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SPECIALTY SECTION

This article was submitted to
Cognition,
a section of the journal
Frontiers in Psychology

RECEIVED 19 July 2022

ACCEPTED 31 August 2022

PUBLISHED 28 September 2022

CITATION

Redondo-Camós M, Cattaneo G,
Alvarez-Schulze V, Delgado-Gallén S,
España-Irla G, Solana-Sanchez J,
Perellón-Alfonso R, Albu S, Tormos JM,
Pascual-Leone A and Bartres-Faz D (2022)
Long-interval intracortical inhibition in
primary motor cortex related to working
memory in middle-aged adults.
Front. Psychol. 13:998062.
doi: 10.3389/fpsyg.2022.998062

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Long-interval intracortical inhibition in primary motor cortex related to working memory in middle-aged adults

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Introduction: Excitability of the primary motor cortex measured with TMS has been associated with cognitive dysfunctions in patient populations. However, only a few studies have explored this relationship in healthy adults, and even fewer have considered the role of biological sex.

Methods: Ninety-seven healthy middle-aged adults (53 male) completed a TMS protocol and a neuropsychological assessment. Resting Motor Threshold (RMT) and Long-Interval Intracortical Inhibition (LICI) were assessed in the left motor cortex and related to attention, episodic memory, working memory, reasoning, and global cognition composite scores to evaluate the relationship between cortical excitability and cognitive functioning.

Results: In the whole sample, there was a significant association between LICI and cognition; specifically, higher motor inhibition was related to better working memory performance. When the sample was broken down by biological sex, LICI was only associated with working memory, reasoning, and global cognition in men. No associations were found between RMT and cognitive functions.

Conclusion: Greater intracortical inhibition, measured by LICI, could be a possible marker of working memory in healthy middle-aged adults, and biological sex plays a critical role in this association.

KEYWORDS

transcranial magnetic stimulation, electromyography, long-interval cortical inhibition, motor cortex, cognition, resting motor threshold

Introduction

The balance of cortical excitation and inhibition (E/I balance) is a core neurophysiologic metric of neuronal and brain network activity believed to determine optimal brain functioning (Sukenik et al., 2021). In patient populations, including autism spectrum disorders or schizophrenia, an E/I imbalance has been observed in different cortical areas and shown to be associated with behavioral and cognitive symptoms (Sohal and Rubenstein, 2019; Bruining et al., 2020; Calvin and Redish, 2021; Maestú et al., 2021). In Alzheimer's disease, cortical motor hyperexcitability has been negatively related to cognitive performance (Zadey et al., 2021), possibly due to enhanced intracortical excitatory circuits (Di Lazzaro et al., 2004; Meder et al., 2021) or/and an inhibitory deficit (Khedr et al., 2011; Pennisi et al., 2011; Joseph et al., 2021; Mimura et al., 2021).

Past research exploring cortical excitability and cognition has produced inconsistent results in healthy, cognitive-unimpaired adults. This variability may be due to differences depending on the cortical area or specific cognitive functions assessed. For example, while higher excitability after stimulation of the left prefrontal cortex has been related to better executive functions and working memory (Redondo-Camós et al., 2022), other studies have observed that excessive excitability of the primary motor cortex was associated with impaired attention and global cognition (Bolden et al., 2017; Akilan et al., 2020). Other aspects that may modulate the association between cortical E/I balance and cognitive functioning may relate to age, given the different degrees of preservation of gamma-aminobutyric acid (GABA) circuits linked to physiological aging (McGinley et al., 2010; Opie and Semmler, 2014; Hermans et al., 2018). Indeed, age-related cortical excitability changes have been previously linked to differences in attention and inhibitory control in healthy adults (Cespón et al., 2022). Also, biological sex could play a key role since differences in brain anatomy and connectivity between men and women, as well as hormonal influences associated with menstrual cycle variations in women, may lead to distinct neural processes involved in cognitive and motor control (Korzhyk et al., 2019; Rezzani et al., 2019). Gender-associated differences could be due to genetic determinants, lifestyle factors including physical activity, alcohol, or tobacco consumption (Rezzani et al., 2019; Travica et al., 2020), or steroid hormone levels, which are higher in women and have been related to GABA neurotransmission, mood and memory (Cosgrove et al., 2007; Rezzani et al., 2019).

Transcranial Magnetic Stimulation (TMS) combined with Electromyography (EMG) is a widely used technique to study inhibitory and excitatory mechanisms in the motor cortex

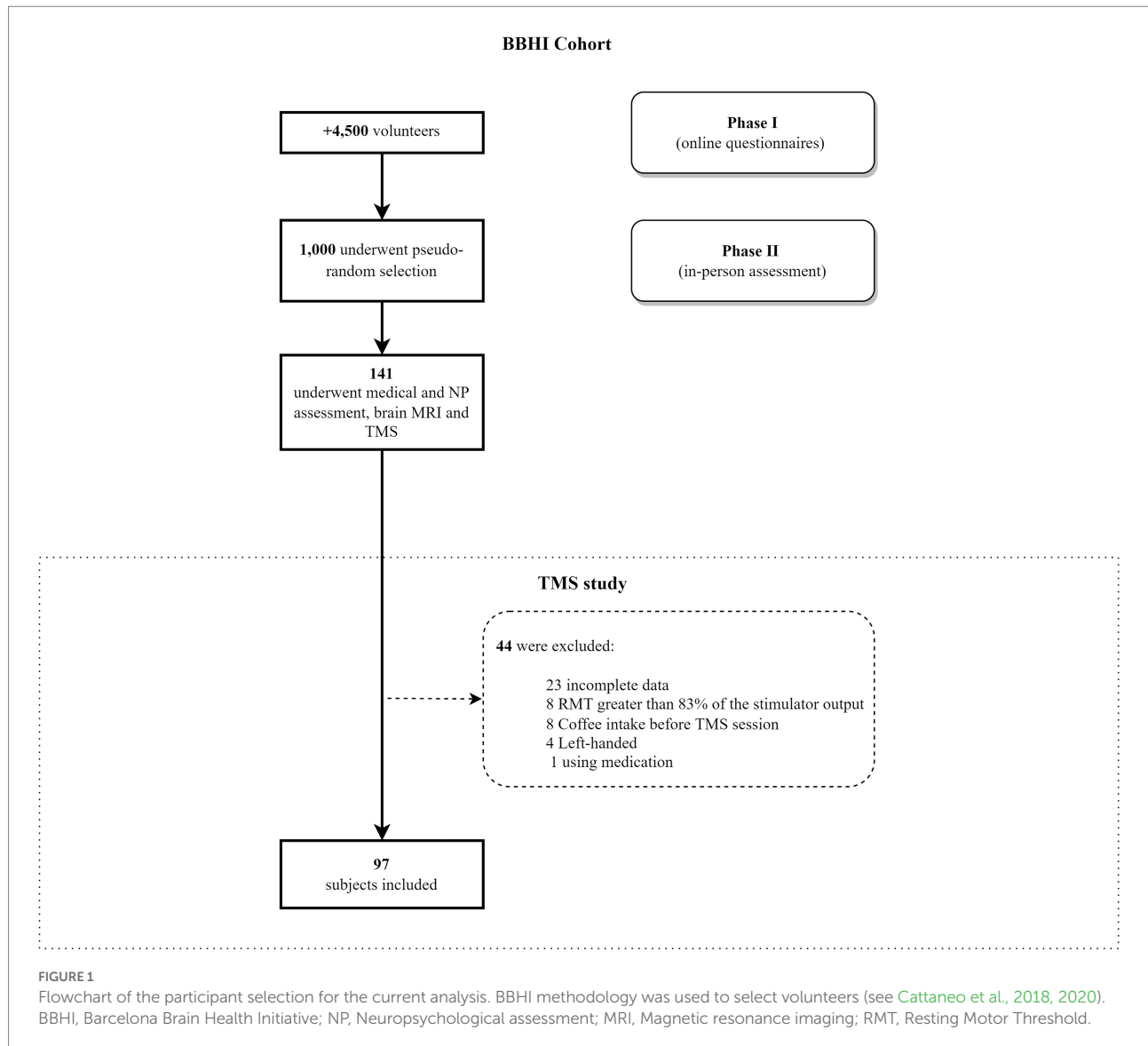
(Kobayashi and Pascual-Leone, 2003; Ferreri and Rossini, 2013). Specifically, single-pulse TMS (spTMS) has been used to explore cortical excitability by measuring Resting Motor Threshold (RMT), which is the minimum intensity that elicits a Motor Evoked Potential (MEP) of more than 50 μ V in 50% of trials (Rossini et al., 2015). Long-Interval Intracortical Inhibition (LICI), where two suprathreshold stimuli separated by an interstimulus interval (ISI) between 50 and 200 ms are applied, has been used to study cortical inhibition (Valls-Solé et al., 1992; Nakamura et al., 1997) and reflects the activity of GABA-B receptors (McDonnell et al., 2006; Opie et al., 2017). While many studies have shown that RMT and LICI offer valuable biological markers in different neurological disorders (Fatih et al., 2021; Guerra et al., 2021; Mimura et al., 2021; Versace et al., 2021), only a few have explored their association with brain health and cognitive performance in healthy, cognitive-unimpaired, middle-aged adults, and how biological sex affects the results (Schickanz et al., 2014; Akilan et al., 2020).

This study aimed to fill this knowledge gap by investigating the relationship between E/I balance in the primary motor cortex measured with RMT and LICI and cognition in healthy middle-aged adults. Since the GABA-B receptor might be a target for improving cognitive dysfunction and memory/learning impairment (Vlachou, 2022), we hypothesized that better cognitive performance would be associated with more intracortical inhibition, estimated with LICI, and reduced cortical excitability, measured with RMT. Also, differences between women and men were expected, at least for LICI, considering biological sex differences in GABA neurotransmitters highlighted above.

Materials and methods

Subjects and study design

Ninety-seven healthy and right-handed volunteers [53 male; laterality $\geq 75\%$, (Oldfield, 1971)], between 41 and 65 years ($M = 54$; $SD = 7.14$), participated in this study. They were part of the Barcelona Brain Health Initiative (BBHI), an ongoing, longitudinal cohort study (Cattaneo et al., 2018). They underwent a TMS session with EMG registration and neuropsychological testing. Exclusion criteria included any neurological or psychiatric diagnosis, currently taking medication that could affect the central nervous system, substance abuse or dependence (alcohol, caffeine, drugs), pregnancy (Rossini et al., 2015; Rossi et al., 2021), and any contraindication for TMS or magnetic resonance imaging (MRI). All participants gave written informed consent, and the local



ethics committee (Comité d'Ètica i Investigació Clínica de la Unió Catalana d'Hospitals) approved the study protocol, which followed the Declaration of Helsinki. A cohort diagram from the BBHI study and the specific selection of this study participants is shown in Figure 1.

TMS protocol

Participants were asked to sit as still as possible in a comfortable armchair, keep their eyes open, and look at a fixation cross at a distance of approximately 1.5 m. A figure of eight TMS coil was placed at a 45-degree angle (relative to the mid-sagittal plane) over the left primary motor cortex (left-M1), resulting in a posterior-to-anterior current flow. Consistency in the stimulation targeting was ensured using a frameless stereotactic neuronavigation system (Brainsight, Rogue Research Inc.,

Montreal, QC Canada) guided by each subject's T1 weighted structural MRI (previously obtained from a 3 T Siemens Magnetom Prisma). MRI was completed for this purpose to increase safety during TMS sessions and exclude any brain lesion that could act as a confounder in interpreting the results.

The TMS procedure lasted approximately 1 h. First, RMT was determined as the minimum TMS intensity that elicited MEPs of more than 50 μ V in five out of 10 trials in the relaxed, contralateral first dorsal interosseus muscle (FDI; Rossini et al., 2015). MEP amplitude was defined as the peak-to-peak difference in EMG activity from the evoked response in this muscle. Next, 120 paired-pulse TMS stimuli were delivered to the left-M1 at random intervals between 3 and 6 s. The intensities of both pulses were applied at 120% of RMT, and the ISI was 100 ms, selecting this interval because it was reportedly optimal (Sanger et al., 2001), and previous research has suggested age-related changes at it (McGinley et al., 2010; Opie et al., 2015, 2018). From this

stimulation, LICI was calculated using the following formula (Guerra et al., 2021):

$$LICI = \left(\frac{\text{MEP amplitude conditioned stimulus}}{\text{MEP amplitude unconditioned stimulus}} \right) * 100$$

Consequently, a greater LICI value indicates lower cortical inhibition, while a smaller LICI indicates greater inhibition.

The protocol was completed using a figure-of-eight Cool-B65 coil connected to a Medtronic MagPro X100 stimulator (MagVenture A/S, Denmark). For the electromyography, a Biopac EMG100C amplifier (BIOPAC Systems INC., California, United States) was used with surface electrodes placed in a belly-tendon montage and the ground electrode on the ulnar styloid.

Neuropsychological assessment

A licensed neuropsychologist performed a battery of neurocognitive paper and pencil evaluations. The battery included the following tests: Trail Making Test A and B (TMT) (Reitan and Wolfson, 1985; Peña-Casanova et al., 2012), Digit-Span Forward and Backward, Corsi block tapping test, Letter-Number Sequencing test (Peña-Casanova et al., 2012), Matrix Reasoning and Block design, the Digit symbol task, the Cancellation test (Wechsler, 2012), the Rey Auditory Verbal Learning Test (RAVLT; Schmidt, 1996; Alviarez-Schulze et al., 2022b), and the Spanish Version of the Face Name Associative Memory Exam (S-FNAME; Alegret et al., 2015; Alviarez-Schulze et al., 2022a).

Statistical analysis

All statistical analyses were performed in SPSS version 22.0 (Statistical Package for Social Sciences, Chicago, IL, United States).

First, raw scores of each cognitive test were z-score normalized, and principal component analysis (PCA) was run to group them into cognitive domains, in line with our and other research groups' previous studies (España-Irla et al., 2021; Cattaneo et al., 2022; Hinchman et al., 2022; Redondo-Camós et al., 2022). Loading values were above 0.3. Kaiser-Meyer-Olkin (KMO=0.689) and Bartlett's test of sphericity ($\chi^2=1074.67$, $df=105$; $p<0.001$) were satisfactory. PCA revealed four components of cognitive domains. The first factor contained TMT B (−0.927), TMT B-A (−0.884), TMT A (−0.615), Digit symbol task (0.554), and cancellation test (0.423), reflecting what can be considered an attentional domain. The second factor characterized memory and involved face name (0.609) and RAVLT measures such as immediate recall (0.885), delayed recall (0.872), and recognition (0.830). The third factor reflected a working memory domain and included the digit forward (0.780), digit backward (0.777), and letter-number sequencing (0.504). The

fourth factor contained Block design (0.758), Corsi blocks (0.678), and matrix reasoning (0.620), representing a reasoning component. Ultimately, a global cognition score was created as the sum of the individual z-scores on each neuropsychological test.

Cognitive composite scores were used as dependent variables (attention, working memory, episodic memory, reasoning, and global cognition) and RMT, LICI, MEP amplitude, age, biological sex, and years of education as predictors. We ran multiple multivariate regressions to identify possible associations between motor cortical excitability (measured by RMT), inhibition (LICI), and cognition. Then, for significant results, we ran multiple linear regressions to assess the direction of the prediction. Assumptions of linearity, independence of residuals, homoscedasticity, multicollinearity, and normality were met in all models. Furthermore, to study how biological sex could affect the predictions, we did all the previous analysis segmenting by biological sex. Lastly, to explore possible differences between means of women and men on each variable, a t-test analysis was performed.

Results

Sample descriptive statistics of RMT, LICI, MEP Amplitude, age, biological sex, and educational level are presented in Table 1, while cognitive scores are in Table 2.

Associations between RMT, LICI, and cognitive functions

Multivariate regression analysis for all the subjects revealed statistically significant associations between LICI and working memory [$F(1, 89)=7.59$, $p=0.007$; partial $\eta^2=0.079$], and biological sex and episodic memory [$F(1, 89)=9.50$, $p=0.003$; partial $\eta^2=0.0996$] and reasoning [$F(1, 89)=4.26$, $p=0.042$; partial $\eta^2=0.046$]. Finally, age was significantly associated to all

TABLE 1 Demographic Variables, RMT and LICI ($n=97$).

	All ($n=97$)		Male ($n=53$)		Female ($n=44$)		<i>p</i>
	Mean	SD	Mean	SD	Mean	SD	
Age	53.69	7.13	53.49	7.40	53.93	6.87	0.762
Years of education	17.85	3.81	17.66	4.17	18.07	3.35	0.595
RMT (%)	62.28	9.60	61.64	10.54	63.05	8.4	0.467
LICI (%)	14.68	18.81	17.35	20.33	11.46	16.45	0.118
MEP amplitude (mV)	0.305	0.201	0.309	0.173	0.323	0.232	0.747

RMT, resting motor threshold; LICI, long-interval intracortical inhibition; MEP, motor evoked potential.

TABLE 2 Cognitive scores ($n=97$).

Cognitive task	All ($n=97$)		Male ($n=53$)		Female ($n=44$)		p
	Mean	SD	Mean	SD	Mean	SD	
S-FNAME	41.62	14.65	39.00	14.12	44.77	14.81	0.054
RAVLT	52.19	9.65	50.60	9.93	54.10	9.06	0.074
immediate recall							
RAVLT	11.46	2.79	11.04	2.78	11.98	2.74	0.098
delayed recall							
RAVLT	14.28	1.25	14.17	1.27	14.41	1.23	0.348
recognition							
Digit-span forward	10.63	2.86	11.02	2.87	10.16	2.79	0.140
Digit-span backward	11.38	2.60	11.68	2.66	11.02	2.50	0.214
Corsi block tapping	14.35	2.41	14.38	2.51	14.32	2.31	0.904
Letter-number sequencing	5.72	1.08	5.66	1.14	5.80	1.00	0.542
Matrix reasoning	13.91	2.58	14.32	2.38	13.41	2.75	0.087
WAIS-IV							
Block design	12.00	3.14	12.74	3.01	11.11	3.10	0.011*
WAIS-IV							
TMT A	11.26	2.51	11.28	2.76	11.23	2.22	0.912
TMT B	8.65	2.18	8.91	2.14	8.34	2.22	0.208
Cancelation test	42.09	8.17	42.04	8.67	42.16	7.63	0.942
Digit symbol task	13.84	2.56	13.51	2.49	14.23	2.60	0.171

S-FNAME, Spanish Version of the Face Name Associative Memory Exam; RAVLT immediate recall, Recall a list of words immediately after hearing it of Rey Auditory Verbal Learning Test; RAVLT delayed recall, RAVLT recall after 30 min; RAVLT recognition, Recognition of words from a word list of RAVLT; Digit-Span Forward, Immediate recall a series of numbers in the same order; Letter-Number Sequencing, Sequence a random order of numbers and letter; Matrix Reasoning WAIS-IV, Logical sequences and series of Wechsler Adult Intelligence Scale-IV; Block Design WAIS-IV, Block Design of Wechsler Adult Intelligence Scale-IV; TMT B, Trail Making Test part B; TMT A, Trail Making Test part A; Digit symbol task, Digit symbol association; Cancelation test, cancelation task of WAIS-IV. All punctuations presented in this table are normalized scores except RAVLT tests that are raw scores.
* $p < 0.05$.

cognitive functions (attention [$F(1, 89) = 17.38, p < 0.001$; partial $\eta^2 = 0.163$], episodic memory [$F(1, 89) = 10.01, p = 0.002$; partial $\eta^2 = 0.101$], working memory [$F(1, 89) = 5.45, p = 0.022$; partial $\eta^2 = 0.058$], reasoning [$F(1, 89) = 6.66, p = 0.011$; partial $\eta^2 = 0.070$], and global cognition [$F(1, 89) = 14.50, p < 0.001$; partial $\eta^2 = 0.140$]).

After running this model, we ran a multiple regression to assess the direction of the prediction using the working memory domain as a dependent variable and LICl, RMT, MEP amplitude, age, biological sex, and education as regressors. The model significantly explained working memory performance,

[$F(6, 89) = 2.630, p = 0.021$, adj. $R^2 = 0.093$], and LICl resulted negatively associated with it (Standardized $\beta = -0.282, t = -2.754, p = 0.007$), being greater motor cortical inhibition related to better working memory (Figure 2).

Effect of biological sex

To investigate possible differences in the association between cognitive performance and cortical E/I, we split the sample according to biological sex and repeated regressions for both groups.

Men

Multivariate regressions were done to test the direct effects of RMT, LICl, MEP amplitude, and covariates on each cognitive domain. They revealed an association between LICl and working memory [$F(1, 47) = 6.60, p = 0.013$, partial $\eta^2 = 0.123$], reasoning [$F(1, 47) = 5.82, p = 0.020$, partial $\eta^2 = 0.110$], and global cognition [$F(1, 47) = 9.22, p = 0.004$, partial $\eta^2 = 0.164$]. Also, education was related to reasoning [$F(1, 47) = 6.02, p = 0.018$, partial $\eta^2 = 0.114$] and episodic memory [$F(1, 47) = 4.15, p = 0.047$, partial $\eta^2 = 0.081$], and age to all cognitive domains (attention [$F(1, 47) = 4.18, p = 0.047$; partial $\eta^2 = 0.082$], episodic memory [$F(1, 47) = 8.37, p = 0.006$; partial $\eta^2 = 0.151$], working memory [$F(1, 47) = 4.64, p = 0.03$; partial $\eta^2 = 0.090$], reasoning [$F(1, 47) = 9.01, p = 0.004$; partial $\eta^2 = 0.161$], and global cognition [$F(1, 47) = 7.40, p = 0.009$; partial $\eta^2 = 0.136$]).

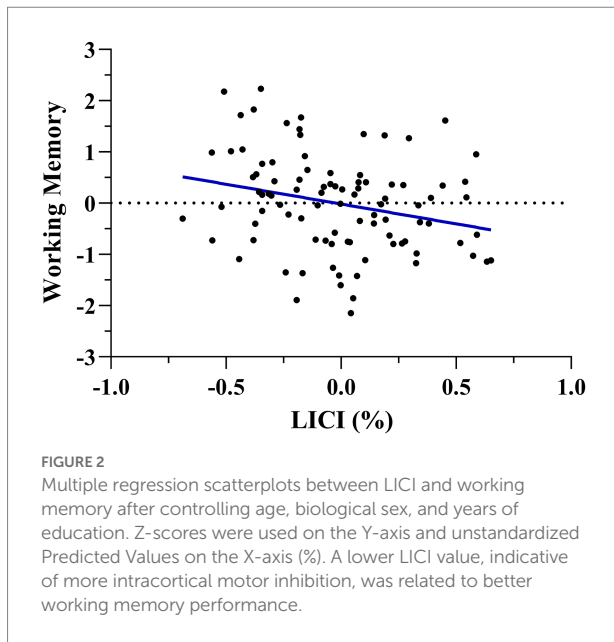
Furthermore, multiple regression models including covariates showed that working memory was associated with LICl (Standardized $\beta = -0.347, t = -2.569, p = 0.013$) and age (Standardized $\beta = 0.284, t = 2.155, p = 0.036$). Also, reasoning was related to LICl (Standardized $\beta = -0.302, t = -2.411, p = 0.020$), age (Standardized $\beta = -0.367, t = -3.022, p = 0.004$) and education level (Standardized $\beta = 0.307, t = 2.454, p = 0.018$). Finally, global cognition was also associated with LICl (Standardized $\beta = -0.380, t = -3.036, p = 0.004$) and age (Standardized $\beta = -0.332, t = -2.721, p = 0.009$). In all three models, LICl was negatively associated with working memory, reasoning, and global cognition in men (Figure 3).

Women

Only were significant associations between age and attention [$F(1, 37) = 11.65, p = 0.002$; partial $\eta^2 = 0.240$]. No significant results were seen between women's cognition and cortical excitability or inhibition.

Discussion

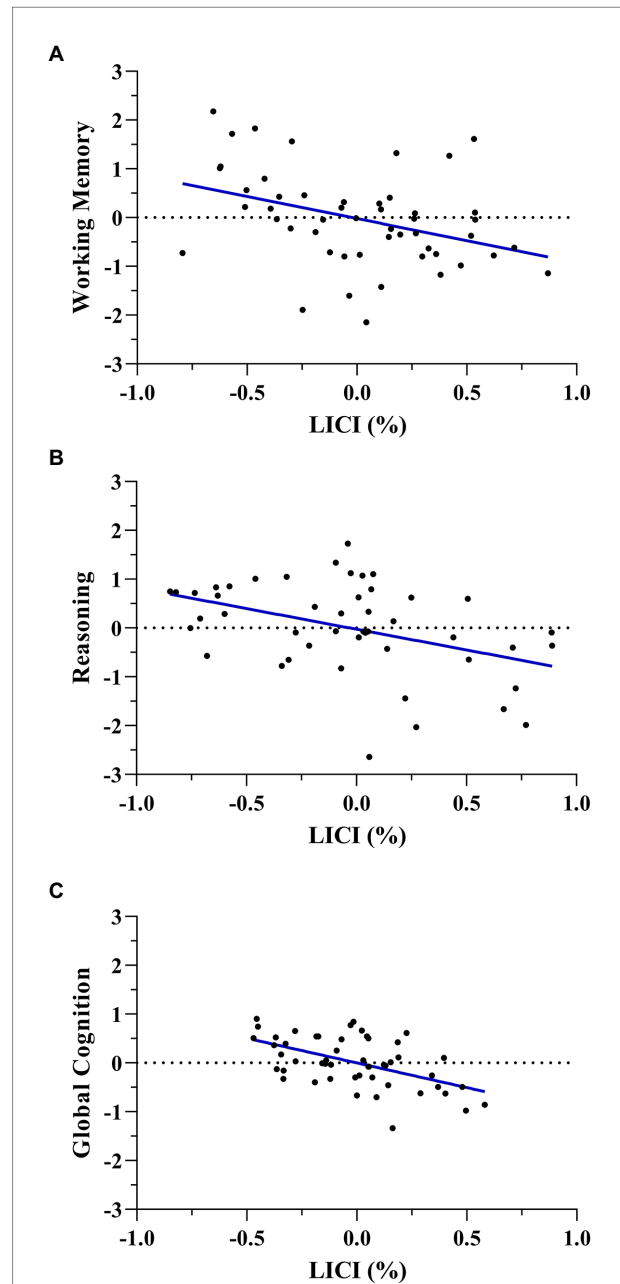
The current study explored the relationship between cortical measures of E/I balance in the primary motor cortex, using TMS measures of RMT and LICl, and cognitive performance in healthy, cognitively-unimpaired middle-aged adults. Moreover, we studied



the impact of biological sex on this association. Our results reveal that lower LICl in the motor cortex is associated with better working memory performance in the whole sample. The effect appears primarily accounted for by men, in whom LICl was found to be related to increased working memory, reasoning, and global cognition. RMT was not associated with cognitive functions in men or women.

Our results are in line with previous research investigating physiological mechanisms of neurological disorders, showing that motor hyperexcitability is related to global cognitive dysfunction (Takahashi et al., 2013; Higashihara et al., 2021; Zadey et al., 2021) due to increased excitatory activity or/and an inhibitory deficit (Joseph et al., 2021; Meder et al., 2021; Mimura et al., 2021). Similarly, in healthy subjects, it has been found that hyperexcitability of the motor cortex is associated with impaired attention (Bolden et al., 2017; Akilan et al., 2020), suggesting that cortical excitatory and inhibitory balance is necessary for optimal brain and cognitive functioning (Páscoa dos Santos and Verschure, 2022).

The relationship between cognition and motor cortex activity could result from the functional connectivity between brain regions involved in cognitive processing (Bates and Goldman-Rakic, 1993; Hasan et al., 2013). For example, the prefrontal cortex is essential for the performance of higher cognitive functions, and the perturbation of its structure or functionality, such as occurs in aging or Alzheimer's disease (Salat et al., 2001; Peters, 2006), could alter the cortical excitability of it (Noda et al., 2017) and highly connected areas such as motor cortex (Freeman et al., 2016). These areas could share evolutive roots, and their interaction is needed to govern the executive function and the intentionality of movements (Mendoza and Merchant, 2014; Leisman et al., 2016). Working memory (Carruthers, 2013; Liao et al., 2014; Leisman et al., 2016), attention, and learning (Bhattacharjee et al., 2021) are



some of the cognitive functions that have been related to motor processes.

Interestingly, only intracortical motor inhibition was positively associated with cognitive performance, particularly working memory, necessary to serve other cognitive functions (Mansouri et al., 2015), and defined as a limited capacity system allowing the temporary storage and manipulation of information required for such complex processes (Baddeley, 2000). Indeed, we found that LICl was also related to reasoning and global

cognition in men, possibly because working memory could play a role in these cognitive functions (Hambrick and Engle, 2003; Wiley and Jarosz, 2012). Given that in our study, intracortical motor inhibition was measured using the LICI paradigm that reflects GABA-B inhibitory neurotransmission (Valls-Solé et al., 1992), we believe that its alteration was associated with cognitive changes. GABA-B receptor indeed has been previously linked to memory formation (Terunuma et al., 2014; Almasi et al., 2018) and working memory (Bañuelos et al., 2014; Schmidt-Wilcke et al., 2018). Furthermore, Freeman et al. (2016) found increased intracortical inhibition in the motor cortex under high working memory load tasks, indicating an association between it and the balance of excitatory/inhibitory activity. These results demonstrate that working memory, even if it strongly involves prefrontal cortex activity, depending on the task's difficulty, requires motor inhibition to work efficiently (Freeman et al., 2016). It was also supported by the results of Liao et al. (2014), which demonstrated the specific involvement of the primary motor cortex and the motor network in working memory processing (Liao et al., 2014).

Specifically, the psychometric measures included in the working memory domain are exclusively auditory-verbal tests. Within the multicomponent working memory model (Baddeley, 2000), one of the most cited in the literature (Chai et al., 2018), our study data reflect the phonological loop subcomponent, responsible for holding verbal information using a temporary store and an articulatory rehearsal system, and the central executive subcomponent responsible for the active manipulation (serial ordering) of the information. Previous findings have shown a double anatomical dissociation in which the subprocess of temporal retention of verbal information depends predominantly on the superior temporal gyrus. However, the subprocess of information manipulation in backward items with higher cognitive load involves, in addition to, the prefrontal area, motor, and somatosensory cortex (Ghaleh et al., 2020).

Furthermore, when we split the sample for biological sex, we observed that women presented subtly higher inhibition than men, which was not statistically significant. This result is in line with previous studies showing that inhibition, usually superior in women, could be influenced by different functional brain maturation of the inhibitory system (Rubia et al., 2013), variations of the brain areas activated (Bell et al., 2006; Li et al., 2006; Korzhyk et al., 2019), and ovarian hormones (Hosseini-Kamkar and Bruce Morton, 2014; Shibuya et al., 2016).

Crucially, we found a positive association between cognition (working memory and reasoning) and intracortical inhibition only in men. Very little is present in the literature on this issue, and the few existing pieces of evidence appear somehow contradictory. Schickntanz et al. (2014) observed that lower motor cortical excitability was related to better working memory in men (Schickntanz et al., 2014), while Akilan et al. (2020) observed that an increase in cortical excitability was related to global cognition in women (Akilan et al., 2020). However, beyond these inconsistencies, which need and deserve deeper study, previous and our results confirm the existence of biological sex differences

(Schickntanz et al., 2014; Akilan et al., 2020) in the relation between cortical excitability/inhibition and cognition.

This research increases our knowledge of this association and suggests that greater intracortical inhibition, measured by LICI, is a possible marker of interindividual differences in working memory performance among healthy middle-aged adults, extending previous suggestions as a biomarker of neuropsychiatric disorders (Fatih et al., 2021).

Finally, the findings in this report are subject to some limitations. First, this is a cross-sectional study, and we cannot determine a cause-effect relationship between cortical excitability measures and cognitive performance. It is necessary to deepen in future research the relationship described in our study, including visuospatial working memory tests and other tasks with different levels of cognitive load and, within the manipulation process, not only serial ordering but updating processing, such as n-back paradigm. Defining which specific working components are related to the TMS measure studied is essential. Also, these processes differ in their sensitivity to advancing age (Jablonska et al., 2020); hence, future investigations should be conducted in other age groups, including middle and older age samples. Furthermore, we explored two TMS measures (RMT and LICI), but it would be interesting to consider other LICI ISI (50 ms, 150 ms, and 200 ms) and paradigms such as short-interval intracortical inhibition or intracortical facilitation. Ultimately, emotional state, sleep quality, and menstrual cycle variations (in particular when considering younger women populations) should be considered in future analysis, being this latter one relevant due to its impact on the female brain and needing specific investigations on this gender group (Hidalgo-Lopez et al., 2020; Meeker et al., 2020).

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 Comitè d'Ètica i Investigació Clínica de la Unió Catalana d'Hospitals. The patients/participants provided their written informed consent to participate in this study.

Author contributions

AP-L, DB-F, and JT participated in the initial conception of the design of the BBHI project. MR-C, DB-F, AP-L, and GC contributed to the conception and design of the present study. MR-C, SD-G, GE-I, VA-S, SA, RP-A, and JS-S contributed to the data acquisition. MR-C and GC analyzed the data. MR-C,

GC, and DB-F contributed to the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

Funding

DB-F and RP-A were funded by a Spanish Ministry of Science, Innovation and Universities (MICIU/FEDER; RTI2018-095181-B-C21) and also supported by an ICREA Academia 2019 grand award. RP-A was supported by a fellowship from “la Caixa” Foundation (ID 100010434, Fellowship code: LCF/BQ/DI19/11730050), JT was partly supported Fundació Joan Ribas (Araquistain_FJRA), AGAUR, Agència de Gestió d'Ajuts Universitaris i de Recerca. Convocatòria 2018 d'Indústria del Coneixement (modalitat PRODUCTE) and FEDER, Fons Europeu de Desenvolupament Regional (2018 PROD 00172), Fundació La Marató De TV3 (201735.10), and European Commission—H2020/Call H2020-SC1-2016-2017 (RIA; grant agreement no. 777107). AP-L was partly supported by the National Institutes of Health (R24AG06142 and P01 AG031720) and the Barcelona Brain Health Initiative funded primarily by “La Caixa” (LCF/PR/PR16/11110004). The funders were not involved in the study design, collection, analysis, interpretation of data, the writing of this article or the decision to submit it for publication.

Acknowledgments

A special thanks is extended to all BBHI participants, the project team and research assistants, and other partners (Ad-Salutem Institute, Sodexo, I.C.A. Informàtica y

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Comunicaciones Avanzadas, Neuroelectrics, Corporació Catalana de Mitjans Audiovisuals, Club Metropolita, Casa Ametller, and Agència de Qualitat i Avaluació Sanitàries de Catalunya-AQuAS) for their collaboration. The organisations listed were not involved in the study design, collection, analysis, interpretation of data, the writing of this article or the decision to submit it for publication.

Conflict of interest

AP-L is a co-founder of Linus Health and TI Solutions AG; serves on the scientific advisory boards for Starlab Neuroscience, Magstim Inc., Radiant Hearts, Skin2Neuron, TetraNeuron, and MedRhythms; is listed as an inventor on several issued and pending patents on the real-time integration of noninvasive brain stimulation with electroencephalography and magnetic resonance imaging.

The remaining 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.

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