Sensorimotor Integration and Pain Perception: Mechanisms Integrating Nociceptive Processing. A Systematic Review and ALE-Meta Analysis

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Pain treatment services and clinical indicators of pain chronicity focus on afferent nociceptive projections and psychological markers of pain perception with little focus on motor processes. Research supports a strong role for the motor system both in terms of pain related disability and in descending pain modulation. However, there is little understanding of the neurological regions implicated in pain-motor interactions and how the motor and sensory systems interact under conditions of pain. We performed an ALE meta-analysis on two clinical cohorts with atypical sensory and motor processes under conditions of pain and no pain. Persons with sensory altered processing (SAP) and no pain presented with greater activity in the precentral and supplementary motor area relative to persons with self-reported pain. In persons with motor altered processing (MAP), there appeared to be a suppression of activity in key pain regions such as the insula, thalamus, and postcentral gyrus. As such, activation within the motor system may play a critical role in dampening pain symptoms in persons with SAP, and in suppressing activity in key pain regions of the brain in persons with MAP. Future research endeavors should focus on understanding how sensory and motor processes interact both to understand disability and discover new treatment avenues.

Keywords: sensorimotor integration (SMI), motor system, chronic pain, sensorimotor processing and motor diseases, pain perception, nociceptive processing, fMRI

INTRODUCTION

The motor system has a poorly understoodd role in nociceptive processing and pain perception. The relationship between nociception and pain is largely understood as sensory in origin; however, acute and chronic pain is associated with significant physical disability (Dudgeon et al., 2002) and motor-inhibitory processes (Le Pera et al., 2001) that implicate the motor system as both a downstream and up-stream effector on pain perception. The prevalence of chronic pain is roughly 20.4% of the US population with ∼8.0% having high-impact chronic pain; meaning chronic pain that limits life or work activities (Dahlhamer, 2018). To date, it remains unclear how the motor and sensory regions of the central nervous system are impacted relative to each other under conditions of pain.

The primary motor and sensory cortex share reciprocal efferent and afferent pathways. Online motor performance has been shown to modulate sensory processing, both prior to and during

active movement (Angel and Malenka, 1982; Starr and Cohen, 1985; Jiang et al., 1990; Buckingham et al., 2010; Seki and Fetz, 2012; Juravle et al., 2017; Fraser and Fiehler, 2018; Voudouris et al., 2019). Physical activity programs have reliably shown a beneficial effect for persons suffering from chronic pain conditions (Ambrose and Golightly, 2015; Daenen et al., 2015; Booth et al., 2017), where motor activity (Hautasaari et al., 2020) and motor imagery (Larsen et al., 2019) directly influence cortical activity during active nociceptive stimulation. This connection may be mediated in part by direct efferent pathways connecting the primary motor and sensory cortex through feed forward and feedback processes (Umeda et al., 2019), or through long range efferent pathways that integrate the peripheral nervous system. It is still not clear how nociception and pain processing interfere with canonical sensorimotor processing.

Short and long-range connections between sensory and motor regions of the brain may be implicated in the processing of nociceptive stimuli and pain perception. Incongruence between *efferent* pathways from the motor cortex with the *afferent* feedback to the primary sensory cortex through indirect connections that integrate peripheral nerve and muscles may underlie chronic pain. We evaluated clinical populations with altered motor and sensory feedback based on (1) the relatively lower prevalence of pain in persons with motor altered processing (MAP) than sensory altered processing (SAP), (2) the connection between motor and descending pain modulation areas of the brain, and (3) sensorimotor incongruence subserving learning and long-term potentiation. We predicted that altered afferent feedback, seen in persons with SAP, would be associated with aberrant processing in motor planning areas of the brain and that atypical efferent activity, seen in persons with MAP, would be associated with activation in pain-related regions of the brain.
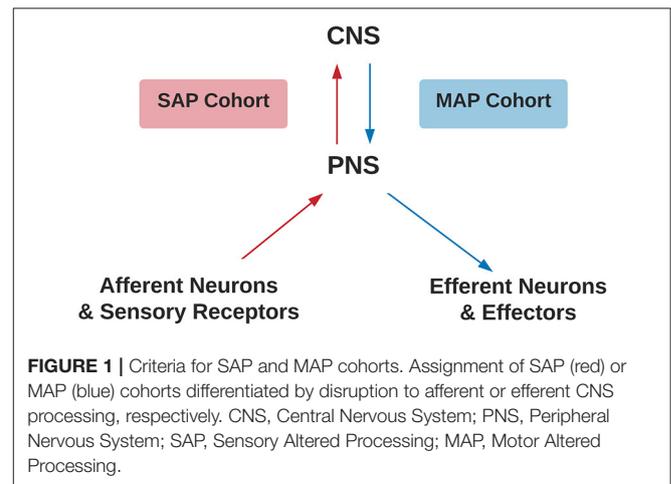
METHODS

Database Search

We conducted a systematic review of the literature according to the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page et al., 2021) and checklist (see **Supplementary Material S1**). Searches were performed in the following databases presented with their respective timelines: Pubmed (1950–2021) and Google Scholar (1950–2021). Database searches were organized according to: *Populations*, *Neuroimaging Methods*, and *Task Specification*. These search terms were combined using the operator "AND" reflecting between parameter combinations and "OR" reflecting within parameter searches. If the Pubmed database was being used, key words were first searched through the Pubmed MeSH database to include additional subheadings or quantifiers within the same context of the key word. See **Figure 2** for an example of the search methodology. *Population* key terms (see **Table 1**) searched were "*spinal cord injury*," "*SCI*," "*amputees*," "*phantom limb pain*," "*pain*." *Neuroimaging Methods* key terms searched were "*MRI*," "*fMRI*," "*task-based fMRI*," "*cerebral activation*." *Task Specification* key terms searched were "*movement execution*," "*movement imagery*." Manual searches were completed through the reference lists of the included articles. All studies that met

TABLE 1 | List of included sensory and motor disorders.

Sensory disorders		Motor disorders	
Spinal cord injury		Dystonia	
	Complete thoracic SCI; complete lumbar SCI		Cervical dystonia; focal upper limb dystonia; generalized idiopathic torsion dystonia; multifocal idiopathic torsion dystonia
Amputees	Unilateral upper limb amputees; bilateral upper limb amputees; unilateral lower limb amputees	Parkinson's disease	Probable PD; akinetic-rigid PD; tremor-dominant PD; mixed type PD; PD with freezing of gait

FIGURE 1 | Criteria for SAP and MAP cohorts. Assignment of SAP (red) or MAP (blue) cohorts differentiated by disruption to afferent or efferent CNS processing, respectively. CNS, Central Nervous System; PNS, Peripheral Nervous System; SAP, Sensory Altered Processing; MAP, Motor Altered Processing.

the inclusion criteria were reviewed in full whereas others were reviewed solely by abstract. One reviewer screened each record independently and the second reviewer screened the studies that met the inclusion criteria for data extraction.
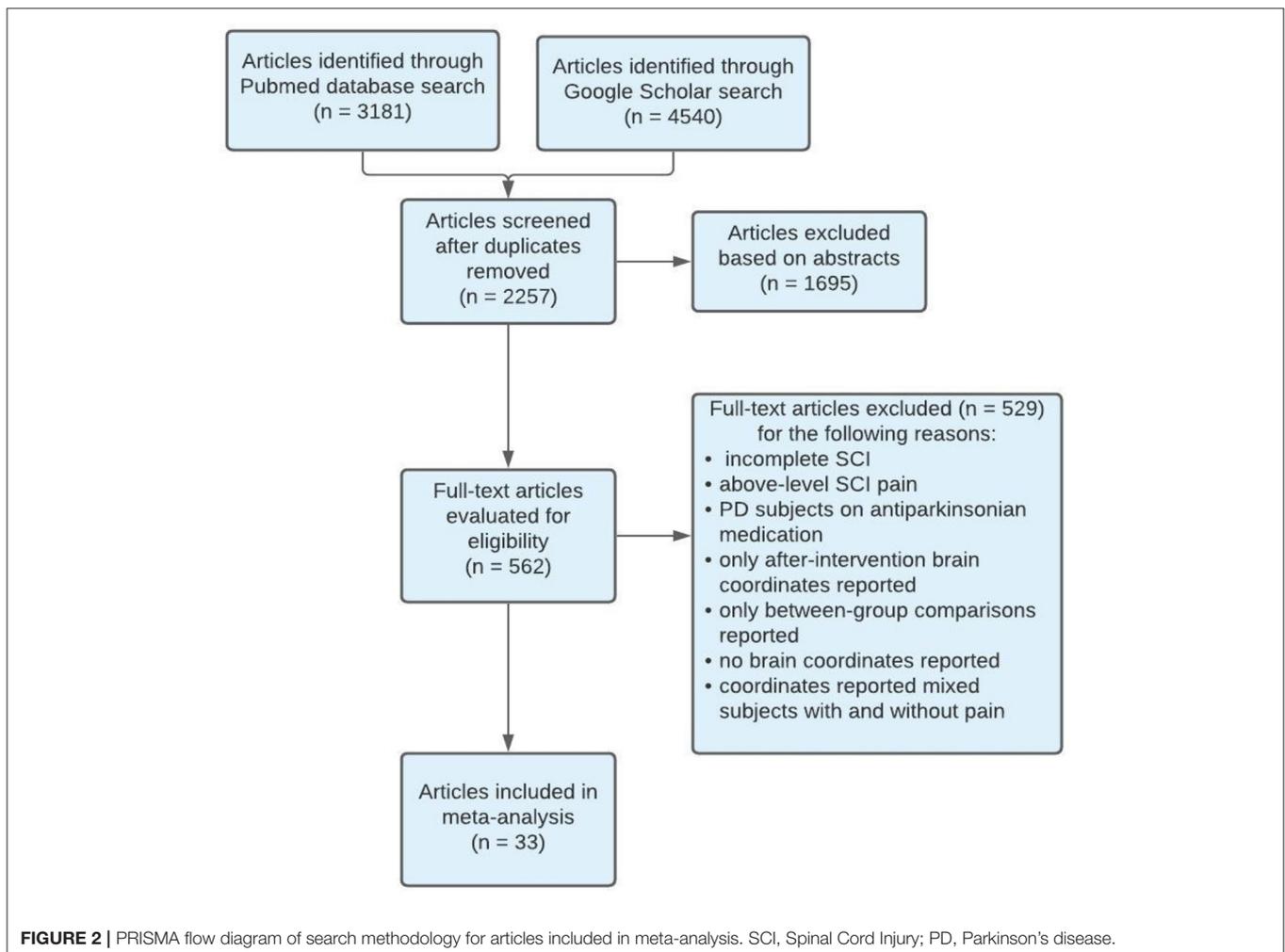
The inclusion criteria were the study provided stereotaxic coordinates of cortical activity averaged within-group comparisons or a single representative subject during a movement imagery or movement execution task in the SAP and MAP cohorts listed in **Table 1** with or without pain. Disruptions to afferent pathways and processing in the CNS were grouped into the SAP cohort (see **Figure 1**). Criteria for SAP included complete spinal cord injuries defined as loss of sensory and motor function below the point of injury and amputees defined as amputation of all or part of an arm or leg. Disruptions to efferent pathways and processing in the CNS were grouped into the MAP cohort (see **Figure 1**). Criteria for MAP included (1) Dystonia: characterized by involuntary and sustained muscle contractions leading to twisting, repetitive movements and abnormal postures (*Dystonia—Symptoms and Causes*, 2020) and (2) Parkinson's disease: defined as a progressive disease of the

nervous system characterized by muscular rigidity and tremor (*Parkinson's Disease—Symptoms and Causes*, 2020). Participants with Parkinson's disease were all studied during the "OFF" period which was defined as withdrawal of antiparkinsonian medication for 12+ h. The criteria for chronic pain in SAP was defined as the self-reported perception of a localized or generalized unpleasant bodily sensation that caused prolonged physical discomfort or mental distress. Phantom limb pain was defined as pain that is perceived as originating from an amputated limb. Movement imagery was defined as a mental execution of a movement without any muscle activation of the limb imagined to be moved that may, or may not, involve a visual cue. Movement execution task was defined as muscle activation of a limb while performing a task. Studies were excluded from analysis if: (1) stereotaxic coordinates were only reported as between-group comparisons; (2) stereotaxic coordinates included subjects with incomplete spinal cord injuries; (3) stereotaxic coordinates included Parkinson's disease subjects actively taking antiparkinsonian medications; (4) stereotaxic coordinates reported did not differentiate between the two groups of subjects with pain and subjects without pain. One reviewer used the National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (see **Supplementary Material S2**) to assess each study's internal validity and assign a rating of good, fair, or poor. Stereotaxic coordinates were extracted and placed into one of the following groups primarily based on their involvement of a SAP or MAP cohort, then movement execution or movement imagery, and with or without chronic pain. Healthy controls were evaluated from each respective study. Due to lack of articles studying movement imagery or self-reported pain in the MAP cohort and limited by articles reporting of within-group stereotaxic coordinates, movement imagery and pain was solely analyzed in the SAP cohort.

ALE/Statistical Analysis

Individual stereotaxic coordinates were extracted from respective articles and stored into an excel sheet by the first reviewer. If stereotaxic coordinates were reported as Talairach coordinates, the BioImage Suite 2.0 MNI 2 Talairach Converter web application (BioImage Suite MNI<->TAL, 2020) was used to convert to MNI space. Coordinates were then converted into

FIGURE 2 | PRISMA flow diagram of search methodology for articles included in meta-analysis. SCI, Spinal Cord Injury; PD, Parkinson's disease.

txt format to be inserted into the software program, *GingerALE*. All coordinates were evaluated using the meta-analytic technique embedded in the *GingerALE* software program that evaluates the overlap between individual stereotaxic coordinates by modeling probabilistic distributions from their coordinate centers. From the generated probabilistic distributions, activation likelihood estimates are generated (see Eickhoff et al., 2009, Human Brain Mapping). A single dataset analysis *via GingerALE* was performed on each of the groups listed in **Table 2**. Contrast dataset analyses were performed under four connditions: (1) Altered afferent feedback during movement execution: comparing SAP cohort relative to healthy controls), (2) Altered afferent feedback in persons *with pain* during movement execution: SAP cohort with pain relative to healthy controls, (3) Altered afferent feedback during movement imagery: SAP cohort relative to healthy controls, and (4) Altered efferent motor commands during movement execution: MAP cohort relative to healthy controls. The single dataset analysis had a cluster forming threshold of p=0.005. The contrast threshold was set to $p = 0.05$ with a minimum cluster volume of 200 mm^3. Brain regions reported in **Tables 5–7** used the Harvard-Oxford Cortical Structural Atlas and the Cerebellar Atlas in MNI152 space after normalization with FMRIB's (Functional Magnetic Resonance Imaging of the Brain) Non-linear Image Registration Tool (FNIRT) from the FSL (FMRIB Software Library) program (Douaud, 2016), reporting the label with the highest probability.

RESULTS

Database Search

Of the included studies, stereotaxic coordinates were extracted from 33 experiments, totaling 651 subjects and 968 coordinates. An example of the search methodology is included in **Table 3** to demonstrate how keywords were used to find related articles. Additionally, **Figure 2** displays the screening process of the database search as articles were excluded or kept for the meta- analysis.

Studies used for SAP cohort included SCI and amputee participants with or without chronic pain and healthy controls performing a movement execution or movement imagery task. The tasks that ranged from simple (plantar flexion) to moderate (hand movement tasks) difficulty. Imaging modalities used were either PET or fMRI. All included studies were a level II cohort study using levels of evidence pyramid by Forrest and Miller (Forrest and Miller, 2016) (see **Supplementary Material S3**). Some studies were rated as fair quality due to differences in the study population, lack of inclusion or exclusion criteria, or lack of statistical adjustment for confounding variables. See **Table 4** for characteristics of studies for SAP.

Studies used for MAP included participants with Parkinson's disease and dystonia without pain and healthy controls performing a movement execution task. The tasks performed ranged from simple (finger tapping) to complex (writing). Imaging modalities used were either PET or fMRI. All included studies were a level II cohort study using levels of evidence pyramid by Forrest and Miller (Forrest and Miller, 2016) (see **Supplementary Material S3**). Some studies were rated as fair

TABLE 2 | List of groups and abbreviations for single dataset analysis.

	Group	Abbreviation
SAP	Healthy controls—movement execution	HC ME
	Healthy controls—movement imagery	HC MI
	Sensory altered processing without pain—movement execution	SAP NP ME
	Sensory altered processing without pain—movement imagery	SAP NP MI
	Sensory altered processing with pain—movement execution	SAP w/P ME
MAP	Healthy controls—movement execution	HC ME
	Motor altered processing—movement execution	MAP ME

SAP, Sensory Altered Processing; MAP, Motor Altered Processing.

TABLE 3 | Example of keyword search methodology used to identify studies for meta-analysis.

Search stage	Search terms	Number of hits
1	"Spinal Cord Injuries" [Mesh]	58,950
2	"Magnetic Resonance Imaging" [Mesh]	576,654
3	Movement execution	14,101
4	Spinal cord injuries AND magnetic execution	Resonance imaging AND movement 7

quality due to differences in the study population, lack of inclusion or exclusion criteria, or lack of statistical adjustment for confounding variables. See **Table 5** for characteristics of studies for MAP.

Meta-Analysis

See **Tables 6–8** for significant results found in activated brain regions with stereotaxic coordinates in MNI space identified by the ALE meta-analyses.

SAP Cohort Analysis Results

See **Tables 6, 7** for more detailed information of activation clusters. A peak activation was found in the right precentral gyrus and the left juxtapositional lobule cortex for the movement execution contrast HC > SAP NP. A peak activation was found in the right juxtapositional lobule cortex and the left precentral gyrus for the movement execution contrast SAP NP > HC. One activation peak was found in the right juxtapositional lobule cortex for the movement execution contrast SAP NP > SAP w/P. One activation peak was found in the left superior parietal lobule for the movement execution contrast SAP w/P > SAP NP (see **Figure 3**). One activation peak was found in the left juxtapositional lobule cortex for the movement imagery contrast HC > SAP NP. No activations were found in the movement imagery contrast SAP NP > HC.

TABLE 4 | Characteristics of studies included in the meta-analysis measuring cortical activity during movement imagery and movement execution in SAP.

	Study	NIH QR	Imaging modality	Participants (n)	Task performed
SAP					
SCI	Curt et al. (2002)	Good	PET	SCI NP (7), HC (8)	Exec: R wrist extension
	Cramer et al. (2005)	Fair	fMRI	SCI NP (12), HC (12)	Exec: R plantar flexion MI: R plantar flexion
	Hotz-Boendermaker et al. (2008)	Good	fMRI	SCI NP (9), HC (12)	Exec: R dorsal and plantar flexion MI: R dorsal and plantar flexion
	Alkadhi et al. (2005)	Good	fMRI	SCI NP (8), HC (8)	Exec: R dorsal and plantar flexion MI: R dorsal and plantar flexion
Limb amputation	Roux et al. (2003)	Fair	fMRI	Amp PLP (10), HC (10)	Exec: R and L flexion and extension of fingers or toes
	Diers et al. (2010)	Good	fMRI	Amp PLP (7), Amp Non-PLP (7), HC (9)	Exec: R and L make a fist MI: R and L make a fist
	Lotze et al. (2001)	Good	fMRI	Amp PLP (7), Amp Non-PLP (7), HC (7)	Exec: R and L make a fist MI: R and L make a fist
	MacIver et al. (2008)	Good	fMRI	Amp PLP (13), HC (6)	Exec: R and L opening and closing of a fist MI: R and L opening and closing of a fist
	Raffin et al. (2012)	Fair	fMRI	Amp Non-PLP (14)	Exec: R and L opening and closing of a fist MI: R and L opening and closing of a fist
	Zheng et al. (2021)	Good	fMRI	Amp PLP (10), Amp Non-PLP (10), HC (10)	Exec: R and L movement of big toe MI: R and L movement of big toe
	Romero-Romo et al. (2010)	Fair	fMRI	Amp Non-PLP (6), HC (6)	Exec: R and L flexion and extension of toes MI: R and L flexion and extension of toes
	Duarte et al. (2020)	Good	fMRI	Amp PLP (18)	Exec: R and L dorsal and plantar flexion
	Foell et al. (2013)	Fair	fMRI	Amp PLP (11)	Exec: Lip pursing and R and L hand movement tasks
	Yu et al. (2014)	Good	fMRI	Amp Non-PLP (6)	Exec: R and L tapping toes

NIH, National Institutes of Health; QR, Quality Rating; SAP, Sensory Altered Processing; SCI, Spinal Cord Injury; Amp, Amputee; PLP, Phantom Limb Pain; Non-PLP, Non-Phantom Limb Pain; HC, Healthy Controls; NP, No Pain; fMRI, functional Magnetic Resonance Imaging; PET, Positron Emission Tomography; Exec, Movement Execution; MI, Movement Imagery; R, right; L, left.

MAP Cohort Analysis Results

See **Table 8** for more detailed information of activation clusters. Five activation peaks were found in the movement execution contrast HC > MAP. Four activation peaks were found in the movement execution contrast MAP > HC (see **Figure 4**).

DISCUSSION

Brain activity in persons with atypical afferent input from peripheral nerve or spinal cord injury is modulated based on the presence of pain. Sensorimotor integration is tightly coupled in the central nervous system and depends on feedback from the peripheral nervous system for proprioceptive input. The primary motor cortex is extensively interconnected with descending pain modulatory regions and sensory processing areas of the brain (Holmes et al., 2021). It remains unclear how the presence of pain modulates central nervous system activity in persons with spinal cord injuries or limb loss. In this ALE meta-analysis, we show (1) that the supplementary motor area has greater activity in persons with atypical afferent activity in persons with *no pain* vs. *in pain*, and (2) that above-normal efferent motor activity is associated with decreased activity in brain regions involved

in affective processing. Findings are outlined in the context of sensorimotor integration.

Changes in Afferent Input and the Perception of Pain

Motor regions are active in persons who do not report elevated pain. The SMA is a brain region located anterior to M1 and is involved in motor planning and learning and prediction (Makoshi et al., 2011). We offer two suggestions for observed differences in brain activity (1) an attempt to engage descending pain modulatory regions of the brain that are downstream from motor-regions or (2) the motor system updating itself to the absence of limb proprioceptive input to sustain behavioral goals and rectify discrepant motor programs.

Engagement of motor regions within the brain, either through endogenous or exogenous sources, have shown to be effective sources of analgesia (Holmes et al., 2021). The use of repetitive transcranial magnetic stimulation or physical therapy-based programs have shown possible to decrease pain symptoms through motor-based approaches (Gatzinsky et al., 2021). At a network level, engagement of the motor system (e.g., M1)

TABLE 5 | Characteristics of studies included in the meta-analysis measuring cortical activity during movement execution in MAP.

	Study	NIH QR	Imaging modality	Participants (*n*)	Task performed
MAP					
Dystonia	de Vries et al. (2008)	Good	fMRI	Dys (8), HC (9)	R wrist flexion/extension, fist clenching
	Kadota et al. (2010)	Good	fMRI	Dys (7), HC (10)	R and L hand tapping
	Preibisch et al. (2001)	Good	fMRI	Dys (12), HC (10)	R writing
	Lerner et al. (2004)	Good	PET	Dys (10), HC (10)	R hand tapping, writing
	Ibáñez et al. (1999)	Fair	PET	Dys (7), HC (7)	R hand tapping, writing, fist sustained contraction
	Ceballos-Baumann et al. (1995)	Good	PET	Dys (6), HC (6)	R hand joystick movement
	Playford et al. (1998)	Good	PET	Dys (6), HC (6)	R hand joystick movement
Parkinson's disease	Baglio et al. (2011)	Good	fMRI	PD (15), HC (11)	R finger button press
	Cerasa et al. (2006)	Good	fMRI	PD (10), HC (11)	R finger tapping
	Haslinger et al. (2001)	Good	fMRI	PD (8), HC (8)	R hand joystick movement
	Katschnig et al. (2011)	Good	fMRI	PD (20), HC (20)	R and L ankle dorsiflexion
	Kraft et al. (2009)	Good	fMRI	PD (12), HC (12)	R and L hand button press
	Maillet et al. (2012)	Good	fMRI	PD (12)	R hand joystick movement
	Mallol et al. (2007)	Good	fMRI	PD (13), HC (11)	R and L hand movements
	Sabatini et al. (2000)	Fair	fMRI	PD (6), HC (6)	R finger to thumb opposition, making and clenching fist
	Yu et al. (2007)	Good	fMRI	PD (8), HC (8)	R thumb button pressing
	Zhao et al. (2014)	Good	fMRI	PD (21), HC (22)	R finger tapping
	Yan et al. (2015)	Fair	fMRI	PD (11), HC (12)	R and L finger to thumb opposition
	Schwingenschuh et al. (2013)	Good	fMRI	PD (20), HC (10)	R and L ankle dorsiflexion

NIH, National Institutes of Health; QR, Quality Rating; MAP, Motor Altered Processing; Dys, Dystonia; PD, Parkinson's Disease; HC, Healthy Controls; fMRI, functional Magnetic Resonance Imaging; PET, Positron Emission Tomography; R, right; L, left.

TABLE 6 | Activated brain regions within each between-group contrast for SAP performing a movement execution task.

	Cluster #	Volume mm³	*P*-value	*Z*-value	x, y, z	Brain region
Movement execution in SAP cohort						
HC > No pain	1	2,752	0.0076	2.43	49.8, 2.9, 13.4	R Precentral Gyrus
	2	2,040	0.0033	2.72	−9.6, 0, 45	L Juxtapositional Lobule Cortex (SMA)
No pain > HC	1	800	0.0041	2.64	9.4, −6, 68.8	R Juxtapositional Lobule Cortex (SMA)
	2	384	0.0052	2.56	−36, −22, 56	L Precentral Gyrus
No pain > pain	1	888	0.0094	2.35	6.8, −6.5, 70.8	R Juxtapositional Lobule Cortex (SMA)
Pain > No pain	1	936	0.0312	1.86	−28, −40, 54	L Superior Parietal Lobule

MNI coordinates (x, y, z) of brain regions surviving a cluster threshold of p < 0.05 for contrast studies and a cluster forming threshold for p < 0.005 for single studies. SAP, Sensory Altered Processing; HC, Healthy Controls; NP, No Pain; w/ P, with Pain; L, Left; R, Right; ALE, Activation Likelihood Estimate. Brain labels automatically generated in GingerALE using the MNI space.

TABLE 7 | Activated brain regions within each between-group contrast for SAP performing a movement imagery task.

	Cluster #	Volume mm³	*P*-value	*Z*-value	x, y, z	Brain region
Movement imagery of SAP cohort						
HC > no pain	1	3,224	0.0024	2.82	0, 0, 60	L Juxtapositional Lobule Cortex (SMA)
No pain > HC	−	−	−	−	−	−

MNI coordinates (x, y, z) of brain regions surviving a cluster threshold of p<0.05 for contrast studies and a cluster forming threshold for p < 0.005 for single studies. SAP, Sensory Altered Processing; HC, Healthy Controls; NP, No Pain; L, Left; ALE, Activation Likelihood Estimate. Brain labels automatically generated in GingerALE using the MNI space.

TABLE 8 | Activated brain regions within each between-group contrast for MAP cohort performing a movement execution task.

	Cluster #	Volume mm^3	P-value	Z-value	x, y, z	Brain region
HC > MAP Cohort						
	1	1,552	0.0018	2.91	−12, 2, 60	L Superior Frontal Gyrus
	2	1,360	0.003	2.75	−20, −22, −4	L Thalamus
	3	816	0.0058	2.52	−42, −4, 8	L Insular Cortex
	4	560	0.0045	2.61	58, −36, 22	R Planum Temporale, R Supramarginal Gyrus, posterior division
	5	312	0.0193	2.07	−42, −36, 60	L Postcentral Gyrus
MAP cohort > HC	1	608	0.0273	1.92	30, −68, −32	R Cerebellum Crus I
	2	448	0.0234	1.99	39, −46, 41	R Supramarginal Gyrus, posterior division
	3	360	0.0039	2.66	30, −18, 50	R Precentral Gyrus
	4	208	0.0231	1.99	−8, −50, −26	L Cerebellum I–IV

MNI coordinates (x, y, z) of brain regions surviving a cluster threshold of p < 0.05 for contrast studies and a cluster forming threshold for p < 0.005 for single studies. MAP, Motor Altered Processing; HC, Healthy Controls; L, Left, R, Right; ALE, Activation Likelihood Estimate. Brain labels automatically generated in GingerALE using the MNI space.

can produce downstream effects on descending pain modulatory regions (e.g., periaqueductal gray) that may act through the brain stem, locus coeruleus, nucleus raphe magnus, and nucleus reticularis gigantocellularis to decrease pain symptoms (Holmes et al., 2021). Findings from the current investigation contrast what would be predicted from this hypothesis as no sub-cortical regions were reported when comparing persons with atypical afferent input with and without pain. Notably, this may be due to the meta-analytic nature of this investigation and loss of statistical resolution. Follow-up investigations that include online neuroimaging to differentiate nociceptive input from pain symptom reporting will be required to fully test this hypothesis.

Atypical afferent processing of nociceptive stimuli may drive motor planning. Comparing cohorts with altered afferent input based on the presence or absence of pain suggests a role for peripherally derived updating of motor programs. That is, M1 has immense connectivity with S1 through corticocortical connectivity, direct connectivity, sub-cortical relays and through peripheral engagement of motor units and sensory neurons (Umeda et al., 2019). The absence, or diminished capacity, of the motor system in persons with a physical disability due to limb loss or spinal cord injury may trigger the SMA to engage novel motor programs that sustain, or attempt to sustain, task goals (Makoshi et al., 2011). Alternatively, having been recently recognized to have a role in the attentional modulation of pain, a continued increased activity within the left superior parietal lobule (Makoshi et al., 2011) could suggest a "voluntary" amplification of attention toward stimuli during movement. While suffering from chronic pain conditions, increased attention to pain (McCracken, 1997; Bushnell et al., 2013) during movement could lead to a conditioned expectation of pain from a motor execution task that produces no noxious stimuli. In other words, the anticipation of pain (Poppe et al., 2011; Zeidan et al., 2015) becomes a learned behavior in which any motor activity can act as a pain-predictive cue and subsequent movements can drive motor relearning in the

context of pain (Dancey et al., 2016). Increased activity with the SMA would suggest engagement of motor planning structures that could be used to tune motor control in line with sensory feedback. This highlights the potential of physical exercise interventions to target both the physical and cognitive experience of pain in programs designed to stress rehabilitative sensorimotor integration.

Changes in Efferent Output and Pain Connectome Suppression

Changes observed in the cohort with atypical efferent motor control may offer insight into the role of the motor system in pain processing. Uncoupling of S1-M1 functional communication has been observed in hyper-kinetic movement disorders such as dystonia (Melgari et al., 2013). Along the lines of a centrally mediated source for elevated motor output, the ALE analysis revealed increased activity in the right precentral gyrus which is a region implicated in the initiation and control of voluntary movement (Papale and Hooks, 2018). Two ALE clusters of the left cerebellum lobules I-IV and the right cerebellum Crus I in subjects with MAP suggests attempts at rectifying incongruence between sensory and motor processes (Stoodley et al., 2012; Mehnert and May, 2019) and online adjustments to motor output.

Decreased activity was found in persons with atypical efferent processing relative to healthy controls in regions implicated in the pain connectome (Kucyi and Davis, 2015; Coghill, 2020). Most salient differences were found in left thalamus and the left postcentral gyrus which have roles in the primary interception of afferent sensory input to the brain (Yen and Lu, 2013). Decreased activity was also observed in the left insular cortex, a region that links sensory experience with emotional value (Nieuwenhuys, 2012) and has been shown to have increased activity in persons with chronic pain (Starr et al., 2009). Observations of decreased activity within the left superior frontal gyrus, a region involved in working memory that influences decision making and goal-driven behavior (du Boisgueheneuc
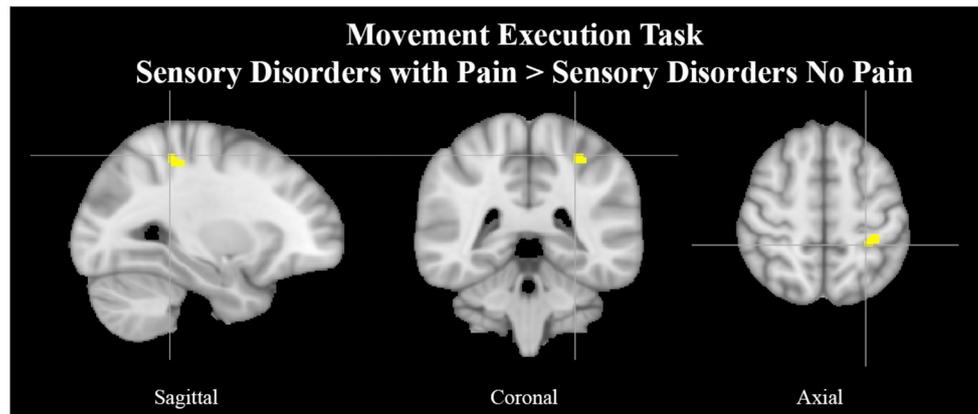
FIGURE 3 | Left superior parietal lobule activation in SAP cohort with pain. Exemplar of a between-group activation peak of the movement execution contrast SAP w/P > SAP NP. Yellow-colored regions show increased brain activity in the left superior parietal lobule (cross-hairs reflect peak activation peak $x = -28$, $y = -40$, $z = 54$). SAP, Sensory Altered Processing; w/P, with Pain; NP, No Pain.
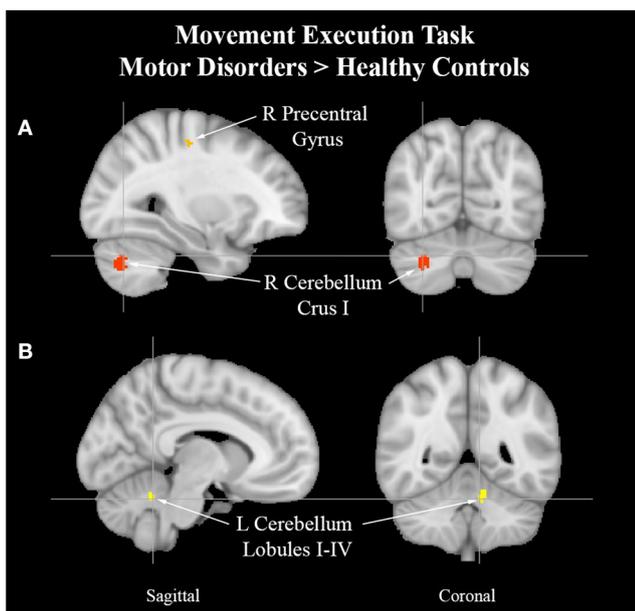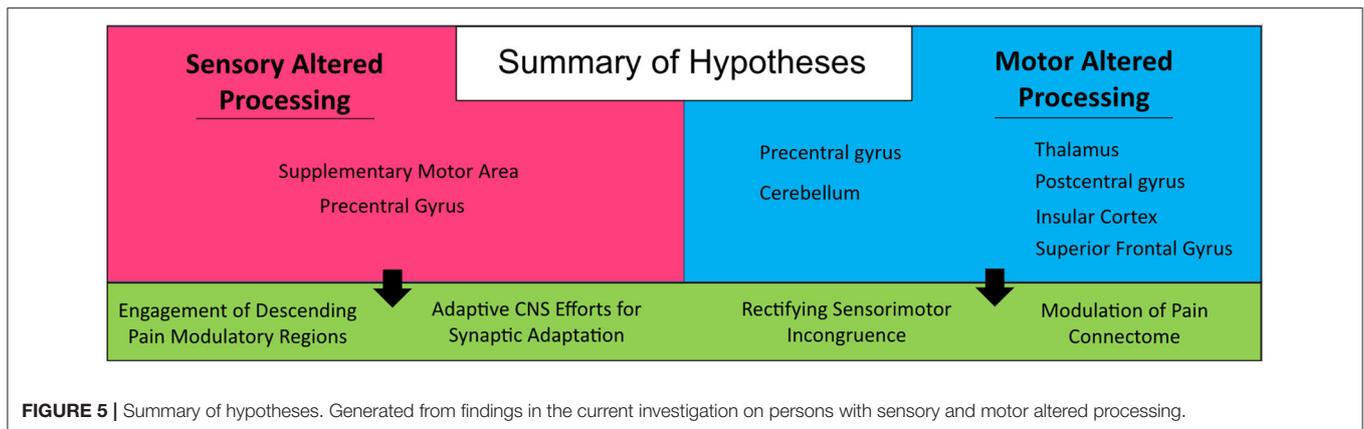

FIGURE 4 | Cerebellum activation peaks in MAP cohort. Exemplar of between-group activation peaks of the movement execution contrast MAP > HC. A. Orange-colored region shows increased brain activity in the right precentral gyrus. Red-colored regions show increased brain activity in the right cerebellum Crus I (cross-hairs reflect activation peak $x = 30$, $y = -68$, $z = -32$). B. Yellow-colored regions show increased brain activity in the left cerebellum lobules I–IV (cross-hairs reflect activation peak $x = -8$, $y = -50$, $z = -26$).

et al., 2006) may provide insight to the nature of the hyper-kinetic movement disorders included, placing emphasis on lower order central nervous system regions such as M1 and sub-cortical structures including the basal ganglia (Mink, 2003). Alternatively, observed depression of activity within frontal

structures may underscore a relative ease of engaging motor processes in persons with sustained output, as a form of motor practice (Wright et al., 2012). Observing mirrored activation of the precentral gyrus and juxtapositional lobule cortex in opposite hemispheres amongst the SAP with no pain cohort and healthy controls may reflect inter-hemispheric functional compensatory adaptation. In particular, such patterns of activation have been observed in cases of stroke where the intact contralateral representation of the ipsilateral lesion may show greater relative activation in response to the damaged area to preserve behavior performance (Takatsuru et al., 2013). More recent data suggests that this process of contralateral may be inflammatory-mediated as inflammation has been observed in regions contralateral to a primary lesion site (Lucas-Ruiz et al., 2021), perhaps giving insight into modulating the local synaptic environment and the suppression of motor system activity in the SAP cohort experiencing chronic pain. We suggest that the alterations observed in the sensorimotor system likely interfere with the distributed nociceptive system which could impact the way that nociceptive stimuli are processed into pain symptom reporting.

Integrating Perspectives

The motor system has an important role in pain management. Acute pain, which comes on quickly and lasts for a short time (<3 months) as opposed to the long-lasting nature of chronic pain (>3 months), has been shown to have an inhibitory effect on the motor cortex (Boudreau et al., 2007; Mercier and Léonard, 2011). However, the relationship of chronic pain and motor cortex reorganization is more complex and unclear whether one causes the other. Chronic pain, either in terms of prolonged nociceptive input or through central sensitization, can have a debilitating impact on human motor behavior that is often neglected in pain treatment services. This negative motor-effect can have malignant tendencies, translating into social isolation, devolving mental health, and potential life-threatening health conditions. The focus of this investigation was to provide

FIGURE 5 | Summary of hypotheses. Generated from findings in the current investigation on persons with sensory and motor altered processing.

hypothesis generating analyses pertaining to the relative impact on the brain of atypical efferent and afferent processing of motor and sensory information, respectively. Findings provide support for four hypotheses between the two cohorts evaluated in this investigation (see **Figure 5**) and provide insight into the impact of motor processes on central brain regions implicated in nociceptive processing. First, increased engagement of the supplementary motor area in persons in the SAP cohort suggests a prominent role for the motor system in responding to pain, either in terms of engaging pain modulatory regions (Hypothesis 1) or in terms of engaging adaptive motor programs in response to elevated nociceptive signaling, minimizing the use of motor programs that result in pain (Hypothesis 2). Alternatively, in the MAP cohort, there is evidence to suggest again attempts at adaptation, but focused on incongruence between deficient motor programs and sensory expectations (Hypothesis 3) and the intended suppression of brain regions (e.g., Thalamus) implicated in pain processing (Hypothesis 4). Notably, these hypotheses are not mutually exclusive, and are conceptually mirrored between cohorts (focused on adaptation and pain modulation). Repetitive occurrence of pain can form a type of muscle memory within the nociceptive system, perhaps resulting from failures at engaging adaptive circuitry or pain modulatory regions that leaves individuals more susceptive to the development of chronic pain conditions (Garcia-Larrea and Bastuji, 2018; McCarberg and Peppin, 2019). As physical therapy regimens have proved to be helpful in the treatment of both sensory and motor disorders (Allen et al., 2015; Borisovskaya et al., 2020; Zaheer et al., 2021), we suggest the motor system may also play an important role in chronic pain management, in terms of both adaptive motor programs and pain modulatory efforts.

LIMITATIONS

There are limitations that require mention based on the ALE meta-analytic approach adopted: (1) included cohorts: atypical afferent and efferent processing represents the basis for a large myriad of neurological conditions. Including other conditions such as multiple sclerosis or amyotrophic lateral sclerosis may impact the specificity of current findings; (2)

hemispheric laterality: based on the limited sample of articles and bilateral projections of sensory and motor circuits, we elected not to split our data based on affected limb; (3) reporting bias: based on the secondary data analysis approach we are limited to the reported data of each study. However, these may be limited to within-group, rather than between-group, stereotaxic coordinates, no reporting of pain, differential reporting basis of pain symptoms, and different clinical standards for neurological disorders.

CONCLUSION

Central nervous system processing of nociceptive input is the basis for understanding acute and chronic pain. To date, research and clinical interests has focused on the primary reception and distributed nature of nociception on the brain; however, there is growing interest on the impact of efferent motor processes on sensory processing. Looking on the other side of sensory processing offers a non-pharmacological source of analgesia that has transcending impacts on physical and mental health. Findings from this investigation point toward an important role of efferent motor processes on dampening central processing of nociception and motor learning in the context of pain.

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

Study conception and design, analysis and interpretation of results, and draft manuscript preparation: CG and SH. Data collection: CG. Both authors reviewed the results and approved the final version of the manuscript.

FUNDING

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnint. 2022.931292/full#supplementary-material

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