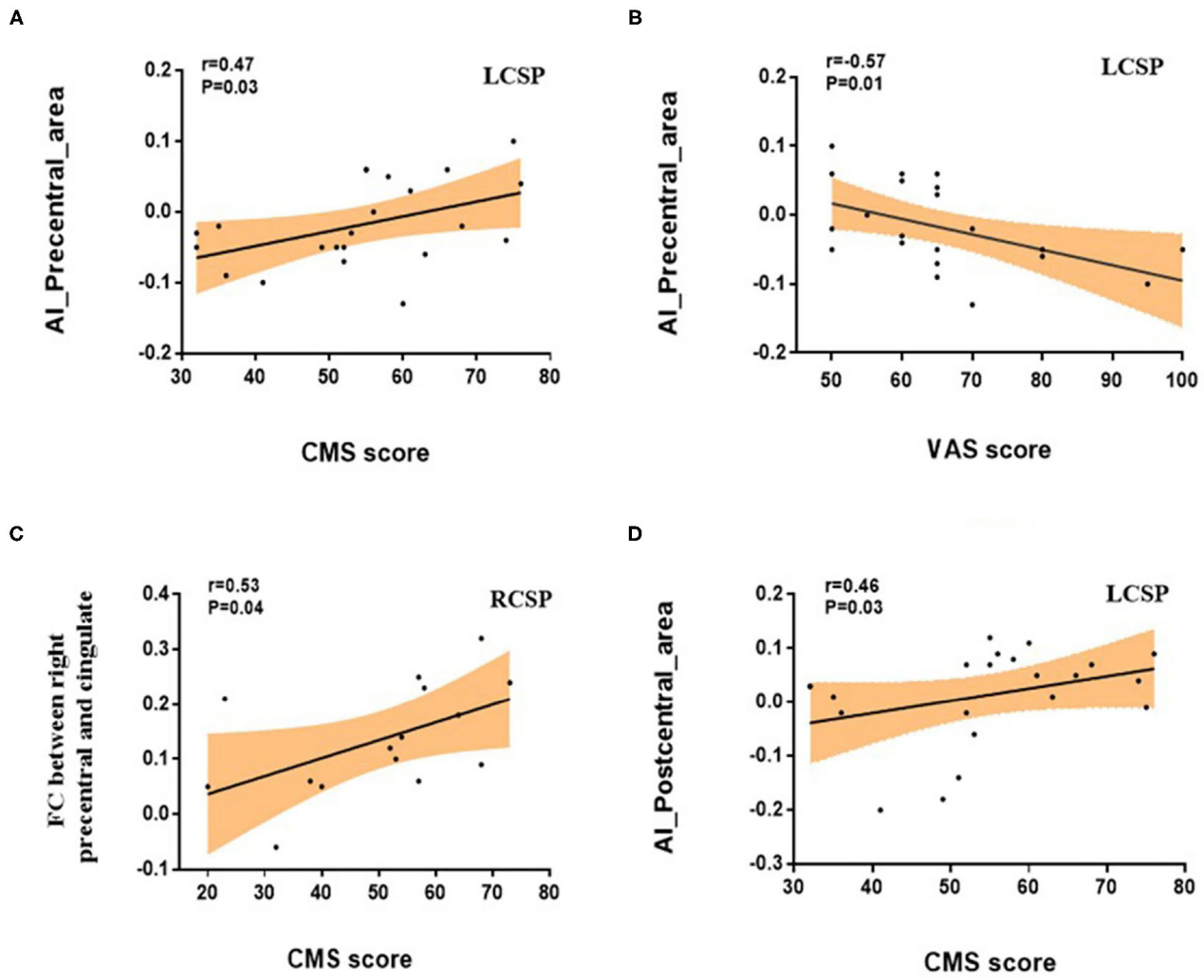


FIGURE 3 | Correlations between brain index and clinical variables in the patients with chronic shoulder pain (CSP). **(A)** Pearson's correlation showed a positive association between the asymmetry index (AI) of precentral surface area and the CMS scores ($r = 0.47$, $p = 0.03$). **(B)** Spearman's correlation showed a negative association between the AI of precentral surface area and the VAS scores ($r = -0.57$ $p = 0.01$). **(C)** Pearson's correlation showed that FC between right precentral gyrus and cingulate gyrus was significantly positively correlated with CMS ($r = 0.53$, $p = 0.04$). **(D)** Spearman's correlation showed a positive association between the AI of postcentral surface area and the CMS scores ($r = 0.46$ $p = 0.03$).

also exist functional asymmetry in the precentral gyrus in patients with CSP.

In this study, four seeds were selected according to the AAL atlas to better disclosure the FC patterns of the different hemispherical precentral and postcentral. Specifically, the paracentral lobule showed increased FC from all three seed points. The paracentral lobule that plays a pivotal role in the location and identification of pain (48) with the postcentral, which is located in the upper medial part of the precentral. It has been reported that the excitability of the motor cortex in patients with chronic pain has changed, such as paracentral lobules, which may be affected by the underlying pathological properties of different diseases (49, 50). For example, in a CLBP study, increased ALFF in the bilateral postcentral, precentral, and paracentral were found in patients (51). In our study, we found only enhanced functional connectivity of the left paracentral lobule with each seed and our findings may support the pivotal role of paracentral lobules in pain regulation of CSP.

The caudate nucleus is an important part of the basal ganglia. It is involved in the reward circuit in chronic pain and involves the motivational and emotional aspects of behavior, such as rewards, which are important for planning and decision-making (52). Many previous studies have reported that the caudate nucleus has hemispheric asymmetry (53–55). For instance, In a KOA imaging study, it was found that the volume of the caudate nucleus was rightward hemispheric asymmetry (56). The

GRF-corrected FC analysis showed that only the FC between the right postcentral and left caudate nucleus had significant group differences. Moreover, decreased bilateral caudate nucleus coactivation has been found in patients with multiple sclerosis (MS) (57). Instead, we found enhanced FC between the right postcentral gyrus and the caudate nucleus. The reason for the difference may be caused by the different pathogenesis and different clinical characteristics of MS and CSP. Our findings add new evidence of brain asymmetry to previously published findings in CSP patients of brain alterations.

Our study has some limitations. First, the sample size of this study is not very large, and there are only four female patients in the RCSP group. Hence, the conclusion needs to be repeated in a large unilateral CSP population having equal numbers of men and women. Second, our research is essentially a cross-sectional study. In the future, we will conduct longitudinal studies with other chronic pain-related diseases, exploring whether the brain structural and functional asymmetry will change after treatment. Third, this study focused only on the impact of lateralization on the two regions. In the future, we will further explore the differences in another brain anatomy (e.g., white matter architecture and gray matter volume), and altered functioning between networks in patients.

CONCLUSION

In summary, our study found that there was significant asymmetry in the cortical surface area of the precentral in patients with CSP, and the asymmetry value of patients with LCSP has a clear correlation with the severity of the condition of patient. Additionally, the precentral and postcentral gyrus in different hemispheres had different FC patterns with the whole brain regions in patients with CSP. What's more, the FC between the right precentral and cingulate gyrus was correlated with the condition of patient in the RCSP group. Our research adds to the literature suggesting a critical role of precentral and postcentral in the pathophysiology of CSP, and the brain asymmetry effect may be an important hallmark of chronic pain diseases.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Committee of the Beijing Hospital of Traditional Chinese Medicine, affiliated with Capital Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XW designed this work. XYW, HZ, and JT analyzed the data. XYW and GS discussed the results. XYW wrote the initial draft. XYW, XW, GS, YD, CL, and CKL substantially revised the manuscript. All authors agreed to be accountable for all aspects of this work.

FUNDING

This work was supported by the Scientific Research Foundation for high-level talents of Beijing University of Chinese Medicine and the Beijing Technology Development of Traditional Chinese Medicine Foundation–Annual Planning Project (ref: JJ 2013-40).

ACKNOWLEDGMENTS

The authors thank all the participants and their families.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.792695/full#supplementary-material

REFERENCES

1. Herin F, Vézina M, Thaon I, Soulat JM, Paris C. ESTEV group. Predictors of chronic shoulder pain after 5 years in a working population. *Pain.* (2012) 153:2253–9. doi: 10.1016/j.pain.2012.07.024
2. Whittle S, Buchbinder R. In the clinic. Rotator cuff disease. *Ann Intern Med.* (2015) 162:ITC1-15. doi: 10.7326/AITC201501060
3. Cools AM, Michener LA. Shoulder pain: can one label satisfy everyone and everything? *Br J Sports Med.* (2017) 51:416–7. doi: 10.1136/bjsports-2016-096772
4. Bron C, de Gast A, Dommerholt J, Stegenga B, Wensing M, Oostendorp RA. Treatment of myofascial trigger points in patients with chronic shoulder pain: a randomized, controlled trial. *BMC Med.* (2011) 9:8. doi: 10.1186/1741-7015-9-8
5. Burbank KM, Stevenson JH, Czarnecki GR, Dorfman J. Chronic shoulder pain: part I. Evaluation and diagnosis. *Am Fam Physician.* (2008) 77:453–60.
6. Gagliese L, Schiff BB, Taylor A. Differential consequences of left- and right-sided chronic pain. *Clin J Pain.* (1995) 11:201–7. doi: 10.1097/00002508-199509000-00007
7. Germann J, Chakravarty MM, Collins DL, Petrides M. Tight coupling between morphological features of the central sulcus and somatomotor body representations: a combined anatomical and functional MRI study. *Cereb Cortex.* (2020) 30:1843–54. doi: 10.1093/cercor/bhz208
8. Wang Y, Fang JL, Cui B, Liu J, Song P, Lang C, et al. The functional and structural alterations of the striatum in chronic spontaneous urticaria. *Sci Rep.* (2018) 8:1725. doi: 10.1038/s41598-018-19962-2
9. Lu Y, Zhao Q, Wang Y, Zhou C. Ballroom dancing promotes neural activity in the sensorimotor system: a resting-state fMRI study. *Neural Plast.* (2018) 2018:2024835. doi: 10.1155/2018/2024835
10. Niddam DM, Lee SH, Su YT, Chan RC. Altered cortical morphology in patients with chronic shoulder pain. *Neurosci Lett.* (2019) 712:134515. doi: 10.1016/j.neulet.2019.134515

11. Yue X, Du Y. Altered intrinsic brain activity and regional cerebral blood flow in patients with chronic neck and shoulder pain. *Pol J Radiol.* (2020) 85:e155–62. doi: 10.5114/pjr.2020.94063
12. Cunningham G, Zanchi D, Emmert K, Kopel R, Van De Ville D, Lädermann A, et al. Neural correlates of clinical scores in patients with anterior shoulder apprehension. *Med Sci Sports Exerc.* (2015) 47:2612–20. doi: 10.1249/MSS.0000000000000726
13. Kong XZ, Boedhoe PSW, Abe Y, Alonso P, Ameis SH, Arnold PD, et al. Mapping cortical and subcortical asymmetry in obsessive-compulsive disorder: findings from the ENIGMA consortium. *Biol Psychiatry.* (2020) 87:1022–34. doi: 10.1016/j.biopsych.2019.04.022
14. Crow TJ. Temporal lobe asymmetries as the key to the etiology of schizophrenia. *Schizophr Bull.* (1990) 16:433–43. doi: 10.1093/schbul/16.3.433
15. Eyler LT, Pierce K, Courchesne E. A failure of left temporal cortex to specialize for language is an early emerging and fundamental property of autism. *Brain.* (2012) 135:949–60. doi: 10.1093/brain/awr364
16. Li X, Liu H, Ge L, Yan Y, Lo WLA, Li L, et al. Cortical representations of transversus abdominis and multifidus muscles were discrete in patients with chronic low back pain: evidence elicited by TMS. *Neural Plast.* (2021) 2021:6666024. doi: 10.1155/2021/6666024
17. Kurth F, Gaser C, Luders E. A 12-step user guide for analyzing voxel-wise gray matter asymmetries in statistical parametric mapping (SPM). *Nat Protoc.* (2015) 10:293–304. doi: 10.1038/nprot.2015.014
18. Leroy F, Cai Q, Bogart SL, Dubois J, Coulon O, Monzalvo K, et al. New human-specific brain landmark: the depth asymmetry of superior temporal sulcus. *Proc Natl Acad Sci USA.* (2015) 112:1208–13. doi: 10.1073/pnas.1412389112
19. Li JL, Yan CQ, Wang X, Zhang S, Zhang N, Hu SQ, et al. Brain functional alternations of the pain-related emotional and cognitive regions in patients with chronic shoulder pain. *J Pain Res.* (2020) 13:575–83. doi: 10.2147/JPR.S220370
20. Wang L, Hong PJ, May C, Rehman Y, Oparin Y, Hong CJ, et al. Medical cannabis or cannabinoids for chronic non-cancer and cancer related pain: a systematic review and meta-analysis of randomised clinical trials. *BMJ.* (2021) 374:n1034. doi: 10.1136/bmj.n1034
21. Lazaridou A, Elbaridi N, Edwards RR. Chapter 5 - pain assessment. In: Benzon HT, Raja SN, Liu SS, editors, *Essentials of Pain Medicine, 4th Edn.* Amsterdam: Elsevier (2018). p. 39–46. doi: 10.1016/B978-0-323-40196-8.00005-X
22. Paavola M, Kanto K, Ranstam J, Malmivaara A, Inkinen J, Kalske J, et al. Subacromial decompression versus diagnostic arthroscopy for shoulder impingement: a 5-year follow-up of a randomised, placebo surgery controlled clinical trial. *Br J Sports Med.* (2021) 55:99–107. doi: 10.1136/bjsports-2020-102216
23. Constant CR, Gerber C, Emery RJ, Søjbjerg JO, Gohlke F, Boileau P, et al. Review of the constant score: modifications and guidelines for its use. *J Shoulder Elbow Surg.* (2008) 17:355–61. doi: 10.1016/j.jse.2007.06.022
24. Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci USA.* (2000) 97:11050–5. doi: 10.1073/pnas.200033797
25. Yan CG, Wang XD, Zuo XN, Zang Y-F. DPABI: data processing & analysis for (resting-state) brain imaging. *Neuroinformatics.* (2016) 14:339–51. doi: 10.1007/s12021-016-9299-4
26. Yan CG, Craddock RC, Zuo XN, Zang YF, Milham MP. Standardizing the intrinsic brain: towards robust measurement of inter-individual variation in 1000 functional connectomes. *Neuroimage.* (2013) 80:246–62. doi: 10.1016/j.neuroimage.2013.04.081
27. Van Dijk KR, Sabuncu MR, Buckner RL. The influence of head motion on intrinsic functional connectivity MRI. *Neuroimage.* (2012) 59:431–8. doi: 10.1016/j.neuroimage.2011.07.044
28. Kong XZ, Mathias SR, Guadalupe T, ENIGMA Laterality Working Group, Glahn DC, Franke B, et al. Mapping cortical brain asymmetry in 17,141 healthy individuals worldwide *via* the ENIGMA consortium. *Proc Natl Acad Sci USA.* (2018) 115:E5154–63. doi: 10.1073/pnas.1718418115
29. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage.* (2002) 15:273–89. doi: 10.1006/nimg.2001.0978
30. Chen Q, Ursini G, Romer AL, Knodt AR, Mezeivtch K, Xiao E, et al. Schizophrenia polygenic risk score predicts mnemonic hippocampal activity. *Brain* 141:1218–28. doi: 10.1093/brain/awy004
31. Zhang Y, Zhang H, Adeli E, Chen X, Liu M, Shen D. Multiview feature learning with multiatlas-based functional connectivity networks for MCI diagnosis. *IEEE Trans Cybern.* (2020) 2020:3016953. doi: 10.1109/TCYB.2020.3016953
32. Shi D, Zhang H, Wang S, Wang G, Ren K. Application of functional magnetic resonance imaging in the diagnosis of Parkinson's disease: a histogram analysis. *Front Aging Neurosci.* (2021) 13:624731. doi: 10.3389/fnagi.2021.624731
33. Wu Z, Xu D, Potter T, Zhang Y. Alzheimer's disease neuroimaging initiative. Effects of brain parcellation on the characterization of topological deterioration in Alzheimer's disease. *Front Aging Neurosci.* (2019) 11:113. doi: 10.3389/fnagi.2019.00113
34. Rolls ET, Huang CC, Lin CP, Feng J, Joliot M. Automated anatomical labelling atlas 3. *Neuroimage.* (2020) 206:116189. doi: 10.1016/j.neuroimage.2019.116189
35. Wang P, Peng ZL, Liu L, An L, Liu Y-X, Cao Q-J, et al. Neural response to trauma-related and trauma-unrelated negative stimuli in remitted and persistent pediatric post-traumatic stress disorder. *Brain Behav.* (2021) 11:e02173. doi: 10.1002/brb3.2173
36. Smallwood RF, Laird AR, Ramage AE, Parkinson AL, Lewis J, Clauw DJ, et al. Structural brain anomalies and chronic pain: a quantitative meta-analysis of gray matter volume. *J Pain.* (2013) 14:663–75. doi: 10.1016/j.jpain.2013.03.001
37. De Pauw R, Coppieters I, Caeyenberghs K, Kregel J, Aerts H, Lenoir D, et al. Associations between brain morphology and motor performance in chronic neck pain: a whole-brain surface-based morphometry approach. *Hum Brain Mapp.* (2019) 40:4266–78. doi: 10.1002/hbm.24700
38. Pud D, Golan Y, Pesta R. Hand dominancy–a feature affecting sensitivity to pain. *Neurosci Lett.* (2009) 467:237–40. doi: 10.1016/j.neulet.2009.10.048
39. Ichesco E, Schmidt-Wilcke T, Bhavsar R, Clauw DJ, Peltier SJ, Kim J, et al. Altered resting state connectivity of the insular cortex in individuals with fibromyalgia. *J Pain.* (2014) 15:815–26.e1. doi: 10.1016/j.jpain.2014.04.007
40. Sarlani E, Farooq N, Greenspan JD. Gender and laterality differences in thermosensation throughout the perceptible range. *Pain.* (2003) 106:9–18. doi: 10.1016/S0304-3959(03)00211-2
41. Ngomo S, Mercier C, Bouyer LJ, Savoie A, Roy JS. Alterations in central motor representation increase over time in individuals with rotator cuff tendinopathy. *Clin Neurophysiol.* (2015) 126:365–71. doi: 10.1016/j.clinph.2014.05.035
42. Ozcan A, Tulum Z, Pinar L, Başkurt F. Comparison of pressure pain threshold, grip strength, dexterity and touch pressure of dominant and non-dominant hands within and between right-and left-handed subjects. *J Korean Med Sci.* (2004) 19:874–8. doi: 10.3346/jkms.2004.19.6.874
43. Pacheco-Barrios K, Pinto CB, Saleh Velez FG, Duarte D, Gunduz ME, Simis M, et al. Structural and functional motor cortex asymmetry in unilateral lower limb amputation with phantom limb pain. *Clin Neurophysiol.* (2020) 131:2375–82. doi: 10.1016/j.clinph.2020.06.024
44. Liu CC, Chien JH, Kim JH, Chuang YF, Cheng DT, Anderson WS, et al. Cross-frequency coupling in deep brain structures upon processing the painful sensory inputs. *Neuroscience.* (2015) 303:412–21. doi: 10.1016/j.neuroscience.2015.07.010
45. Wagner IC, Rütgen M, Lamm C. Pattern similarity and connectivity of hippocampal-neocortical regions support empathy for pain. *Soc Cogn Affect Neurosci.* (2020) 15:273–84. doi: 10.1093/scan/nsaa045
46. Wager TD, Atlas LY, Lindquist MA, Roy M, Woo CW, Kross E. An fMRI-based neurologic signature of physical pain. *N Engl J Med.* (2013) 368:1388–97. doi: 10.1056/NEJMoa1204471
47. Coppieters I, Cagnie B, De Pauw R, Meeus M, Timmers I. Enhanced amygdala-frontal operculum functional connectivity during rest in women with chronic neck pain: associations with impaired conditioned pain modulation. *Neuroimage Clin.* (2021) 30:102638. doi: 10.1016/j.nicl.2021.102638
48. Kim W, Kim SK, Nabekura J. Functional and structural plasticity in the primary somatosensory cortex associated with chronic pain. *J Neurochem.* (2017) 141:499–506. doi: 10.1111/jnc.14012

49. Parker RS, Lewis GN, Rice DA, McNair PJ. Is motor cortical excitability altered in people with chronic pain? A systematic review and meta-analysis. *Brain Stimul.* (2016) 9:488–500. doi: 10.1016/j.brs.2016.03.020
50. Kregel J, Meeus M, Malfliet A, Dolphens M, Danneels L, Nijs J, et al. Structural and functional brain abnormalities in chronic low back pain: a systematic review. *Semin Arthritis Rheum.* (2015) 45:229–37. doi: 10.1016/j.semarthrit.2015.05.002
51. Zhang B, Jung M, Tu Y, Gollub R, Lang C, Ortiz A, et al. Identifying brain regions associated with the neuropathology of chronic low back pain: a resting-state amplitude of low-frequency fluctuation study. *Br J Anaesth.* (2019) 123:e303–11. doi: 10.1016/j.bja.2019.02.021
52. O'Doherty JP. Reward representations and reward-related learning in the human brain: insights from neuroimaging. *Curr Opin Neurobiol.* (2004) 14:769–76. doi: 10.1016/j.conb.2004.10.016
53. Wartolowska K, Hough MG, Jenkinson M, Andersson J, Wordsworth BP, Tracey I. Structural changes of the brain in rheumatoid arthritis. *Arthritis Rheum.* (2012) 64:371–9. doi: 10.1002/art.33326
54. Lucarelli RT, Peshock RM, McColl R, Hulsey K, Ayers C, Whittemore AR, et al. MR imaging of hippocampal asymmetry at 3T in a multiethnic, population-based sample: results from the Dallas Heart Study. *Am J Neuroradiol.* (2013) 34:752–7. doi: 10.3174/ajnr.A3308
55. Guadalupe T, Zwiers MP, Teumer A, Wittfeld K, Vasquez AA, Hoogman M, et al. Measurement and genetics of human subcortical and hippocampal asymmetries in large datasets. *Hum Brain Mapp.* (2014) 35:3277–89. doi: 10.1002/hbm.22401
56. Mao CP, Bai ZL, Zhang XN, Zhang QJ, Zhang L. Abnormal subcortical brain morphology in patients with knee osteoarthritis: a cross-sectional study. *Front Aging Neurosci.* (2016) 8:3. doi: 10.3389/fnagi.2016.00003
57. Seixas D, Palace J, Tracey I. Chronic pain disrupts the reward circuitry in multiple sclerosis. *Eur J Neurosci.* (2016) 44:1928–34. doi: 10.1111/ejn.13272

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Wei, Shi, Tu, Zhou, Duan, Lee, Wang and Liu. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers | Frontiers in Neurology

TYPE Review
PUBLISHED 26 August 2022
DOI 10.3389/fneur.2022.856874

Check for updates

OPEN ACCESS

EDITED BY
Flavia Di Pietro,
Curtin University, Australia

REVIEWED BY
Edina Szabo,
Boston Children's Hospital and
Harvard Medical School, United States
Patrick Stroman,
Queen's University, Canada

*CORRESPONDENCE
Gil Sharvit
gil.sharvit@balgrist.ch

SPECIALTY SECTION
This article was submitted to
Applied Neuroimaging,
a section of the journal
Frontiers in Neurology

RECEIVED 17 January 2022
ACCEPTED 25 July 2022
PUBLISHED 26 August 2022

CITATION
Sharvit G and Schweinhardt P (2022)
The influence of social signals on the
self-experience of pain: A
neuroimaging review.
Front. Neurol. 13:856874.
doi: 10.3389/fneur.2022.856874

COPYRIGHT
© 2022 Sharvit and Schweinhardt. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

The influence of social signals on the self-experience of pain: A neuroimaging review

Gil Sharvit[1,2]* and Petra Schweinhardt[1,2]

[1]Department of Chiropractic Medicine, Integrative Spinal Research, Balgrist University Hospital, University of Zurich (UZH), Zurich, Switzerland, [2]Neuroscience Center Zurich (ZNZ), University of Zurich (UZH), Zurich, Switzerland

Researchers in cognitive neuroscience have investigated extensively how psychological factors shape the processing and perception of pain using behavioral, physiological, and neuroimaging methods. However, social influences of pain, an essential part of biopsychosocial pain models, have received relatively little attention. This is particularly true for the neurobiological mechanisms underlying social modulations on pain. Therefore, this review discusses the findings of recent neuroimaging studies measuring the effects of social manipulations on pain perception (e.g., verbal and non-verbal social signals, social interaction style, conformity, social support, and sociocultural mediators). Finally, a schematic summary of the different social modulatory themes is presented.

KEYWORDS

pain, social, neuroimaging, social effects, pain modulation

Introduction

In 2020, the International Association for the Study of Pain (IASP) revised the original definition of pain from 1979 (1), which now reads: "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage". Notably, the updated definition includes the following integral note: "Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors". Thus, the IASP's new definition recognizes that pain can also be influenced by social factors, which was not contained in the original definition. This recognition stems from accumulating evidence for biopsychosocial models of pain, which illustrate that different social contexts can influence an individual's experience of pain.

Over the centuries, different pain models have emerged to conceptualize the root causes of pain to offer better treatment for those who suffer. One of the significant milestones in this progress was made by Engel (2), who proposed a new conceptualization of illness that was different from existing biomedical frameworks, which viewed illness and its symptoms, such as pain, as an integration of social, psychological, and behavioral influences. Since Engle's initial model, other biopsychosocial models, variants of the initial model, have been theorized in the pain field (3–6).

With the advancements in noninvasive experimentation and measurement techniques in humans (e.g., neuroimaging), substantial knowledge on how pain is experienced, processed in the brain, and modulated by different biological and psychological or cognitive factors has been accumulated [see Schweinhardt and Bushnell (7), Villemure and Bushnell (8), and Tracey and Mantyh (9) for detailed reviews]. Cognitive factors include attention (8), cognitive appraisals (10), and expectations (11).

In contrast to the research on psychological and biological influences on pain, modulation by social factors receive less attention. This conclusion is based on three primary assessments: first, the original IASP definition of pain did not include any aspect of potential social influence on pain. This recognition only came with the new, revised IASP definition within its notes (1). Second, a simple search in PubMed using the word combinations of "pain" with "psychological factor," "biological factor," or "social factor" reveals 84,134 hits, 56,953 hits, and 13,016 hits, respectively. Furthermore, looking at the first date of published studies, the first combination starts in 1912, whereas the combination of "pain" with "social" shows the studies starting only from 1964. Third, the first conceptualization of biopsychosocial models of pain was only published in 1977 by Engel (2). Consequentially, there are also fewer review articles on pain modulation that include social factors, even though a biopsychosocial conceptualization of pain is today's gold standard (5, 6, 12).

At the time of this review, the most recent review examining the influence of a range of social factors on pain was published by Krahé et al. (13) and included only three neuroimaging studies. More recent neuroimaging-focused reviews on social pain exist; however, they either focus on one specific social factor (14–16) or are not solely focused on pain modulation (17).

Therefore, there is a need to close the gap in the neuroimaging literature on pain modulations by social factors. This review provides an updated view on the topic by including studies up to March 2021. In addition, an essential aim of this review is to synthesize the findings of the individual studies across different social factors regarding the brain structures involved in the social modulation of pain. First, it is predicted that social manipulations modulate pain processing in pain-related brain areas (e.g., insular cortex, cingulate cortex) (9, 18, 19). Second, it is hypothesized that brain regions mediating such modulations are consistently recruited across several social themes. In particular, the prefrontal cortex is expected to mediate social context effects on pain because it has been previously shown that the prefrontal regions (e.g., the dorsolateral prefrontal cortex [DLPFC]) modulate pain expectancy effects on subjective ratings (11, 20, 21).

In this review, at first, a search using combinations of general keywords ("social," "neuroimaging," and "pain") was applied to extract a large number of studies. Then, more specific keywords were used in later search iterations. These specific keywords were based on previous reviews of social modulations on pain—both behavioral and neuroimaging (13–16). Accordingly, relevant keywords that were mentioned/investigated previously with this topic, such as "attachment"/"social attachment" (22–24), were included.

After applying both general and specific search queries across all databases, the data were filtered for relevance, inclusion, and exclusion criteria (as specified in the Methods section), and duplicates were removed from the total of all the search iterations (as summarized in Figure 1, and fully detailed in the Supplementary material section).

Next, the remaining studies were clustered into logical thematic classifications. The naming of the clusters was chosen based on either a known classification used in the literature (e.g., "Social Support," "Group Membership," and "Social Feedback") or by choosing a name based on social manipulation features that were common across the different manipulations (e.g., "Egocentric Interpersonal Perceptions," and "Helping others"). After presenting the results, an overall synthesis of the findings within and across all the resulting themes is provided in the Discussion.

Methods

Search strategy

On March 15, 2021, a search of the online databases PubMed, Google Scholar, and Scopus was conducted using different combinations of some (but not all) of the following keywords with "pain": "interpersonal," "attachment," "social context," "social interaction," "social support," "social presence," "social modulation," "social media," "social manipulation," "social intervention," "social behavior," "peer support," "social signals," "social cues," "social communication" and "communication". These topical combinations were searched in conjunction with words describing neuroimaging approaches such as "neuroimaging," "imaging," "fMRI," "functional magnetic resonance imaging," "PET," "positron emission tomography," "EEG," "electroencephalogram," "EP," "evoked potentials," "MEG," and "magnetoencephalography".

For full details on the different searches conducted (consisting of all the keywords used in each database and search iteration), please see the Supplementary methods section.

The primary search included these combinations using the title and abstract of the publications. Next, the search was repeated using keywords integrated within each database, such as the medical subject headings (MeSH) terms in PubMed and index terms (controlled vocabulary terms assigned to the document) in Scopus.

In addition, reference lists of relevant articles were searched. No restrictions regarding the publication date were applied.

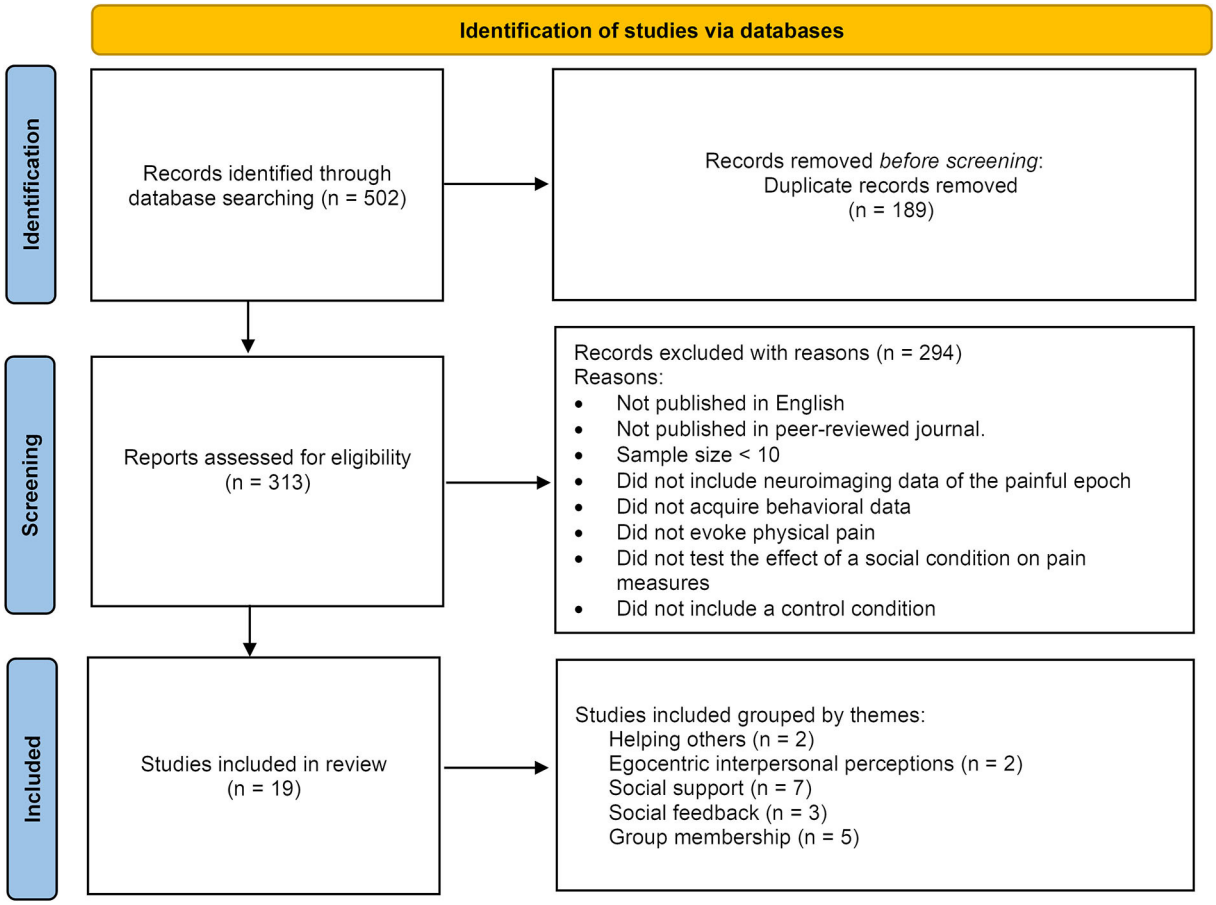


FIGURE 1
Summary of the study selection pipeline.

Study selection—inclusion/exclusion criteria

PubMed, Google Scholar, and Scopus were used for the search in a step-by-step approach (removing duplicates, applying exclusion criteria, and manually reviewing and rechecking the final extract), as seen in Figure 1.

The core aim of this review is to present and discuss the main findings of studies investigating how social signals can alter the processing and the perception of pain. For this purpose, three guiding rules were set in advance regarding the definition of social manipulation, the pain induction method, and the pain delivery target. A social manipulation was considered as one in which the main test/condition includes interaction between a participant and others—either in real time (e.g., having another person present with the participant) or in offline mode (e.g., observing evaluations of other people). In comparison, psychological manipulation does not include any form of social interaction (e.g., anxiety induction, fear conditioning, stimulus expectancy, learning task, etc.). Purposefully, only studies in which pain was administered to the individual by physical means (e.g., thermal pain, electrical pain, pressure pain) and not by non-physical means (e.g., inferred/believed pain) were included. The rationale here was to focus on studies that investigate modulations occurring on a type of pain in which the biological mechanisms of the induced pain i) are mostly known, ii) easily replicated and controlled, and iii) allows for better dissociation of any external modulations (e.g., social manipulations) on one type of pain, and iv) avoid mixing different types of pain in a single review.

This yielded two thematic concepts that were left out from this review: studies focusing on empathy for pain ("others' pain") without examining how empathy affects individuals experiencing pain and those using social inclusion/exclusion tasks to induce "social pain"—a concept which is still debated regarding the degree of shared features with physical pain (25–28). Please note that studies on empathy for pain were included in this review only when empathy for pain was used as a social manipulation of which the effect on individuals' perception or processing of physical pain stimuli was tested. Similarly, studies

using social inclusion/exclusion tasks were included if they tested the effect of the social inclusion/exclusion perception or processing of physical pain stimuli.

Following the thematic restrictions, the following inclusion/exclusion criteria were applied to the search results:

Inclusion criteria

The inclusion studies were neuroimaging studies that

1. Delivered experimental painful stimuli to healthy participants or clinical pain patients by using, e.g., thermal stimuli (e.g., by a thermode, laser, or a cold-water bath), electrical stimuli, or mechanical stimuli (e.g., by an inflatable cuff).
2. Reported behavioral and/or physiological data.
3. Reported the main effect of a social manipulation on neural activation in response to painful stimuli (i.e., not only reporting effects of external modulators (e.g., questionnaires data) on neural activation).
4. Published in English in a peer-reviewed scientific journal.
5. Conducted controlled experiments on human participants older than 18 years old.

Exclusion criteria

The exculsion criteria were as follows:

1. Clinical painful procedures (e.g., wisdom teeth extraction);
2. Neuroimaging studies that tested a very small sample (< 10 participants);
3. Neuroimaging studies on empathy for pain ("others' pain"); and
4. Those using social inclusion/exclusion tasks to induce "social pain"—unless the effects of the observation of "others' pain" or social inclusion/exclusion tasks were used as a manipulation to test for effects on pain perception during pain delivery.

Validation of coordinates

All the studies included in this review reported the fMRI coordinates in the Montreal Neurological Institute (MNI) space. To ensure that the studies assigned the reported activation clusters to the correct brain region, the studies' peak-voxel coordinates were cross-checked for each cluster by entering the reported coordinates into the Automated Anatomic Labeling (aal3v1) brain atlas, accessed by the WFU PickAtlas SPM toolbox (http://fmri.wfubmc.edu/software/pickatlas). In addition, the reported coordinates were double-checked with Neurosynth (http://neurosynth.org) (24) and NeuroQuery (https://neuroquery.org/) (25), which are automated meta-analytic tools that produce fMRI brain maps. NeuroQuery focuses on producing a brain map that predicts where in the brain a study on the topic of interest is likely to report observations, while Neurosynth tests the consistency of observations reported in the literature. An MNI coordinate was classified as a true positive if is located within the labeled regions by the aa3v1 brain atlas and lying within the Neurosynth or NeuroQuery meta-analytic brain region.

Results

Search results

A total of 502 studies were retrieved initially, and after the study selection step (applying inclusion/exclusion criteria described in the Methods section above) and duplicates removal (see Supplementary methods), the search results yielded a final selection of 19 studies for this review (Table 1). Based on the manipulation used, these studies were grouped into five thematic subjects: helping others, egocentric interpersonal perceptions, social support, social feedback, and group membership. In the following sections, the results of these studies are presented and discussed in the context of these thematic groups.

Table 1 summarizes the 19 studies that were retained after the selection process. For readability, each study's core findings and the main conclusion for each thematic group were summarized.

In consideration of a potential limitation of the search results, please note that, in the search strategy (see "Search strategy" section, *Methods*), the term "fNIRS" was not included as a keyword. It is possible that studies that were tagged in the databases with the specific keyword "fNIRS" without being also tagged with any "neuroimaging" or neuroimaging-related keyword, topical word, or MeSH term might have been missed. However, using the general keywords, many identified studies were conducted with fMRI, few with EEG, fewer with EEG-TMS, and none with PET or another neuroimaging method (see Table 1). It seems, therefore, unlikely that a sizeable number of fNIRS studies was missed, although this possibility cannot be excluded.

Social signals' themes and their influence on self-pain

Helping others

Studies in this thematic group focus on situations in which an individual can help others in a certain way, before or during, the experience of a painful event. The motivation behind these studies is to explore whether the subjective experience of pain can be altered when one decides to give support to another person. Two fMRI studies showed that helping others reduces stimulus intensity rating and attenuates activation in response to

TABLE 1 Summary of results.

Theme	Topic	Ref.	Group(s)	Main conditions	Main contrasts	Behavioral results	Neuroimaging results*	Modulations/Mediations
Helping others	***Altruistic behavior***	Wang et al. (29)	32 HC (14M|18F)	*Altruistic decision* Donate/do not donate money to an orphan	Altruistic vs. Control (matching visual task)	↓pain ratings	↓ pain-related areas (bil INS, ACC, SI), r caudate, MFG, IPL ↑ FC: VMPFC—dACC ↑ FC: VMPFC (donation phase)—r AI	↑ perceived helpfulness ∞ ↓ dACC, ↓ bil INS Number of altruistic (vs. control) decisions ∞ ↑ VMPFC (at donation phase) ↑ VMPFC (at donation phase) ∞ ↑ perceived helpfulness, ↓ dACC, ↓ bil INS
	Prosocial meaning	López-Solà et al. (30)	29 HC(29F) + Partners (> 3 months)	*Prosocial decision* accept % of partner's pain stimuli (25%-75%) *Baseline* (without prosocial decision)	Accept-Partner-Pain vs. Control (pain without a decision)	↑positive thoughts ↓pain unpleasantness ↔ pain intensity	↓ l AI, r OFC ↑ VMPFC, r thalamus ↔ NPS	↑ partner pain acceptance ∞ ↓ pain ratings, ↑ positive thoughts, ↑VMPFC ↑ positive thoughts ∞ ↓ NPS ↓ (MCC, bil AI, SI, r LPFC, OFC) ∞ ↓ pain ratings, ↓ NPS ↑ VMPFC, ↓ r OFC ∞ ↓pain-related areas (bil AI, MCC, SI)
Egocentric interpersonal perceptions	***Observing others***	Valeriani et al. (31)	12 HC (7M|5F)	*Video watching* Static Hand/Needle in Hand/Q-tip on Hand/Needle in Foot/Needle in Tomato	Across all conditions	↔ pain ratings		N.A.
					Needle in Hand vs. All other conditions	↑self/other-referred pain ratings	↓ N1, P1 LEPs ↔ N2, P2 LEPs	↑ difference in self-other referred pain ratings ∞ ↓ N1/P1 LEPs ↑ stimulus pain ratings ∞ ↑ self-referred pain ratings

(Continued)

10.3389/fneur.2022.856874

TABLE 1 (Continued)

Theme	Topic	Ref.	Group(s)	Main conditions	Main contrasts	Behavioral results	Neuroimaging results*	Modulations/Mediations
					Needle in Hand/Foot vs. all other conditions	↑self/other referred pain ratings Rating: Other-referred pain > Stimulus pain > Self-referred pain		N.A.
	Patient-clinician interaction	Ellingsen et al. (32)	17 FM Patients (17F) 17 Clinicians (5M|12F)	*Social interaction* (clinical interview, pre-task): Interaction/No interaction *Sham treatment* (pre-task, unobservable) *Clinician treatment decision(observable)* Electroacupuncture (EA) Treatment/No treatment	Social interaction vs. No interaction	↔pain ratings		N.A.
					EA vs. Sham EA	↔pain ratings		

(Continued)

10.3389/fneur.2022.856874

TABLE 1 (Continued)

Theme	Topic	Ref.	Group(s)	Main conditions	Main contrasts	Behavioral results	Neuroimaging results*	Modulations/Mediations
					Treat vs. No Treat observed decision	↓pain ratings ↓ clinicians' vicarious pain ratings ↑ patient/clinician positive feeling	↑ VLPFC, TPJ, DLPFC, MPFC, Precuneus, IPL	↓ pain ratings ∞ ↓ clinicians' vicarious pain ratings, ↑ relationship quality ratings (during scanning session), ↑ clinicians' accuracy in treatment efficacy estimation ↑ patient-clinician facial mirroring (at anticipation) ∞ ↓ pain ratings, ↑ therapeutic alliance ratings (during the pre-scan social interaction) ↑ treatment analgesia ∞ ↑ r VLPFC, Precuneus, IPL, SMG
Social support	***Social viewing***	Younger et al. (33)	15 HC (7M|8F) + Partners (< 9 months)	*Viewing task* Partner's picture/Baseline (acquaintance's picture) *Distraction task*	Partner viewing/Distraction vs. Baseline	↓pain ratings	N.A.	↓ pain ratings ∞ ↑ r OFC
					Partner viewing vs. Distraction/Baseline	↓pain ratings	↓ bil PI, l thalamus, r DLPFC, r SI ↑ ACC, MCC, bil OFC, l Amyg, Precuneus	↓ pain ratings ∞ ↑ r thalamus, bil caudate, bil Nac, r DLPFC, bil OFC, l Amyg, r STG ↓ pain ratings ∞ ↓ l AI, ACC, l SFG, r brainstem, l hippocampus
					Partner viewing vs. Distraction	↔pain ratings		N.A.
		Eisenberger et al. (34)	21 HC (21F) + Partners (9 months to 13 years)	*Viewing task* Partner's picture/Stranger's picture/Object's picture	Stranger vs. Object viewing	↔ pain ratings		N.A.

(Continued)

10.3389/fneur.2022.856874

TABLE 1 (Continued)

Theme	Topic	Ref.	Group(s)	Main conditions	Main contrasts	Behavioral results	Neuroimaging results*	Modulations/Mediations
					Partner vs. Stranger/Object viewing	↓ pain ratings	↓ pain-related areas (dACC, bilateral AI) ↑ VMPFC, SMA	↑ VMPFC ∞ ↓ dACC, ↑ relationship-length, ↑ perceived support ↓ pain ratings ∞ ↑ VMPFC, ↓ dACC
					Stranger vs. Partner viewing	↑ pain ratings	↑ l caudate	N.A.
		Che et al. (35)	20 HC (8M|12F) + Partners (identified as being in a romantic relationship)	*Viewing task* Partner's picture/Stranger's picture *TMS on DMPFC* Pre iTBS/Post iTBS/Sham.	Partner vs. Stranger viewing (Pre l DMPFC- iTBS)	↓pain ratings ↑ perceived support		N.A.
					Partner vs. Stranger viewing (Post vs. Pre l DMPFC-iTBS)	↓pain ratings		
					Partner viewing (Post vs. Pre l DMPFC-iTBS)	↔ pain ratings ↓ perceived support	↑fronto-central gamma activity ↑fronto-occipital alpha connectivity	↑ gamma activity ∞ ↑ N100 amplitude
					Stranger viewing (Post vs. Pre l DMPFC-iTBS)	↑ pain ratings ↔ perceived support	↑central-parietal gamma activity ↑central-frontal & central-parietal theta connectivity	N.A.
	Social touch	von Mohr et al. (36)	29 HC (29F) + Partners (>1 year)	*Receiving a tactile touch from the partner** Affective (slow) touch / Neutral (fast) touch *locations differ from noxious stimuli	Affective (slow) vs. Neutral (fast) touch	↓pain ratings ↑ comfort, pleasantness	↓ N1, N2, P2 LEPs	↑ attachment anxiety score ∞ ↓ diff in pain ratings between slow & fast touch

(Continued)

10.3389/fneur.2022.856874

TABLE 1 (Continued)

Theme	Topic	Ref.	Group(s)	Main conditions	Main contrasts	Behavioral results	Neuroimaging results*	Modulations/Mediations
		Kreuder et al. (37)	46 HC (30M|16F) + Partners (> 5 months)	*Social Support* Handholding with Partner/Handholding with Stranger / No handholding	Across all conditions	Pain ratings: Partner < Stranger < No support	N.A.	N.A.
					Partner/Stranger support vs. No support	↓pain ratings	↓l AI	
					Partner vs. Stranger/No support	↓pain ratings	↑r MFG ↓FC: r MFG—r AI, r MFG—l Amyg	
					Partner vs. Stranger support (females only)	↓pain ratings	↑r VMPFC	
					Partner vs. No support (females only)	↓pain ratings	↑l thalamus, l caudate	
					Stranger support vs. No support (females only)	↓pain ratings	↑r VMPFC, l OFC	
		López-Solà et al. (38)	30 HC (30F) + Partners (> 3 months)	*Social Support* Handholding with partner/Baseline (Holding rubber)	Partner support vs. Object (rubber squeeze ball)	↓pain ratings ↑emotional comfort	↓ pain-related areas (ACC, l AI, PAG, S1, l thalamus), frontal areas (bil DLPFC, bil OFC, bil MPFC), l Amyg ↓ NPS ↑FC: NPS with DMN, NAc, MTG, SI	↓ prefrontal brain areas (DLPFC, VLPFC, DMPFC, VMPFC, OFC), Amyg, ACC, PAG ∞ ↓ pain ratings ↑ emotional comfort ∞ ↓ pain ratings, ↑ perceived relationship quality ↓ NPS didn't correlate with ↓ pain ratings ↑ FC between NPS-SI ∞ ↓ pain ratings

(Continued)

10.3389/fneur.2022.856874

TABLE 1 (Continued)

Theme	Topic	Ref.	Group(s)	Main conditions	Main contrasts	Behavioral results	Neuroimaging results*	Modulations/Mediations
	Social presence	Krahé et al. (39)	31 HC (31F) + Partners (> 1 year)	*Partner presence*/Absence *Partner focus* Participant/Stranger	Partner presence vs. Absence	↔ pain ratings	↑ P2 LEP	↑ attachment avoidance ∞ ↑ pain ratings, ↑ N2 and P2 LEPs ↑ attachment anxiety ∞ ↓ latency of N1 and N2 LEPs ↑ attachment avoidance ∞ ↑ local peak amplitude of N2 LEP
Social feedback	***Social conformity***	Yoshida et al. (40)	17 HC (8M|9F)	*Cue observation from others (stimulus-related)* Mean score—below or above the participant / Variance (uncertainty) – small/large	Observed mean across all conditions	↓↑ pain ratings followed observed mean	↓↑ followed the observed mean: ACC, bil AI, bil DLPFC	↑ r bil AI, ACC, bil DLPFC ∞ ↑ pain ratings ↑uncertainty-induced hyperalgesia ∞ ↑PAG ↑uncertainty sensitivity ∞ ↑uncertainty-induced analgesia
					High variance vs. Low variance	↑ regardless of the observed mean	↑ PAG	
		Koban et al. (41)	36 HC (16M|20F)	*Cue observation from others (stimulus-related)* Conditioned—learned cues of low or high intensity / Social—others' ratings higher or lower than the participant	Social/Conditioned cues high vs. low	↑pain ratings	↔ NPS ↔ SIIPS	N.A.
					Social vs. Conditioned cues (high vs. low)	↑pain ratings ↑SCR	N.A.	SCR was only modulated by Social information (and not by Conditioned cues)

(Continued)

10.3389/fneur.2022.856874

TABLE 1 (Continued)

Theme	Topic	Ref.	Group(s)	Main conditions	Main contrasts	Behavioral results	Neuroimaging results*	Modulations/Mediations
					Social cues high vs. low	↑pain ratings	↑ pain-related areas (ACC, bil AI, thalamus), bil DLPFC, l Amyg, IPS	Mediators of social information on pain (social high>low): ↑bil VLPFC, DMPFC, bil DLPFC, l IPS, visual cortex ↑ frontoparietal & dorsal attention networks, associated with cognitive control
	Empathetic feedback	Fauchon et al. (42)	30 HC (16M|14F)	*Listening to auditory comments about participants' pain attitude* Empathetic/Neutral/Unempathetic comments	Empathetic vs. Neutral	↓pain ratings	↑ r AI, r PPC, r DLPFC ↓ l MFG ↑FC: VMPFC-AI, VMPFC-PI, PI-AI ↓FC: VMPFC-PCC	N.A.
					Empathetic vs. Unempathetic	↓pain ratings	↑ PCC, Precuneus ↑FC: VMPFC-AI ↓FC: VMPFC-PCC	
					Unempathetic vs. Neutral	↔pain ratings	↑r AI ↓ VMPFC, PCC, Precuneus ↑FC: PI-AI	
Group membership	***Social exclusion***	Bungert et al. (43)	20 BPD patients (20F) 20 HC (20F)	*Cyberball task* with Exclusion/Inclusion / Control (instructed motor response)	HC/ BPD: Exclusion vs. Inclusion/CTRL	↑pain ratings	↑ l AI, r thalamus, r Amyg	HC_Exclusion: ↑ r Amyg ∞ ↑ pain ratings
					BPD (vs. HC) in Exclusion	N.A.	↑ r PI	N.A.
		Bach et al. (44)	17 OMT patients (16M|1F) 21 HC (19M|2F)	*Cyberball task with* Exclusion/Inclusion/Control (instructed motor response)	HC/OMT Exclusion vs. Inclusion/Control	↑pain ratings ↑exclusion rating	N.A.	No effect of partnership status on exclusion or inclusion conditions. HC/OMT_Exclusion: ↑ bil Amyg, AI ∞ ↑ pain ratings

(Continued)

10.3389/fneur.2022.856874

TABLE 1 (Continued)

Theme	Topic	Ref.	Group(s)	Main conditions	Main contrasts	Behavioral results	Neuroimaging results*	Modulations/Mediations
					HC Exclusion vs. Control	↑pain ratings ↑exclusion rating	↑ pain-related brain areas (ACC, MCC, bil AI, bil thalamus), bil caudate, bil MFG, bil VMPFC, PCC, Precuneus	
					HC Inclusion vs. Control	↓pain ratings ↑inclusion rating	↑ MCC, PCC, Precuneus	
					HC Exclusion vs. Inclusion	↑pain ratings ↑exclusion rating	↑ ACC, l OFC, bil caudate, bil MFG, bil MTG	
					OMT vs. HC Inclusion	↔pain ratings ↑ exclusion ↓ inclusion	N.A.	
		Landa et al. (45)	20 HC (10M|10F)	*Cyberball task* with Acceptance/Rejection/Re-Acceptance	Rejection vs. Acceptance	↑pain ratings ↑rejection-related feelings	↑ pain-related brain areas (bil AI, r thalamus), pons ↓ MCC, bil MTG, l IPL,	Rejection: ↑ exclusion feeling ∞ ↑ r AI Acceptance: ↑ exclusion feeling ∞ ↑ pain ratings, ↑ l AI Re-Acceptance/ Acceptance: ↑ perceived rejection ∞ ↑ pain ratings
					Re-Acceptance vs. Acceptance	↔pain ratings ↑rejection-related feelings	↑ bil AI, r thalamus, pons ↓ pain-related brain areas (ACC, bil PI, r SI) r Amyg, bil MFG, Precuneus	N.A.

(Continued)

10.3389/fneur.2022.856874

TABLE 1 (Continued)

Theme	Topic	Ref.	Group(s)	Main conditions	Main contrasts	Behavioral results	Neuroimaging results*	Modulations/Mediations
	Stereotypes	Schwarz et al. (46)	34 HC (34M)	*Stereotype priming* Men are less sensitive to pain (MLPS) / Women are less sensitive to pain (WLPS) / No priming (CTRL)	Across all conditions	Pain ratings: MLPS < CTRL < FLPS		N.A.
					MLPS/FLPS vs. CTRL	↔pain ratings		N.A.
					FLPS vs. MLPS	↑pain ratings	↑ ACC, r PI, bil thalamus, bil NAc,	N.A.
					MLPS vs. FLPS	↓pain ratings	N.A.	MLPS: ↓ l NAc ∞ ↓ pain ratings
	In/Out group	Hein et al. (47)	36 HC (36M)	*Receiving pain relief (treatment)* from Ingroup member (Swiss)/Outgroup member(Balkan ethnicity)	Outgroup member: Post vs. Pre treatment	↓pain ratings	↓bil AI, l SI	↑ learning signal in r AI ∞ ↓ impression ratings, ↓ pain ratings r AI mediates social impression effect on pain ratings.
					Ingroup member: Post vs. Pre treatment	↔pain ratings	↔ bil AI	N.A.
					Outgroup vs. Ingroup	↓pain ratings ↓impression rating (of treatment provider)		N.A.

*Please note, the neuroimaging results reported in the table are the ones during the application period of painful stimuli—unless otherwise noted.
Ref., Reference; ∞, Correlate; ↑, Increase; ↓, Decrease; bil, bilateral; r, right; l, left; d, dorsal; M, Male; F, Female, N.A, Not applicable, result or analysis was not provided; FC, Functional connectivity, HC, Healthy controls.
Anterior cingulate cortex (ACC), Anterior insula (AI), Amygdala (Amyg), Borderline personality disorder (BPD), Control (CTRL), Dorsolateral prefrontal cortex (DLPFC), Default mode network (DMN), Dorsomedial prefrontal cortex (DMPFC), Insular cortex (INS), Inferior parietal lobe (IPL), Intermittent theta burst stimulation (iTBS), Laser evoked potentials (LEPs), Lateral prefrontal cortex (LPFC), Mid cingulate cortex (MCC), Middle frontal gyrus (MFG), Mid insula (MI), Medial prefrontal cortex (MPFC), Middle temporal gyrus (MTG), Nucleus accumbens (NAc), Neurologic Pain Signature (NPS), Orbitofrontal cortex (OFC), Opioid maintenance treatment (OMT), Periaqueductal gray (PAG), Posterior cingulate cortex (PCC), Posterior insula (PI), Posterior parietal cortex (PPC), Skin conductance response (SCR), Superior frontal gyrus (SFG), Primary somatosensory cortex (SI), Stimulus intensity independent pain signature (SIIPS), Supramarginal gyrus (SMG), Superior temporal gyrus (STG), Temporoparietal junction (TPJ), Ventrolateral prefrontal cortex (VLPFC), Ventromedial prefrontal cortex (VMPFC).

10.3389/fneur.2022.856874

painful stimuli in pain-related brain areas—either by donating to a stranger (29) or by taking the suffering from a close one (30).

In the first study, Wang et al. (29) found that when participants faced altruistic decisions and chose to donate part of their initial allowance to an orphan, they perceived subsequent electric shocks to be less painful (vs. a control condition with a matched visual decision task). It should be noted that 94% of the participants chose to donate in the donation trials; therefore, comparing the conditions could be regarded as exerting altruistic behavior vs. not (Control condition). At the neural level, the altruistic (vs. Control) condition led to reductions in response to painful stimuli in pain-related brain areas (dACC, bilateral insula [posterior insula (PI), middle insula (MI), anterior insula (AI)], right thalamus, primary somatosensory cortex [SI]), and in the right caudate, the left middle frontal gyrus (MFG), and the right inferior parietal lobe (IPL). The more the participants considered their donations helpful (measured by perceived helpfulness rating post-experiment), the more the attenuation of neural activation in the dACC and the bilateral insula was observed. Attenuating neural activation in the dorsal anterior cingulate (dACC) and the bilateral insula also correlated with increased neural activation in the ventromedial prefrontal cortex (VMPFC) at the donation phase.

Similarly, López-Solà et al. (30) reported a reduction in pain ratings (unpleasantness, but not intensity ratings) when participants chose to receive painful stimulations that were intended for their romantic partner (Accept-Partner-Pain vs. Baseline). In addition, trials in the Accept-Partner-Pain condition resulted in increased engagement in positive thoughts (vs. Baseline). Neural activation in the Accept-Partner-Pain (vs. Baseline) condition decreased in the left AI and the right orbitofrontal cortex (OFC) but increased in the right thalamus and the VMPFC. Although the Accept-Partner-Pain condition did not modulate the Neurological Pain Signature (NPS) (48), engagement in positive thoughts was positively correlated with NPS reduction. An increase in partner pain acceptance (i.e., the percentage of trials in which participants chose to accept the partner's pain) correlated with decreases in pain ratings, increased neural activation in the VMPFC, and increased engagement in positive thoughts. A whole-brain mediation analysis was used to interrogate brain areas mediating the effect of accepting the partner's pain on pain ratings. The analysis showed that neural activation reduction in the midcingulate cortex (MCC), bilateral AI, SI, the right lateral prefrontal cortex (LPFC), and OFC predicts the reduction in pain ratings and the NPS. Finally, reductions in the neural activation of pain-related areas (bilateral AI, MCC, SI) were mediated by an increase in neural activation in the VMPFC and a decrease in the right OFC.

Egocentric interpersonal perceptions

This theme focuses on experiments exploring how specific interpersonal actions such as observation (31) and evaluation of others' feeling states (32) can directly influence individuals' pain experiences. The first study (48) measured pain using laser-evoked potentials (LEPs).

The functional roles of pain evoked potentials have been widely explored in neurophysiological studies delineating four main components (N1, P1, N2, and P2), of which the amplitudes and latencies are modulated by different experimental manipulations [see Chen et al. (49) for a detailed overview]. Specifically, the early components N1-P1 (∼100 ms latency) have been shown to reflect activations from the operculo-insular cortex and SI and therefore are interpreted to be associated with the sensory processing of pain (50). Later components such as N2-P2 and P3 seem to originate from brain areas, such as the AI and ACC, and are thus thought to reflect affective pain processing (51). However, it has been posited that none of the LEPs are specific to pain but reflect a more general, salience-related processing of the noxious stimulus (52).

Using laser-evoked potentials (LEPs), Valeriani et al. (31) investigated how being in pain can be affected by observing others in pain. In their study, while receiving a painful stimulus on the hand, participants watched several videos differing in contexts regarding the nociceptive potential of a stimulus (Needle/Q-tip/None) applied to a specific model target (a person's hand, a person's foot, a tomato). Participants were asked to rate their pain from the stimulus, the movie (self-referred pain), and the model (other-referred pain). The study found that none of the observation contexts modulated participants' stimulus pain ratings. As for the referred pain ratings, however, observing a needle penetrating another's hand or foot (vs. all other conditions) resulted in increased self- and other-referred pain ratings. Also, participants rated the stimulus pain higher than the self-referred pain but lower than the other-referred pain. At the neural level, modulations were observed only with the Needle in Hand condition (vs. all other conditions). Specifically, the amplitudes of the N1 and P1 LEP components [associated with sensory processing of pain (50)] were decreased, and there was no effect on the N2/P2 LEP components [associated with affective processing of pain (51)]. Furthermore, an increase in the difference between self and other referred pain ratings correlated with a decrease in the N1/P1 LEP components. That is, the more participants rated the pain induced by the movie higher in themselves than in the model, the greater the reduction in the amplitude of the N1/P1 LEPs. Lastly, although there was no direct effect of the observation context on stimulus pain ratings, an indirect effect was found: a *post-hoc* analysis revealed a positive correlation between self-referred pain ratings and the stimulus pain ratings.

In 2020, Ellingsen et al. (32) published an fMRI-hyperscanning experiment investigating pain-related social effects of a clinician-patient interaction. In the study, chronic pain patients (diagnosed with fibromyalgia) were connected to an electroacupuncture (EA) device while in a scanner. Pairs of patients and clinicians could see the face of each other during the experiment *via* MRI-compatible cameras that were attached to a table-mounted mirror on each MRI scanner and manually adjusted to capture the entire face.

During the task, participants received painful stimuli (pressure evoked pain) after an anticipatory period with cues predictive of the clinician's decision whether to execute (or not) the EA treatment during the pain delivery to the participant. Two manipulations were tested for their influence on participants' pain experience: execution of the EA treatment (vs. no EA treatment) and patient-clinician interaction (vs. no interaction). The interaction condition was in the form of a brief clinical intake interview with the clinician (done on a separate day before the scanning), which ended with the requirement for both to rate their perceived relationship with each other during the intake (therapeutic alliance ratings). In addition, the two EA conditions were compared against a Sham condition. During the task, pain ratings (by participants) and vicarious pain ratings (clinicians' estimated rating of participants' pain) were collected, as well as the perceived relationship of a patient/clinician with each other during the scanning session (relationship quality ratings). Comparison between the EA (vs. sham) treatment on pain ratings revealed no significant effect, and therefore, both trial types were grouped together as treatment conditions in subsequent analyses. The treatment (vs. no treatment) condition reduced participants' pain ratings and clinicians' vicarious pain ratings and increased patients' and clinicians' positive feeling ratings. Moreover, the decrease in participants' pain ratings correlated with a decrease in clinicians' vicarious pain ratings but an increase in clinicians' accuracy in treatment-efficacy estimation (i.e., the degree of correlation between patient's vicarious pain rating with participants' pain rating before/after treatment) and in relationship quality scores. Further, stronger treatment-related analgesia was reported by participants with higher therapeutic alliance ratings. Interestingly, during the anticipation period of participants, increased facial mirroring between participants and clinicians positively correlated with an increase in treatment-related analgesia (decrease in pain ratings) and therapeutic alliance scores. The more the participants and their clinicians mimicked each other's facial expressions during the anticipatory phase, the better the participants perceived their relationship with the clinicians and the stronger the feeling of analgesia they experienced. Participants' neuroimaging results showed increased neural activation in the prefrontal regions (ventrolateral prefrontal cortex [VLPFC], medial prefrontal cortex (MPFC), and bilateral DLPFC), the left superior temporal sulcus (STS), and the bilateral temporoparietal junction (TPJ) in the treatment (vs. no treatment) condition. Specifically, the reduction in pain ratings positively correlated with increased neural activation in the right VLPFC, precuneus, the IPL, and the supramarginal gyrus [SMG]. The study found no effect of the Patient-Clinician interaction (a brief interview) on the subjective pain ratings.

Social support

Within the research literature investigating social effects on pain, social support is the most explored theme. In this theme, the feeling of support in individuals undergoing painful experiences is often induced experimentally by asking the participants to view a photo of their romantic partner, feel their touch, or simply inform them about their presence. Hence, social support can be achieved by relatively passive (viewing, general presence) or active (affective touch) means. Seven studies were identified in the search, sub-grouped by the support induction method: social viewing, affective touch, and social presence.

Social viewing

Two fMRI studies (33, 34) and one brain stimulation study with EEG (35) explored how viewing the photo of a romantic partner while receiving a noxious stimulus can alter participants' pain perception (relative to viewing a photo of an acquaintance or engaging in a distracting task).

Younger et al. (33) found that viewing a partner's photo or engaging in a distraction task while being in pain reduced pain ratings (relative to viewing a photo of an acquaintance). Comparing the analgesic effect of the two conditions (partner viewing vs. distraction task) on behavioral ratings revealed no significant difference. Hence, both tasks reduced pain ratings with a similar magnitude. In contrast, examination of the neuroimaging data revealed differences in the recruitment and modulation of specific brain areas. Viewing the partner's photo during pain (vs. all other conditions) reduced neural activation in pain-related sensory areas (bilateral PI, thalamus, SI) and the right DLPFC. Moreover, partner-related analgesia (reduced pain ratings) also correlated with decreased neural activation in pain-related affective processing areas [left AI and anterior-dorsal part of the ACC (adACC)]. Increased neural activation during partner viewing (vs. all other conditions) was observed in the subgenual ACC (sgACC), MCC, bilateral OFC, left amygdala, and precuneus. Furthermore, partner-related analgesia correlated with increased neural activation in a cortical network that is associated with reward processing (e.g., bilateral nucleus accumbens [NAc], bilateral caudate, bilateral OFC, left amygdala) (53–56), as well as with the right DLPFC and the right thalamus. Similar analysis showed that distraction-related analgesia was correlated with increased activation in the pregenual ACC (pgACC), the bilateral OFC, the left DLPFC, and the left MFG. The only significant functional overlap was seen

in the right OFC, which positively correlated with partner and distraction related analgesia.

Using a similar paradigm, Eisenberger et al. (34) investigated how viewing a partner's photo can influence participants' experienced pain. Differently from Younger et al. (33), the control viewing conditions included either a photo of a stranger or an object, and the neuroimaging investigation focused on two structural regions of interest (ROIs) associated with physical pain—the dACC and bilateral AI, and functional ROIs discovered in the contrast partner's (vs. stranger/object) photo viewing—the VMPFC and the premotor cortex. Furthermore, the study also tested the modulation effects of two trait measures: perceived partner support and relationship duration. The behavioral results showed reductions in pain ratings in the partner (vs. stranger/object) condition. No difference in pain ratings was found between the stranger and object conditions, so they were collapsed into one Control condition. Viewing the partner's photo (vs. stranger/object conditions) was also accompanied by reduced neural activation in the two pain-related ROIs (dACC and bilateral AI) and increased activation in the VMPFC and premotor cortex. This increase in VMPFC activation was correlated with decreased neural activation in the dACC, as well as with higher ratings of perceived support and longer relationship duration. Finally, reductions in pain ratings correlated with increased neural activation in the VMPFC and decreased activation in the dACC.

The third study on this theme applied the same photo-viewing task described in the previous studies. However, it offered a causal (rather than correlational) examination of neural activation and network connectivity by applying a facilitatory intermittent Theta Burst Stimulation (iTBS) on the left dorsomedial prefrontal cortex (DMPFC). Specifically, gamma-band activity has been suggested to encode the subjective pain experience (57, 58). The effects of iTBS on behavioral ratings, neural activity, and network connectivity using EEG were examined. In this study, Che et al. (35) found that partner's (vs. stranger) photo viewing during pain delivery reduced pain ratings (before applying iTBS) and correlated with increased perceived support ratings. Applying the iTBS further increased the reduction in pain ratings in the partner (vs. stranger) condition. Within the partner condition, examination of the iTBS effect (partner condition: pre vs. post iTBS) resulted in no change in pain ratings but increased the fronto-central gamma activity, increased the connectivity between frontal and occipital regions, and decreased perceived support ratings. In comparison, iTBS in the stranger condition increased pain ratings, central-parietal gamma activity, and connectivity between central and frontoparietal regions but did not change the perceived support ratings. Finally, a source estimation analysis using TMS-EEG showed that the increased gamma activity was found to be correlated with increased pain-related N100 amplitude.

Social touch

Three studies (36–38) investigating the effects of social support on pain modulation used a more active approach to induce support in participants undergoing pain—a supportive, tactile touch (termed "social touch"). Two of these studies (37, 38) examined changes in pain perception when participants held hands (static touch, without movement) with their romantic partner, with a stranger, or held an object. The third study examined participants' pain when they held hands with their romantic partner in either a slow-affective or a fast-neutral manner (dynamic touch, with movement) (36).

Consistently with the effects reported by the studies using social viewing described above, social touch by a romantic partner (vs. control conditions) was found to increase emotional comfort (38) and decrease pain ratings (36–38), the NPS (38), and activity in brain areas (37, 38) and evoked potentials (36) associated with pain processing.

A particular insight into the mechanisms underlying social touch analgesia comes from the study of von Mohr et al. (36). This study examined what type of touch is effective in reducing pain. By changing the pace of the partner's touch, the results show that, even when coming from the partner, the supportive touch has to be slow (i.e., "affective") rather than fast (i.e., "neutral") in order to lead to reductions in pain ratings and related neural processing (decreased local peak amplitudes of N1, N2, and P2 LEPs). Moreover, the study also found a significant interaction between attachment anxiety and pain ratings, indicating that higher attachment anxiety scores lower the pain rating difference between slow and fast touch.

Interestingly, Kreuder et al. (37) found that social support received by holding the hand of either a romantic partner or a stranger reduced pain unpleasantness ratings (vs. no support). However, when comparing the two support conditions, being touched by a partner leads to stronger analgesia than being touched by a stranger. The neuroimaging results showed that both partner and stranger support (vs. no support) reduced the pain-related activation in the left AI. Contrasting these two conditions demonstrated increased neural activation in the right MFG in the partner (relative to the stranger) support condition. As Kreuder et al. tested both men and women, they examined gender-specific neural activation and found differences across the conditions that occurred only for female subjects: relative to no support, increases in neural activation were found in the left thalamus and the left caudate with partner support and in the VMPFC and the left amygdala with the stranger support. Comparing the two support conditions showed increased activation in the VMPFC with the partner (vs. stranger) support. These results suggest a gender-specific difference in the neural modulation of pain by social support.

Lastly, López-Solà et al. (38) found that holding the hand of a partner (vs. object holding) reduced pain ratings and decreased neural activation in pain-related brain areas (ACC, left AI,

left thalamus), the prefrontal areas (bilateral MPFC, bilateral DLPFC, bilateral OFC), the left amygdala, the periaqueductal gray (PAG), and the SI. Moreover, partner support also reduced NPS activation (but was not correlated with the reduction in pain rating). It increased connectivity between the NPS and the primary sensory cortex (SI), the default mode network (DMN) regions (MPFC, posterior cingulate cortex [PCC], precuneus), the NAc, and the middle temporal gyrus (MTG). A whole-brain multi-level mediation analysis revealed that the most potent mediators of the observed touch-induced analgesia were activation reductions in prefrontal brain areas (DLPFC, VLPFC, DMPFC, VMPFC), OFC, amygdala, ACC, and PAG. Finally, the results showed that increased emotional comfort ratings correlated with reductions in pain ratings (during the partner condition) and increases in perceived relationship quality scores.

Social presence

The last study on this theme showed how the mere presence of a person could affect the individual experience in a counterintuitive way. Krahé et al. (39) showed that informing participants experiencing pain about the presence of their loved one (in the same room) did not affect their ratings (relative to when the partner was absent) but increased the peak amplitude of pain-related LEP components (increased P2 local peak amplitude of the P2-N2 complex). The study also compared conditions in which participants were told about the partner's presence and their focus—the partner either focused on the participant being in pain or on the ratings of another participant. No difference was found between these two focus conditions. In the partner presence (vs. absence) condition, higher attachment avoidance scores correlated with increases in pain ratings and local peak amplitudes of N2 and P2 LEPs. Regardless of the partner's presence, attachment avoidance scores positively correlated with the increase in local peak amplitude of N2 LEP. Finally, higher attachment anxiety scores correlated with decreases in the latency of N1 and N2 LEPs.

Social feedback

As the previous section shows, familiarity and closeness in social interactions can significantly influence the individual pain experience when receiving support. In other social contexts, unfamiliar strangers can also shape individuals' perceptions of pain. This section reports on three papers (40–42) that explored how different forms of feedback from strangers can modulate the pain experience (i.e., social feedback effects). In the first two studies (40, 41), social conformity manipulation was employed to test how others' evaluations of a painful event might alter the individual's self-experience of a similar event.

In a study by Yoshida et al. (40), participants were shown stimulus pain ratings of a group of strangers who experienced the same stimulus beforehand. The group ratings were shown as a distribution line graph, characterized by a specific mean (below or above the participant rating) and variance (small/large) values. Consistent with conformity studies, the behavioral results showed that the ratings of others influenced participants: participants' pain ratings followed the experimental group means (in both directions). Accordingly, the observed mean modulated neural activation in the bilateral AI, the ACC, and the DLPFC, which was correlated with pain intensity. Interestingly, it was found that high (vs. low) variance increased participants' pain ratings—regardless of the observed mean. This uncertainty-induced hyperalgesic effect correlated with neural activation in the PAG.

Koban et al. further demonstrated the strong influence of social conformity on an individual's pain perception (41). In their study, participants were presented with two cues predictive of the intensity of upcoming painful stimulations. The first cue presented the pain ratings of other people (social cue), while the second cue displayed a photo that was conditioned, before the task, to a specific pain intensity (conditional cue). The authors found that both cues modulated expectancy and pain ratings in line with the predicted information (high/low intensity). However, stronger cue effects (i.e., greater increase/decrease) on the subjective ratings were observed with the social cues (vs. conditional cues). Moreover, the study found that social information (but not conditioned learning) increased skin conductance responses during painful stimulation. The neuroimaging data revealed that social cues of high (vs. low) pain increased neural activation in pain-related brain areas (ACC, AI, thalamus), as well as areas involved in somatosensory integration (MI, parietal operculum), emotion processing (amygdala), cognitive control and top-down attention modulation (DLPFC, IPL, and IPS). In contrast, different neural structures were associated with the modulation of conditional cues on pain (e.g., hippocampus, caudate, cerebellum). A mediation analysis revealed that the brain regions contributing most to mediating social information on pain ratings were the DLPFC, the DMPFC, the VLPFC, the IPS, and the visual cortex. Interestingly, neither the social information nor the conditioned learning directly affected the two neural signatures associated with pain that was tested in the study—the NPS and the stimulus intensity independent of pain signature (SIIPS). Instead, both effects were mediated by expectancy ratings (acquired before the stimulus).

The studies above illustrate how social feedback (presented as ratings of similar experiences by unfamiliar others) significantly impacts the individual's pain experience. However, the nature of information, i.e., the group's perceived pain intensity, is often not visible or easily disclosed to individuals in everyday life. Another type of social feedback that is more common in a natural setting concerns signals from another person (a stranger, a clinician, etc.), such as direct comments or expressions about the state of individual suffering. The final study on this theme by Fauchon et al. (42) varied the content

of auditory comments by a stranger regarding the participant in pain. The behavioral results show that only participants who heard empathetic comments about their suffering rated the pain stimuli less intense (vs. neutral or unempathetic comments). Between the neutral and unempathetic comments, no significant difference was found. During pain, empathetic (vs. neutral) comments increased neural activation in the right AI, the right DLPFC, and the right posterior parietal cortex (right posterior parietal cortex [PPC]), and decreased activation of the left MFG. In the unempathetic (vs. neutral) comments condition, neural activations in the rAI and the PPC were increased and decreased in the VMPFC and thePCC/precuneus. Finally, connectivity analysis revealed that, in the empathetic (vs. neutral/unempathetic) comments condition, functional connectivity increased between VMPFC-AI and VMPFC-PI and decreased between VMPFC-PCC.

Group membership

In the previous theme about social support, it became clear that the quality of a romantic relationship can influence pain modulation by support. A related yet distinct topic of investigation focuses on investigating pain modulatory effects stemming from a relationship with a group. This relationship can be very brief, and the group members can be utterly unfamiliar with the individual. For this theme, five studies (43–47) were identified in the search. The first three studies (43–45) investigated group membership effects using a computer game (Cyberball), triggering the individual's experience of inclusion or exclusion from a group. The two other studies explored how inherent in- and out-group perceptions about others (47) or oneself (46) change pain-related perceptions and processing.

Social exclusion

Consistently with behavioral studies on social exclusion and pain, three recent neuroimaging studies (43–45) found that, after healthy participants were excluded (vs. included/control condition) in the Cyberball game, they perceived fewer interactions, rated subsequent pain stimulations as more intense, and felt more excluded, rejected, ignored, and invisible (45). A hyperalgesic effect of social exclusion has also been observed in patients with borderline personality disorder (BPD) (43) and in patients on opioid maintenance treatment (OMT)(44). The interpretation of the latter two studies is beyond this review's scope because it focuses on healthy participants and chronic pain patients. The reported results nevertheless show the consistency of the finding across different populations.

Reviewing the neural activation evoked during pain after social rejection (vs. inclusion) across the three studies on healthy participants revealed consistent activation increases in the insula and the thalamus in response to painful stimulation: the AI [left AI (43), the bilateral AI (44, 45)], and the right thalamus (43–45). Within the cingulate cortex, the results were less consistent, and included neural activation that increased in ACC and MCC (44), decreased in MCC (45), or did not change significantly (43). Moreover, Bungert et al. (43) also observed increased neural activation in the right amygdala in the social exclusion condition. As for parametric modulations, Bach et al. (44) found that subjective pain ratings positively correlated with neural activation in a cluster that included the bilateral AI, the hippocampus, and the amygdala during social exclusion. Only within the exclusion condition, a positive relationship between neural activation and pain ratings in the amygdala was also observed by Bungert et al. (43). Finally, Landa et al. (45) found that, among a set of Interpersonal emotions (exclusion, rejection, ignoration, feel invisible, feel liked) and non-specific emotions and comfort (feel good, feel comfortable, feel powerful), only exclusion ratings correlated with neural activation in the right AI.

The study by Landa et al. (45) introduced a new Cyberball condition in their experiment—"re-acceptance," which was always presented after participants had undergone the rejection condition. During the re-acceptance condition, the other players renewed the individual's membership in the group by including them in the game again. It was observed that, even after the rejection condition had ended, feelings of exclusion persisted: participants felt more excluded, rejected, and ignored (comparing re-acceptance vs. acceptance). Moreover, the more the participants felt rejected during reacceptance, the more intense they felt the painful stimulus (higher pain ratings). However, in contrast to the rejection condition (vs. acceptance), the reacceptance (vs. acceptance) condition showed decreased neural activation in pain-related (bilateral PI, ACC) and affective brain areas (amygdala, MTG) but increased activation in the pons.

Stereotypes

Whereas social exclusion tasks are manipulations in which other individuals actively dictate the status of an individual's relationship with a group (by accepting/rejecting an individual to/from the group), a study conducted by Schwarz et al. (46) primed male participants with a gender-specific stereotype about pain to allow them to join a "conceptual group" (by believing the stereotype). Specifically, male participants who were primed with the information before the experiment that "males are less sensitive to pain" (MLPS group) showed decreased pain intensity and increased heat pain thresholds (vs. control group with no priming). The exact opposite effects were found when another group of male participants was primed with the information that "Females are less sensitive to pain" (FLPS group) relative to a control group. The stereotype-based priming modulated the pain processing, suggesting that the behavioral effects are unlikely to be caused

solely by response bias: FLPS (vs. MLPS) priming led to increased neural activation mainly in pain-related brain areas (ACC/MCC, right PI, thalamus) and bilateral NAc. A correlation between neural activations and pain ratings was found only in the MLPS priming group, where a decrease of neural activation in the left NAc was observed (compared to testing the MLPS group without priming) associated with lower pain ratings.

Finally, the authors tested the effect of individuals' perceived masculinity (acquired as trait ratings) on pain ratings but found no significant correlation. The results suggest that stereotypes about pain can alter both the subjective experience and the neural processing of pain, adhering to the stereotype contextual direction.

In-group/out-group effects

In a recent study by Hein et al. (47), the authors investigated whether in/out-group exert their effects directly on pain perception or indirectly *via* influencing pain-relief learning (i.e., learning from cues/individuals associated with pain-relief). Therefore, following a classical conditioning paradigm in which a visual cue was associated with an upcoming painful stimulus, participants had to learn a new association during "treatment sessions". In those sessions, the cue was primarily associated (75% of the time) with a pain-relief treatment, which was achieved by omitting the painful stimulus from either an in-group or out-group member referred to as the "treatment provider" (a confederate). Participants were only told that the treatment provider would make decisions that could affect their pain stimulation. The group membership manipulation was executed by letting the treatment providers introduce themselves to participants with their full names before the treatment session. The names indicated whether they were of the same (Swiss) or different nationalities (Balkan descent) as the participant. The out-group nationality was picked to be a minority in the study's country and against which the local population held a negative prejudice). After the short introduction, participants rated their impressions of the in- and out-group members. The social manipulation was validated by showing that the out-group members were rated significantly more negatively (vs. in-group members) on perceived group membership, similarity, and likability.

The behavioral data showed that learning (captured by changes in ratings of anticipated emotions during the treatment period) occurred in the in- and out-group treatment conditions without any difference in learning rate. Pain-relief learning was reflected by neural activation in the AI (mostly the right AI). Somewhat counterintuitively, pre-to-post treatment analysis showed that the out-group, but not in-group, treatment condition led to reductions in pain intensity ratings and pain-related neural activation (left AI, SI). A mediation analysis revealed that the analgesic mechanism was learning-based and mediated by the rAI. That is, increased neural activation in the rAI of the out-group condition correlated with larger reductions in pain ratings. Finally, it was observed that the more negative impression participants gave about the out-group member, the greater the analgesic effect they exhibited on pain ratings and pain-related processing.

Discussion

Main summary

The studies included in this review examined how different social manipulations changed the experience of pain and pain-related effects using different readout measures (e.g., pain ratings, emotion ratings, decision-making, physiological signals, and changes in neural activity) in a controlled lab environment. The findings will be synthesized in the following sections, focusing on overlapping and distinctive processes and the neural mechanisms that contribute to pain perception and processing modulation. Finally, a conclusive summary of the reviewed topic is also provided (see Figure 2 for a summary sketch).

Social signals alter subjective pain ratings and pain-related neural processing

Across the studies reviewed here, social manipulation altered the individuals' pain ratings in 16 out of 19 studies. In three studies, social manipulation did not modulate pain intensity ratings. These include an fMRI study within the "Helping Others" theme (30) and two EEG studies within the "Egocentric Interpersonal Perceptions" (31) and "Social Support" themes (39). Two of these studies (30, 31) also assessed pain unpleasantness ratings, but only one on social modulation was observed (30). Across the 19 studies, 14 studies only measured pain intensity, two studies measured only pain unpleasantness, and three studies measured both.

Examining the neuroimaging results during periods when painful stimuli were administered confirms that social manipulations modulated neural activation in pain-related brain areas in 14 of the 15 fMRI studies. The most consistent modulations across the themes were located in areas primarily associated with the sensory (thalamus, SI) and affective processing of nociceptive signals (AI, ACC). Similar modulations were also observed in areas associated with pain modulation (VMPFC, DLPFC) and affect processing (amygdala). Clustering the results of studies that performed correlation analysis with subjective reports revealed that neural activation in the AI was most frequently (6 studies) correlated with changes in pain ratings due to social manipulations [all

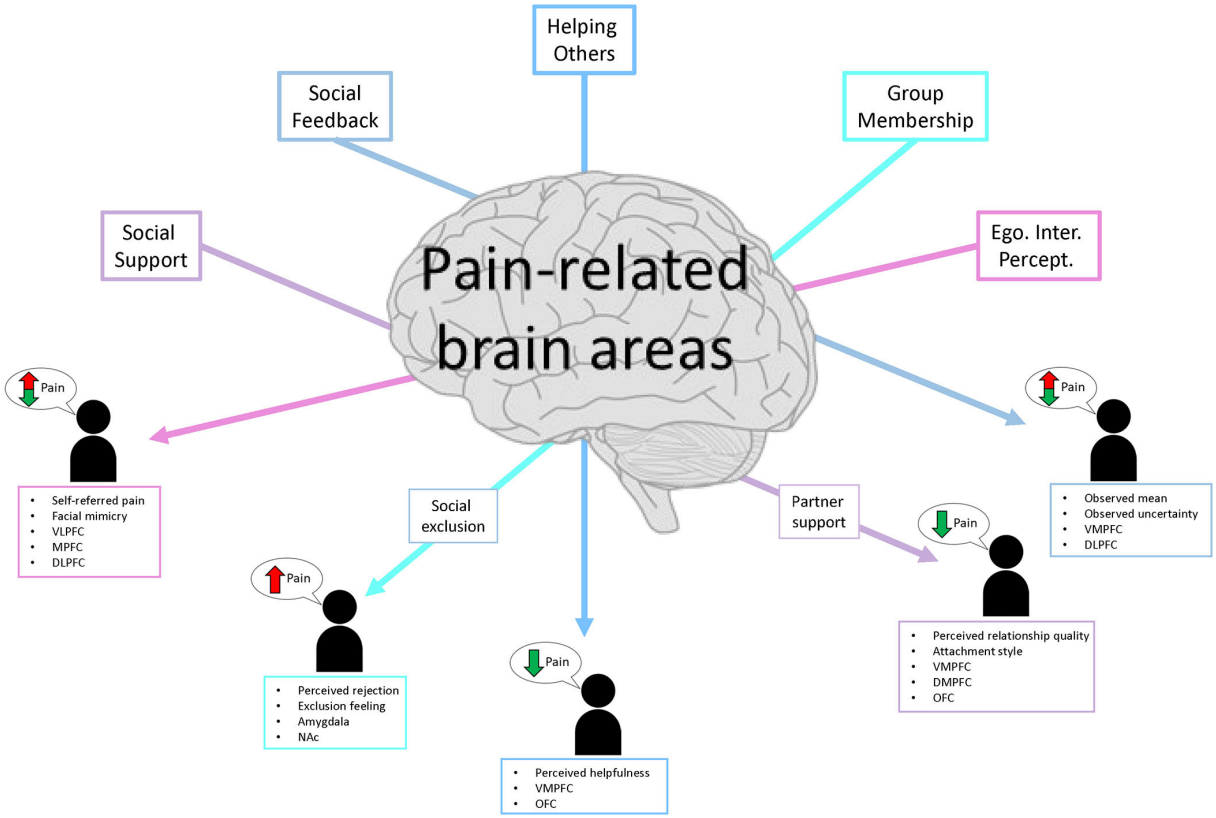


FIGURE 2
Sketch summary of the five social themes, the direction of their influence on pain ratings, and the main modulatory/mediating brain regions.

positive correlations, higher (or lower) AI activation correlated with higher (or lower) pain ratings, respectfully)], followed by the ACC, the VLPFC, the DLPFC, and the amygdala (4 studies each). Only one fMRI study (32) did not show modulation of activation in pain-related brain areas, which might be because the experiment did not have a control condition without pain but a treatment and a no-treatment condition, both with pain.

Across the four evoked related potential (ERP) EEG studies reviewed here (mainly using laser-evoked potentials [LEPs]), social manipulations on the N100 pain-related LEP component were observed only in three studies either directly (31, 36) or indirectly (35). Other LEPs were found to be modulated either one time (P1, N2) (31, 36) or two times (P2) (36, 39) across the four studies. Concerning a relationship between pain-stimulus ratings and specific LEP components, either no correlation was found (31, 35) or such correlation was not tested (36, 39). The absence of a relationship between pain-stimulus ratings and the LEP component is consistent with the pain neurophysiology literature, which shows that LEPs are a good indicator of the occurrence of pain but are weak predictors of subjective pain ratings (49, 59, 60).

Shared and distinct features of social modulations on pain perception

The findings within each theme are now examined to understand better the underlying mechanisms of social modulations on pain and the roles of modulating factors and mediating brain areas.

In the *helping others* theme, two studies examined pain perceptions and processing changes after helping a stranger (29) or a close romantic partner (30). The shared features seem independent of the help's target, helping others reduce neural activation in the AI (associated with affective pain processing during painful stimulations) and pain ratings. In terms of modulations, elevated helping-related feelings, i.e., increased feelings following the decision to help [higher perceived helplessness (29) or positive thoughts (30)] decreased both sensory and affective pain-related neural activation [reduction in NPS (30) and dACC, PI, and AI (29)]. Moreover, the more the individuals chose to help others, the higher the level of activation observed in the VMPFC—shown by a mediation analysis (30) or indirectly by a series of separate correlations (29), and the better they felt about it [higher help-related feelings (29, 30)]. In both

studies, VMPFC increased neural activation was associated with decreased pain-related activation (both affective and sensory). These findings suggest that helping another person—regardless of whether they are familiar—reduces pain, which seems to be mediated mainly by the VMFPC.

Nonetheless, the two studies also had distinct features. Helping a total stranger (vs. romantic partner) (29) decreased a larger cluster of pain-related neural activation, which also included brain areas associated with the sensory processing of pain (e.g., SI, PI, thalamus). Helping a romantic partner (30) reduced mainly neural activation related to affective pain processing (reduction in AI, unchanged NPS, increase in the thalamus). This is also consistent with the observed difference in the reduction of pain intensity in the study of Wang et al. (29) but not in the study of Lee et al. (30), where only unpleasantness was decreased. Finally, in addition to the mediation by the VMPFC discussed above, helping a familiar person appears to be mediated by the OFC (as seen by mediation analysis showing that greater activation reductions in the OFC predicted reductions in pain ratings neural activations of pain-related brain areas) (30).

In the *egocentric interpersonal perceptions* theme, one EEG study (31) and one fMRI (32) study investigated how observing or interacting with others affects the individual during pain. Despite the two different neuroimaging modalities, several shared features could be extracted. While in pain, viewing photos of human/non-human parts or a live video of a clinician before deciding to give a treatment did not affect pain ratings. However, pain ratings increased when there was more detachment from the other person. Participants rated the painful stimulus higher when they focused much more on themselves than on the observed others (31). Similarly, stimulus pain ratings increased when participants exerted less facial mimicking of the other [a form of social bonding (53)]. Finally, observing a human model or another person in pain decreased pain-related LEPs (31) and increased pain-modulating areas (32).

Examining the differences between the two studies also revealed distinct outcomes. When the location of the delivered painful stimulus (the dorsum of the right hand) matched the stimulus location of the observed person in the video, LEPs associated with sensory processing of pain (N1, N2) were reduced while stimulus pain ratings were not affected (31). In contrast, observing a person (a clinician deciding whether to give treatment or not) affected pain intensity ratings but not pain-related brain areas. Instead, it affected pain-modulating brain areas (32). These two studies illustrate how pain perception can be modulated by observing or mimicking others' actions. Moreover, the findings show that even brief interpersonal encounters can significantly impact treatment effectiveness, for which prefrontal regions (VLPFC, MPFC, and bilateral DLPFC) appear to be the critical pain-modulating players. Finally, it seems that inferring about others' feelings in relation to oneself (i.e., self-referred pain) can affect one's pain perception and processing.

Examining the *social support* theme, this review's largest cluster of studies revealed that pain ratings decreased by social support from a romantic partner in six of the seven studies. Moreover, the more concrete the partner support was, the stronger the observed modulations of pain. The strongest modulations were seen by social support given by touching or handholding (36–38), relative to those by viewing a partner photo (33–35). The weakest modulation was seen in a study in which participants were notified of the presence or absence of their partner without being able to see them (or any photo of them) (39). In this study, pain ratings were not affected directly by the social manipulation but only when attachment styles were included as covariates (39).

Based on the findings of (35), it is plausible to assume that visual processing related to social support might be essential to the modulation of partner support on pain and might explain the lack of change in pain ratings when participants do not see their partner during the painful experience. In future studies, one could examine such requirements by including belief scores, which measure the degree to which participants believed their romantic partner was present/observing them during the pain delivery (or during the whole task).

Regarding neuroimaging, partner support modulated neural activation associated with sensory (33, 35–38) and affective (33, 34, 36–39) pain processing. Similar to the behavioral results, the EEG study investigating social presence effects showed no reduction in any LEPs associated with pain (but rather an increased P2 LEPs) (39). When examining the mediating brain areas of social support on pain, prefrontal regions such as the VMPFC, the DLPFC, and the OFC again seemed to be the key players. However, this modulation depends on the relationship quality, attachment style, and individual perception of support during pain. From aggregating the findings of the social support studies, several core concepts were extracted that give insights into the mechanism of social support modulation on pain. First, for highly effective pain analgesia to occur, it is essential that the source of support would be given by "a significant other" in which the relation to the supporter has to be intimate (partner), extended (relationship length), perceived as valuable/joyful (relationship quality) and not associated with relationship fears (attachment anxiety or avoidance). Moreover, the support should be concrete (touch, viewing, rather than imagining the supporter) and with care (slow affective touch). Second, the support given by a stranger could also be beneficial (even if weaker than a supporting partner) to individuals in pain but might depend on the support modality (37). When it comes to physical touch, the intimate context of touch might provide pain alleviation irrespective of familiarity (35, 37). Alternatively, this could also manifest a distraction-based mechanism when support is given by an unfamiliar (or unexpected) stranger. This alternative is supported by the results showing a decrease in

stimulus salience (like distraction) in stranger support (seen as reduced AI activation) and increased neural activation in the MFG. This region is part of the reorienting attention network (61), increasing trust toward attachment figures (seen as increased MFG neural activation) (37). Finally, evaluation of the support meaning is necessary to form a perception of the received support, which significantly influences the final analgesic effect once support is given. Taken together, partner-related analgesia might work through multiple mechanisms—encoding of the partner support as a reward/safety signal that reduces pain and pain-related stress (33), increasing the perceived support (34, 35), and shifting local and distributed network connectivity of pain-modulating brain areas (35). Finally, prefrontal regions such as the VMPFC and the DMPFC seem to be core brain areas mediating this modulation of social viewing on pain perception, where the DMPFC seems to be involved in encoding and processing the individual's perceived support.

The *social feedback* theme shows that information about a similar painful experience of others influences the direction of participants' pain ratings (40, 41). Two primary mechanistic factors can be extracted. First, it seems that an increased range of others' feedback (i.e., the variability of the social feedback) causes more uncertainty regarding deriving/learning the expected experience and, therefore, enhances the pain experience, regardless of the average feedback direction. This is consistent with evidence showing that higher uncertainty in predicting aversive events such as pain led to decreased individuals' safety feelings and increased pain perception (reflected by pain ratings and neural correlates) (62). Second, the study by Koban et al. (41) suggests that social feedback information regarding pain works differently from a conditioned learning cue. Although both cause pain ratings to divert toward the predicted cue pain intensity, social information influences appear more robust (higher pain rating and skin conductance response) and involve a different neural network. In addition to social information about pain, even stimulus-independent social information directed to the participants' coping performance (through social comments) has been shown to influence the individual's pain experience (42). This shows how social information received from others—whether specific or non-specific to pain- impacts the individual pain experience. In summary, pain ratings were modulated in all the social feedback studies in this review. The neuroimaging results show that social feedback manipulations primarily influence brain areas related to the affective processing of pain (AI, ACC) and are mediated mainly by the DLPFC, a region associated with cognitive control and pain modulation (63, 64). From the results by Koban et al. (41), in which the two sensory-related neural pain signatures (NPS and SIIPS) were not affected by the modulation, it is plausible to suggest that social feedback influences pain through its affective features. For future studies, it would be essential to test whether one can capture such dissociation at the behavioral level by comparing pain intensity and unpleasantness ratings.

Interestingly, social modulations by the VMPFC were seen only in the study using comments directed at the participant (42) with empathetic comments leading to decreased pain intensity ratings and increased functional connectivity between the VMPFC and anterior and posterior parts of the insula. In that sense, it is reasonable to view the two sub-themes as active vs. passive social information, which might explain such neural difference: social information that is obtained passively (i.e., through observing others' pain ratings) integrates neural processes associated with the attention network and cognitive control [as shown in (41)], while active reception of information by hearing live comments, which are directed at the participant may require further processing related to encoding and integrating of social information, which was shown to recruit the VMPFC (65). Specifically, the pain reduction observed following empathetic comments during pain could also be regarded as a form of social support from the experimenter (who is not a total stranger and has a sense of authority) and, therefore, recruits the VMPFC as shown in the studies of the social support theme. Lastly, some specific effects were also discovered. The study by Yoshida et al. (40) suggests that the PAG encodes the observed uncertainty information from others, leading to uncertainty-induced hyperalgesia. The PAG has been extensively acknowledged for its role in pain modulation (66, 67), which seems to extend to situations with social feedback.

Finally, examining the *group membership* theme studies revealed that manipulations involving entering, exiting, or evaluating group membership concerning an individual can modulate pain ratings. The evidence consistently suggests that being excluded from a group lead individuals to feel negative emotions associated with the experience of rejection, which is followed by an overall increase in pain perception (seen as higher pain ratings during exclusion conditions) (43–45). In turn, including an individual in a group appears to have an analgesic effect (seen by the reduction of pain ratings and increased positive feelings) (43–45). These results are consistent with previous behavioral findings on social rejection and pain (68). Nonetheless, several unique insights can be extracted from this theme. Using a new paradigm, Landa et al. (45) demonstrated that when individuals revisit an inclusive social situation after an experience of being rejected, the hyperalgesic effect could persist depending on whether they still perceived the experience as rejecting (45). Another core new insight regarding group membership comes from the study by Schwarz et al. (46), which showed how stereotypes could direct individuals' pain perceptions and processing according to specific primers. Hence, these findings suggest that group-membership effects can be directional based on a learned primer with a beneficial context (learned from the associated group) or not (45). These findings

could open an array of clinical treatments. The patients are assigned/told that their profile/condition is part of another group that exhibits a particular recovery/clinical outcome following treatment.

Interestingly, the finding by Hein et al. (47) that treatment by an outer group member reduced pain (both pain ratings and pain-related neural activation) seems counterintuitive and contradicts those of the studies on social exclusion (i.e., exclusion increases pain while inclusion reduces pain) and social support (support from a close person reduces pain). However, this result might be explained by two critical feature differences—purpose and learned outcome-membership association: In social exclusion, individuals are presented with a particular social interaction with unfamiliar others to which they would prefer to belong (rather than being excluded from the group). In social support, individuals' sense of belongingness to their partner is already grounded. Therefore, in those two themes, the purpose is either to belong (in social exclusion) or to have a sense of belonging (in social support) to others. Whereas, in the in/out-group membership studies, the purpose of the individual is to decide whether/how many others belong to their group. In addition, in the social support and exclusion manipulations, there is no direct control of the other person on participants' pain stimulus *per se*, whereas, in the in/out-group manipulation, the other person directly affects participants' pain. Therefore, prior expectations about the other should be learned and updated if the outcome is wrong (generating a prediction error). In both in/out-group membership and the social exclusion studies, the individual's beliefs about themselves and others shape and modulate pain. In the in/out-group manipulation, beliefs about others help form (and update) a person-outcome association by learning. In the group inclusion/exclusion studies, self-related beliefs affect the degree of perceived exclusion from a group (regardless of whether the individual is excluded). In contrast to the social support and social feedback studies reviewed here, the neuroimaging data show that group-membership manipulations affect sensory (MCC, PI, and thalamus) and affective (ACC and AI) pain-related brain areas. In addition, the amygdala was activated in all the social exclusion manipulations (30, 31, 48), and its activation was also found to be positively correlated with increased pain ratings (43, 44). As the amygdala was previously shown to be involved mainly in the processing of negative emotions (69) as well as in pain modulation (70), it is plausible to suggest its conjoined role with the AI to mediate between the elevated rejection-related emotions (during social exclusion) and their hyperalgesic effects on pain. In the study done by Schwarz et al. (46), the NAc activation was found to decrease with a stereotype associated with decreased pain sensitivity (MLPS vs. FLPS) and to correlate with decreased pain ratings.

Based on previous studies that linked activation changes in the dopaminergic system to stress in which dopaminergic inputs from the ventral tegmental area were shown to be modulated by glutamatergic projections from the amygdala (71–73), activation in the NAc might reflect attenuation of a stress-related signal (during the pain-reducing stereotype).

Finally, it seems that, differently from the other social themes, the primary modulating brain areas of group membership effects on pain are areas of the limbic system (AI, amygdala) rather than prefrontal brain areas such as the VMPFC and DLPFC. Taken together, the yearning to belong or be accepted by a group seems to influence the individual's experience of pain significantly. Even without needing a shared experience with others (like in social feedback), group belonging has a unique and independent effect that adds/subtracts from the negative pain experience by altering mood more generally due to social validation. Group-membership effects seem not to be grounded on others solely but rather a combination of self and other actions/impressions.

Prefrontal involvement in the modulation of social signals on pain

Next, synthesizing the results of the neural activity during the pain epochs, correlations with pain ratings, and the mediation analyses allow us to infer the role of different prefrontal brain regions and check which are the key players (showing a consistent function) involved in the influence of social cues on pain perception.

VMPFC

Overall, the social manipulations within the themes of helping others, social support, and social feedback reduced pain ratings. This pain reduction was mostly accompanied by increased neural activity in the VMPFC (30, 34, 37) [but not in (38)] or increased functional connectivity between the VMPFC and pain-related brain areas (29, 42). Reversely, social rejection increased pain ratings, which was accompanied by increased neural activity in the VMFPC (44). These findings imply a selective modulation of pain by the VMPFC, which depends on the valence of the social cue.

Meta-analyses of prefrontal neuroimaging data (21, 74–76) outline that the VMPFC is involved in encoding and representing conceptual information relevant for survival (for the present and the prospective individual's physical and social wellbeing) from environmental and internal cues and in transducing this information into affective behavioral and physiological responses. To generate affective meaning and coordinate emotional behavior, the VMPFC functions as a hub that links systems involved in episodic and semantic memory (77, 78), emotion (79) and emotion regulation (80, 81), social

cognition (82, 83), interoceptive signals (80), and subjective values (84).

The role of the VMFPC to modulate pain across different social situations, as identified in this review, fits the suggested function of being a critical hub that integrates different internal and external inputs (visceral, sensory, social) to conceive the meaning of a specific social scenario in order to direct the appropriate behavior/action. Such behavior might be to withdraw from an unpleasant social situation/from others (after social exclusion) or to stay and appreciate the bond with others (e.g., during social support).

DLPFC

The relationship between neural activity in the DLPFC and pain ratings was positive in the social feedback manipulations (40, 41) and inconsistent in social support (33, 38) and the egocentric interpersonal perception manipulation (32).

As the results are inconsistent within some of the themes, it is only possible to draw general conclusions on the underlying processing of the DLPFC within the reviewed studies. The observed recruitment of the DLPFC might reflect different pain-related processes compared to previous research and might be more prominent in certain themes. These include pain detection (85, 86), pain sensitivity encoding (87), integration of incoming nociceptive signals with cue-based expectation (20), and cognitive control of pain (88). In the reviewed studies, DLPFC involvement could reflect processing related to nociceptive integration, pain detection, and controlling the perceived pain.

DMPFC

The recruitment of the DMPFC was found in studies employing social manipulations of social support (35, 38) and social conformity (41). From the mediation analyses (41), the positive correlation with pain ratings (38), and the outcome of social support on pain ratings following a DMPFC-iTBS procedure (35), the DMPFC seems to be involved in the encoding of the pain and its modulation during a social situation.

Based on recent meta-analyses on the role of the prefrontal cortex (21, 74), the DMPFC in those themes may be involved in processes related to the appraisal of others' mental states concerning one's well-being (mentalizing and reflection on the self and others) (74), emotion regulation, encoding representation of negative emotions, and general representation of pain (21).

OFC

In the case of the OFC, the results revealed inconsistent patterns (30, 33, 38), suggesting that the OFC involvement might be exerted indirectly (by influencing other PFC regions) in a pattern that depends on task-specific features/processes.

It appears that the OFC is recruited when an individual is giving (30) or receiving (33, 38) support to/from others. However, as the inconsistent activation pattern also occurs within the social themes, it is difficult to conclude the specific processes within each social theme.

From meta-analytic data of the prefrontal cortex (74, 76), it is plausible to assume that the observed neural activity in the OFC reflects the processing of internal states such as affect and motivation (e.g., when deciding whether to offer help) (76). In addition, it might reflect processes related to goal-directed behavior (giving or preparing to receive help), which include encoding value-outcome associations, and appraisal of episodic memories and imagined future events (anticipated pleasantness of imagined future scenario, real and imagined rewards, imagined future emotional events, and pleasantness and autobiographical memories) (74).

Critical remarks and suggestions for future research

In this review, several potential issues were noted that would be beneficial to be considered in future studies. The most critical issue was the selection bias of female over male participants (either women only or a highly skewed ratio). Although one could justify such selection by having a more gender-homogenous participant sample, the conclusions of such studies are limited if gender selection is not controlled, matched, and tested for differences. This issue is particularly critical as one study of this review that sampled both genders found a significant difference in social modulation and neural activation during pain (37). In that matter, including more gender identities could be significant and exciting to investigate in future studies on social effects on pain. Many results point to modulations grounded on self-perception that interacts with a particular social situation.

Another critical issue concerns the lack of necessary control conditions: several studies only compared the main manipulation with a contrasting condition without including a control condition independent of the investigated social context. This issue could significantly impact the interpretation of some reported results (e.g., whole-brain neural activations).

A few studies also lacked full/partial details on whole-brain activations (e.g., missing activation tables for each examined condition) and offered brief, vague, or insufficient written descriptions or provided only selected images.

From the pain assessment perspective, there is an imbalance in the usage of the core pain rating scales. While three studies measured pain intensity and unpleasantness, most of the studies measured only intensity (14/19) or unpleasantness (2/19). Indeed, including two sets of rating scales during an experimental task can significantly increase the duration of an experiment. This can be particularly problematic in neuroimaging studies because of the necessity of trial repetition, leading to more subject fatigue, loss of attention, and limiting the inclusion of other conditions in the experiment.

While in most of the studies reviewed here, only pain intensity was measured, several studies included other measures not related to pain (emotion or mood ratings often as a one-time question at the end of the experiment) to provide some insight into the affective-motivational aspect of the painful experience. However, as previous research has shown that perceived pain intensity and unpleasantness are associated with distinct and shared neural representations in the brain (18, 89–92), it should be a consideration in most pain studies to include intensity as well as affective pain scales as outcome measures. This seems especially critical for studies of supraspinal pain modulation.

In the social support theme, there is a large variability in the selection and/or definition of a "romantic partner" by the relationship duration. Therefore, developing a more logical consensus that could be compared across studies is recommended. In addition, a large sample could be tested and used as a covariate or correlational measure in the analyses. Furthermore, it would be essential to compare social support conditions with a neutral condition ("Stranger support") and to compare negative and positive forms of social support from the same source of support. Allowing to explore the full spectrum of social manipulation might potentially answer whether and when exerting one form of support can have an opposite effect (e.g., viewing a negative facial expression from a romantic partner might still show a positive effect on pain or a positive expression from a stranger might still have a negative effect on pain).

Finally, future studies are encouraged to include chronic pain patients and compare them to healthy populations. Such inclusion might provide critical information for health care providers and clinicians to assess the effectiveness and efficacy of different socially-oriented treatment programs (93–95).

Summary and conclusion

This review presents and discusses the results of 19 neuroimaging studies examining how social signals influence the individual's experience of pain (see Figure 2 for a summary sketch). By classifying the studies into thematic groups, intra- and inter-thematic mechanisms were discussed and shared, in which distinct modulating factors were identified. As previously theorized by psychosocial pain models, social manipulations robustly influence pain at the level of behavior and neural processing. The final modulatory effect of most social manipulations seems to be dependent on social traits grounded within the self (e.g., perceived helpfulness, perceived rejection, perceived relationship quality, uncertainty sensitivity) and mediated mainly by prefrontal regions (e.g., VMPFC, DLPFC) and brain areas associated with affective processing of pain—mainly the anterior insular cortex. This review adds essential information about neural and behavioral mechanisms to previous reviews on a single thematic topic (14, 16, 17). Hopefully, this review provides a broader perspective and stimulating suggestions for researchers and clinicians.

Author contributions

GS wrote the manuscript. PS edited it and had manuscript oversight. All authors contributed to the article and approved the submitted version.

Funding

GS received a salary from a Swiss National Science Foundation (SNSF) project grant to PS (Grant number 320030_179191/1).

Acknowledgments

GS would like to thank Preston Liang and Yana Tishler for the social support they provided him throughout the review work.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.856874/full#supplementary-material

References

1. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *Pain.* (2020) 161:1976–82. doi: 10.1097/j.pain.0000000000001939

2. Engel GL. The need for a new medical model: a challenge for biomedicine. *Science.* (1977) 196:129–36. doi: 10.1126/science.847460

3. Lumley MA, Cohen JL, Borszcz GS, Cano A, Radcliffe AM, Porter LS, et al. Pain and emotion: a biopsychosocial review of recent research. *J Clin Psychol.* (2011) 67:942–68. doi: 10.1002/jclp.20816

4. Rabbitts JA, Palermo TM, Lang EA. A conceptual model of biopsychosocial mechanisms of transition from acute to chronic postsurgical pain in children and adolescents. *J Pain Res.* (2020) 13:3071–80. doi: 10.2147/JPR.S239320

5. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. *Psychol Bull.* (2007) 133:581–624. doi: 10.1037/0033-2909.133.4.581

6. Moseley GL, Butler DS. Fifteen years of explaining pain: the past, present, and future. *J Pain.* (2015) 16:807–13. doi: 10.1016/j.jpain.2015.05.005

7. Schweinhardt P, Bushnell MC. Pain imaging in health and disease–how far have we come? *J Clin Invest.* (2010) 120:3788–97. doi: 10.1172/JCI43498

8. Villemure C, Bushnell MC. Cognitive modulation of pain: How do attention and emotion influence pain processing? *Pain.* (2002) 95:195–9. doi: 10.1016/S0304-3959(02)00007-6

9. Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. *Neuron.* (2007) 55:377–91. doi: 10.1016/j.neuron.2007.07.012

10. Vlaeyen JWS, Hanssen M, Goubert L, Vervoort T, Peters M, van Breukelen G, et al. Threat of pain influences social context effects on verbal pain report and facial expression. *Behav Res Ther.* (2009) 47:774–82. doi: 10.1016/j.brat.2009.05.008

11. Sharvit G, Corradi-Dell'Acqua C, Vuilleumier P. Modality-specific effects of aversive expectancy in the anterior insula and medial prefrontal cortex. *Pain.* (2018) 159:1529–42. doi: 10.1097/j.pain.0000000000001237

12. Schwartz GE. Testing the biopsychosocial model: the ultimate challenge facing behavioral medicine? *J Consult Clin Psychol.* (1982) 50:1040–53. doi: 10.1037/0022-006X.50.6.1040

13. Krahé C, Springer A, Weinman JA, Fotopoulou A. The social modulation of pain: others as predictive signals of salience—a systematic review. *Front Hum Neurosci.* (2013) 7:386 doi: 10.3389/fnhum.2013.00386

14. Che X, Cash R, Chung S, Fitzgerald PB, Fitzgibbon BM. Investigating the influence of social support on experimental pain and related physiological arousal: a systematic review and meta-analysis. *Neurosci Biobehav Rev.* (2018) 92:437–52. doi: 10.1016/j.neubiorev.2018.07.005

15. Koban L, Jepma M, Geuter S, Wager TD. What's in a word? How instructions, suggestions, and social information change pain and emotion. *Neurosci Biobehav Rev.* (2017) 81:29–42. doi: 10.1016/j.neubiorev.2017.02.014

16. Che X, Cash R, Ng SK, Fitzgerald P, Fitzgibbon BM. A systematic review of the processes underlying the main and the buffering effect of social support on the experience of pain. *Clin J Pain.* (2018) 34:1061–76. doi: 10.1097/AJP.0000000000000624

17. Inagaki TK. Neural mechanisms of the link between giving social support and health: Giving social support and health. *Ann N Y Acad Sci.* (2018) 1428:33–50. doi: 10.1111/nyas.13703

18. Singh A, Patel D, Li A, Hu L, Zhang Q, Liu Y, et al. Mapping cortical integration of sensory and affective pain pathways. *Curr Biol.* (2020) 30:1703–15.e5. doi: 10.1016/j.cub.2020.02.091

19. Tracey I. Nociceptive processing in the human brain. *Curr Opin Neurobiol.* (2005) 15:478–87. doi: 10.1016/j.conb.2005.06.010

20. Atlas LY, Bolger N, Lindquist MA, Wager TD. Brain mediators of predictive cue effects on perceived pain. *J Neurosci.* (2010) 30:12964–77. doi: 10.1523/JNEUROSCI.0057-10.2010

21. Kragel PA, Kano M, Van Oudenhove L, Ly HG, Dupont P, Rubio A, et al. Generalizable representations of pain, cognitive control, and negative emotion in medial frontal cortex. *Nat Neurosci.* (2018) 21:283–9. doi: 10.1038/s41593-017-0051-7

22. Romeo A, Tesio V, Castelnuovo G, Castelli L. Attachment Style and Chronic Pain: Toward an Interpersonal Model of Pain. *Front Psychol.* (2017) 8:284. doi: 10.3389/fpsyg.2017.00284

23. Porter LS, Davis D, Keefe FJ. Attachment and pain: Recent findings and future directions. *Pain.* (2007) 128:195–8. doi: 10.1016/j.pain.2007.02.001

24. Vrtička P, Vuilleumier P. Neuroscience of human social interactions and adult attachment style. *Front Hum Neurosci.* (2012) 6:212. doi: 10.3389/fnhum.2012.00212

25. Perini I, Gustafsson PA, Hamilton JP, Kämpe R, Zetterqvist M, Heilig M. The salience of self, not social pain, is encoded by dorsal anterior cingulate and insula. *Sci Rep.* (2018) 8:6165. doi: 10.1038/s41598-018-24658-8

26. Ferris LJ, Jetten J, Hornsey MJ, Bastian B. Feeling hurt: revisiting the relationship between social and physical pain. *Rev Gen Psychol.* (2019) 23:320–35. doi: 10.1177/1089268019857936

27. Meyer ML, Williams KD, Eisenberger NI. Why social pain can live on: different neural mechanisms are associated with reliving social and physical pain. *PLoS ONE.* (2015) 10:e0128294. doi: 10.1371/journal.pone.0128294

28. Eisenberger NI. Social pain and the brain: controversies, questions, and where to go from here. *Annu Rev Psychol.* (2015) 66:601–29. doi: 10.1146/annurev-psych-010213-115146

29. Wang Y, Ge J, Zhang H, Wang H, Xie X. Altruistic behaviors relieve physical pain. *Proc Natl Acad Sci USA.* (2020) 117:950–8. doi: 10.1073/pnas.1911861117

30. López-Solà M, Koban L, Wager TD. Transforming pain with prosocial meaning: a functional magnetic resonance imaging study. *Psychosom Med.* (2018) 80:814–25. doi: 10.1097/PSY.0000000000000609

31. Valeriani M, Betti V, Le Pera D, De Armas L, Miliucci R, Restuccia D, et al. Seeing the pain of others while being in pain: a laser-evoked potentials study. *Neuroimage.* (2008) 40:1419–28. doi: 10.1016/j.neuroimage.2007.12.056

32. Ellingsen D-M, Isenburg K, Jung C, Lee J, Gerber J, Mawla I, et al. Dynamic brain-to-brain concordance and behavioral mirroring as a mechanism of the patient-clinician interaction. *Sci Adv.* (2020) 6:eabc1304. doi: 10.1126/sciadv.abc1304

33. Younger J, Aron A, Parke S, Chatterjee N, Mackey S. Viewing pictures of a romantic partner reduces experimental pain: involvement of neural reward systems. *PLoS ONE.* (2010) 5:e13309. doi: 10.1371/journal.pone.0013309

34. Eisenberger NI, Master SL, Inagaki TK, Taylor SE, Shirinyan D, Lieberman MD, et al. Attachment figures activate a safety signal-related neural region and reduce pain experience. *Proc Natl Acad Sci USA.* (2011) 108:11721–6. doi: 10.1073/pnas.1108239108

35. Che X, Cash R, Chung SW, Bailey N, Fitzgerald PB, Fitzgibbon BM. The dorsomedial prefrontal cortex as a flexible hub mediating behavioral as well as local and distributed neural effects of social support context on pain: a Theta Burst Stimulation and TMS-EEG study. *Neuroimage.* (2019) 201:116053. doi: 10.1016/j.neuroimage.2019.116053

36. von Mohr M, Krahé C, Beck B, Fotopoulou A. The social buffering of pain by affective touch: a laser-evoked potential study in romantic couples. *Soc Cogn Affect Neurosci.* (2018) 13:1121–30. doi: 10.1093/scan/nsy085

37. Kreuder A-K, Wassermann L, Wollseifer M, Ditzen B, Eckstein M, Stoffel-Wagner B, et al. Oxytocin enhances the pain-relieving effects of social support in romantic couples. *Hum Brain Mapp.* (2019) 40:242–51. doi: 10.1002/hbm.24368

38. López-Solà M, Geuter S, Koban L, Coan JA, Wager TD. Brain mechanisms of social touch-induced analgesia in females. *Pain.* (2019) 160:2072–85. doi: 10.1097/j.pain.0000000000001599

39. Krahé C, Paloyelis Y, Condon H, Jenkinson PM, Williams SCR, Fotopoulou A. Attachment style moderates partner presence effects on pain: a laser-evoked potentials study. *Soc Cogn Affect Neurosci.* (2015) 10:1030–7. doi: 10.1093/scan/nsu156

40. Yoshida W, Seymour B, Koltzenburg M, Dolan RJ. Uncertainty increases pain: evidence for a novel mechanism of pain modulation involving the periaqueductal gray. *J Neurosci Off J Soc Neurosci.* (2013) 33:5638–46. doi: 10.1523/JNEUROSCI.4984-12.2013

41. Koban L, Jepma M, López-Solà M, Wager TD. Different brain networks mediate the effects of social and conditioned expectations on pain. *Nat Commun.* (2019) 10:4096. doi: 10.1038/s41467-019-11934-y

42. Fauchon C, Faillenot I, Quesada C, Meunier D, Chouchou F, Garcia-Larrea L, et al. Brain activity sustaining the modulation of pain by empathetic comments. *Sci Rep.* (2019) 9:8398. doi: 10.1038/s41598-019-44879-9

43. Bungert M, Koppe G, Niedtfeld I, Vollstädt-Klein S, Schmahl C, Lis S, et al. Pain processing after social exclusion and its relation to rejection sensitivity in borderline personality disorder. *PLoS ONE.* (2015) 10:e0133693. doi: 10.1371/journal.pone.0133693

44. Bach P, Frischknecht U, Bungert M, Karl D, Vollmert C, Vollstädt-Klein S, et al. Effects of social exclusion and physical pain in chronic opioid

maintenance treatment: fMRI correlates. *Eur Neuropsychopharmacol.* (2019) 29:291–305. doi: 10.1016/j.euroneuro.2018.11.1109

45. Landa A, Fallon BA, Wang Z, Duan Y, Liu F, Wager TD, et al. When it hurts even more: The neural dynamics of pain and interpersonal emotions. *J Psychosom Res.* (2020) 128:109881. doi: 10.1016/j.jpsychores.2019.109881

46. Schwarz KA, Sprenger C, Hidalgo P, Pfister R, Diekhof EK, Büchel C. How stereotypes affect pain. *Sci Rep.* (2019) 9:8626. doi: 10.1038/s41598-019-45044-y

47. Hein G, Engelmann JB, Tobler PN. Pain relief provided by an outgroup member enhances analgesia. *Proc Biol Sci.* (2018) 285:20180501. doi: 10.1098/rspb.2018.0501

48. Wager TD, Atlas LY, Lindquist MA, Roy M, Woo C-W, Kross E. An fMRI-based neurologic signature of physical pain. *N Engl J Med.* (2013) 368:1388–97. doi: 10.1056/NEJMoa1204471

49. Chen ACN, Arendt-Nielsen L, Plaghki L. Laser-evoked potentials in human pain. *Pain Forum.* (1998) 7:174–84. doi: 10.1016/S1082-3174(98)70001-7

50. Lee MC, Mouraux A, Iannetti GD. Characterizing the cortical activity through which pain emerges from nociception. *J Neurosci Off J Soc Neurosci.* (2009) 29:7909–16. doi: 10.1523/JNEUROSCI.0014-09.2009

51. Garcia-Larrea L, Frot M, Valeriani M. Brain generators of laser-evoked potentials: from dipoles to functional significance. *Neurophysiol Clin Clin Neurophysiol.* (2003) 33:279–92. doi: 10.1016/j.neucli.2003.10.008

52. Mouraux A, Iannetti GD. Nociceptive laser-evoked brain potentials do not reflect nociceptive-specific neural activity. *J Neurophysiol.* (2009) 101:3258–69. doi: 10.1152/jn.91181.2008

53. Cloutier J, Heatherton TF, Whalen PJ, Kelley WM. Are attractive people rewarding? Sex differences in the neural substrates of facial attractiveness. *J Cogn Neurosci.* (2008) 20:941–51. doi: 10.1162/jocn.2008.20062

54. Baxter MG, Murray EA. The amygdala and reward. *Nat Rev Neurosci.* (2002) 3:563–73. doi: 10.1038/nrn875

55. Aron A, Fisher H, Mashek DJ, Strong G, Li H, Brown LL. Reward, motivation, and emotion systems associated with early-stage intense romantic love. *J Neurophysiol.* (2005) 94:327–37. doi: 10.1152/jn.00838.2004

56. Xu X, Aron A, Brown L, Cao G, Feng T, Weng X. Reward and motivation systems: a brain mapping study of early-stage intense romantic love in Chinese participants. *Hum Brain Mapp.* (2011) 32:249–57. doi: 10.1002/hbm.21017

57. Nickel MM, May ES, Tiemann L, Schmidt P, Postorino M, Ta Dinh S, et al. Brain oscillations differentially encode noxious stimulus intensity and pain intensity. *Neuroimage.* (2017) 148:141–7. doi: 10.1016/j.neuroimage.2017.01.011

58. Zhang ZG, Hu L, Hung YS, Mouraux A, Ianetti GD. Gamma-band oscillations in the primary somatosensory cortex-a direct and obligatory correlate of subjective pain intensity. *J Neurosci.* (2012) 32:7429–38. doi: 10.1523/JNEUROSCI.5877-11.2012

59. Zaslansky R, Sprecher E, Katz Y, Rozenberg B, Hemli JA, Yarnitsky D. Pain-evoked potentials: what do they really measure? *Electroencephalogr Clin Neurophysiol Potentials Sect.* (1996) 100:384–91. doi: 10.1016/0168-5597(96)95654-3

60. Huang G, Xiao P, Hung YS, Iannetti GD, Zhang ZG, Hu L, et al. novel approach to predict subjective pain perception from single-trial laser-evoked potentials. *Neuroimage.* (2013) 81:283–93. doi: 10.1016/j.neuroimage.2013.05.017

61. Corbetta M, Patel G, Shulman GL. The reorienting system of the human brain: from environment to theory of mind. *Neuron.* (2008) 58:306–24. doi: 10.1016/j.neuron.2008.04.017

62. Brown C a, Seymour B, Boyle Y, El-Deredy W, Jones AKP. Modulation of pain ratings by expectation and uncertainty: behavioral characteristics and anticipatory neural correlates. *Pain.* (2008) 135:240–50. doi: 10.1016/j.pain.2007.05.022

63. Seminowicz DA, Moayedi M. The dorsolateral prefrontal cortex in acute and chronic pain. *J Pain Off J Am Pain Soc.* (2017) 18:1027–35. doi: 10.1016/j.jpain.2017.03.008

64. Gbadeyan O, McMahon K, Steinhauser M, Meinzer M. Stimulation of dorsolateral prefrontal cortex enhances adaptive cognitive control: a high-definition transcranial direct current stimulation study. *J Neurosci.* 36:12530–36. doi: 10.1523/JNEUROSCI.2450-16.2016

65. De Martino B, Bobadilla-Suarez S, Nouguchi T, Sharot T, Love BC. Social information is integrated into value and confidence judgments according to its reliability. *J Neurosci.* 37:6066–74. doi: 10.1523/JNEUROSCI.3880-16.2017

66. Hemington KS, Coulombe M-A. The periaqueductal gray and descending pain modulation: why should we study them and what role do they play in chronic pain? *J Neurophysiol.* (2015) 114:2080–3. doi: 10.1152/jn.00998.2014

67. Mills EP, Keay KA, Henderson LA. Brainstem pain-modulation circuitry and its plasticity in neuropathic pain: insights from human brain imaging investigations. *Front Pain Res.* (2021) 2:34. doi: 10.3389/fpain.2021.705345

68. Eisenberger NI, Jarcho JM, Lieberman MD, Naliboff BD. An experimental study of shared sensitivity to physical pain and social rejection. *Pain.* (2006) 126:132–8. doi: 10.1016/j.pain.2006.06.024

69. Hamann SB, Ely TD, Hoffman JM, Kilts CD. Ecstasy and agony: activation of the human amygdala in positive and negative emotion. *Psychol Sci.* (2002) 13:135–41. doi: 10.1111/1467-9280.00425

70. Neugebauer V. Amygdala pain mechanisms. In: Schaible H-G, ed. *Pain Control. Handbook of Experimental Pharmacology*. Berlin, Heidelberg: Springer (2015). p. 261–84.

71. Altier N, Stewart J. The role of dopamine in the nucleus accumbens in analgesia. *Life Sci.* (1999) 65:2269–87. doi: 10.1016/S0024-3205(99)00298-2

72. Navratilova E, Porreca F. Reward and motivation in pain and pain relief. *Nat Neurosci.* (2014) 17:1304–12. doi: 10.1038/nn.3811

73. Deutch AY, Roth RH. The determinants of stress-induced activation of the prefrontal cortical dopamine system. *Prog Brain Res.* (1990) 85:367–402. doi: 10.1016/S0079-6123(08)62691-6

74. Dixon ML, Thiruchselvam R, Todd R, Christoff K. Emotion and the prefrontal cortex: an integrative review. *Psychol Bull.* (2017) 143:1033–81. doi: 10.1037/bul0000096

75. Roy M, Shohamy D, Wager TD. Ventromedial prefrontal-subcortical systems and the generation of affective meaning. *Trends Cogn Sci.* (2012) 16:147–56. doi: 10.1016/j.tics.2012.01.005

76. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. *Annu Rev Neurosci.* (2001) 24:167–202. doi: 10.1146/annurev.neuro.24.1.167

77. Buckner RL, Carroll DC. Self-projection and the brain. *Trends Cogn Sci.* (2007) 11:49–57. doi: 10.1016/j.tics.2006.11.004

78. Binder JR, Desai RH, Graves WW, Conant LL. Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cereb Cortex.* (2009) 19:2767–96. doi: 10.1093/cercor/bhp055

79. Schiller D, Delgado MR. Overlapping neural systems mediating extinction, reversal and regulation of fear. *Trends Cogn Sci.* (2010) 14:268–76. doi: 10.1016/j.tics.2010.04.002

80. Critchley HD, Nagai Y, Gray MA, Mathias CJ. Dissecting axes of autonomic control in humans: Insights from neuroimaging. *Auton Neurosci Basic Clin.* (2011) 161:34–42. doi: 10.1016/j.autneu.2010.09.005

81. Wager TD, Barrett LF, Bliss-Moreau E, Lindquist KA, Duncan S, Kober H, et al. The neuroimaging of emotion. *Handbook of Emotions, 3rd ed.* New York, NY, US: The Guilford Press (2008). p. 249–271

82. Northoff G, Bermpohl F. Cortical midline structures and the self. *Trends Cogn Sci.* (2004) 8:102–7. doi: 10.1016/j.tics.2004.01.004

83. Amodio DM, Frith CD. Meeting of minds: the medial frontal cortex and social cognition. *Nat Rev Neurosci.* (2006) 7:268–77. doi: 10.1038/nrn1884

84. Rangel A, Hare T. Neural computations associated with goal-directed choice. *Cogn Neurosci.* (2010) 20:262–70. doi: 10.1016/j.conb.2010.03.001

85. Bornhövd K, Quante M, Glauche V, Bromm B, Weiller C, Büchel C. Painful stimuli evoke different stimulus–response functions in the amygdala, prefrontal, insula and somatosensory cortex: a single-trial fMRI study. *Brain.* (2002) 125:1326–36. doi: 10.1093/brain/awf137

86. Lorenz J, Minoshima S, Casey KL. Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. *Brain.* (2003) 126:1079–91. doi: 10.1093/brain/awg102

87. Sevel LS, Letzen JE, Staud R, Robinson ME. Interhemispheric dorsolateral prefrontal cortex connectivity is associated with individual differences in pain sensitivity in healthy controls. *Brain Connect.* (2016) 6:357–64. doi: 10.1089/brain.2015.0405

88. Wiech K, Kalisch R, Weiskopf N, Pleger B, Stephan KE, Dolan RJ. Anterolateral prefrontal cortex mediates the analgesic effect of expected and perceived control over pain. *J Neurosci.* (2006) 26:11501. doi: 10.1523/JNEUROSCI.2568-06.2006

89. Price DD. Psychological and neural mechanisms of the affective dimension of pain. *Science.* (2000) 288:1769–72. doi: 10.1126/science.288.5472.1769

90. Rainville P, Carrier B, Hofbauer RK, Bushnell CM, Duncan GH. Dissociation of sensory and affective dimensions of pain using hypnotic modulation. *Pain.* (1999) 82:159–71. doi: 10.1016/S0304-3959(99)00048-2

91. Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC. Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science.* (1997) 277:968–71.

92. Melzack R, Casey K. Sensory motivational and central control determinants of pain a new conceptual model. International Symposium on the Skin Senses. Geneseo, IL: Springfield (1968). p. 423–43. Available online at: https://eurekamag.com/research/025/438/025438547.php

93. Polomano RC, Droog N, Purinton MC, Cohen AS. Social support web-based resources for patients with chronic pain. *J Pain Palliative Care Pharmacother*. (2007) 21:49–55.

94. Cano A. Pain catastrophizing and social support in married individuals with chronic pain: the moderating role of pain duration. *Pain*. (2004) 110:656–64. doi: 10.1016/j.pain.2004.05.004

95. López-Martínez AE, Esteve-Zarazaga R, Ramírez-Maestre C. Perceived social support and coping responses are independent variables explaining pain adjustment among chronic pain patients. *J Pain*. (2008) 9:373–9. doi: 10.1016/j.jpain.2007.12.002

Glossary

Abbreviation	Term
∞	Correlate
↑	Increase
↓	Decrease
aal3v1	Automated Anatomic Labeling
ACC	Anterior cingulate cortex
adACC	anterior-dorsal ACC
AI	Anterior insula
Amyg	Amygdala
bil	Bilateral
BPD	Borderline personality disorder
CTRL	Control
d	Dorsal
dACC	Dorsal anterior cingulate cortex
DLPFC	Dorsolateral prefrontal cortex
DMN	Default mode network
DMPFC	Dorsomedial prefrontal cortex
EA	Electroacupuncture
EEG	Electroencephalogram
EP	Evoked potential
F	Female
FC	Functional connectivity
fMRI	Functional magnetic resonance imaging
HC	Healthy control
IASP	International Association for the Study of Pain
INS	The whole insular cortex
IPL	Inferior parietal lobe
iTBS	Intermittent theta burst stimulation
l	Left
LEP	Laser evoked potential
LEPs	Laser evoked potentials
LPFC	Lateral prefrontal cortex
M	Male
MCC	Mid cingulate cortex
MEG	Magnetoencephalography
MeSH	Medical subject headings
MFG	Middle frontal gyrus
MI	Mid insula
MNI	Montreal Neurological Institute
MPFC	Medial prefrontal cortex
MTG	Middle temporal gyrus
N.A.	Not applicable. Result or Analysis was not provided.
N1/N100	early (negative) pain evoked potential
N2/N200	late (negative) pain evoked potential
NAc	Nucleus accumbens
NPS	Neurologic Pain Signature
OFC	Orbitofrontal cortex
OMT	Opioid maintenance treatment
P1/P100	early (positive) pain evoked potential
P2/P200	late (positive) pain evoked potential
PAG	Periaqueductal gray
PCC	Posterior cingulate cortex
PET	Positron emission tomography
pgACC	pregenual ACC
PI	Posterior insula
PPC	Posterior parietal cortex
r	Right
Ref.	Reference
ROIs	regions of interests
SCR	Skin conductance response
SFG	Superior frontal gyrus
sgACC	subgenual ACC
SI	Primary somatosensory cortex
SIIPS	Stimulus intensity independent pain signature
SMG	Supramarginal gyrus
STG	Superior temporal gyrus
STS	Superior Temporal Sulcus
TPJ	Temporoparietal junction
VLPFC	Ventrolateral prefrontal cortex
VMPFC	Ventromedial prefrontal cortex

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: frontiersin.org/about/contact

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership