Local Prefrontal Cortex TMS-Induced Reactivity Is Related to Working Memory and Reasoning in Middle-Aged Adults

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Introduction: The prefrontal cortex (PFC) plays a crucial role in cognition, particularly in executive functions. Cortical reactivity measured with Transcranial Magnetic Stimulation combined with Electroencephalography (TMS-EEG) is altered in pathological conditions, and it may also be a marker of cognitive status in middle-aged adults. In this study, we investigated the associations between cognitive measures and TMS evoked EEG reactivity and explored whether the effects of this relationship were related to neurofilament light chain levels (NFL), a marker of neuroaxonal damage.

Methods: Fifty two healthy middle-aged adults (41–65 years) from the Barcelona Brain Health Initiative cohort underwent TMS-EEG, a comprehensive neuropsychological assessment, and a blood test for NFL levels. Global and Local Mean-Field Power (GMFP/LMFP), two measures of cortical reactivity, were quantified after left prefrontal cortex (L-PFC) stimulation, and cognition was set as the outcome of the regression analysis. The left inferior parietal lobe (L-IPL) was used as a control stimulation condition.

Results: Local reactivity was significantly associated with working memory and reasoning only after L-PFC stimulation. No associations were found between NFL and cognition. These specific associations were independent of the status of neuroaxonal damage indexed by the NFL biomarker and remained after adjusting for age, biological sex, and education.
Conclusion: Our results demonstrate that TMS evoked EEG reactivity at the L-PFC, but not the L-IPL, is related to the cognitive status of middle-aged individuals and independent of NFL levels, and may become a valuable biomarker of frontal lobe-associated cognitive function.

Keywords: transcranial magnetic stimulation (TMS), Electroencephalography, TMS-EEG, cortical reactivity, prefrontal cortex (PFC), cognition

INTRODUCTION

Cognitive functioning refers to a set of multiple mental abilities that involve the overall dynamics of information processing of stimuli (acquisition, coding, storage, retrieval, thinking, and decision making) to generate an adequate response (motor or verbal) to the environment (Lezak et al., 2004). The characterization of cognitive performance and cognitive profiles is typically carried out through specific domains referring to different processes and abilities within the global term “cognition” (Harvey, 2019), such as attention, episodic memory, working memory, reasoning, fluid intelligence, language, cognitive flexibility, visuospatial skills, and processing speed.

These cognitive domains have been related to specific anatomic areas and brain networks (Wu et al., 2020), and amongst them, the prefrontal cortex (PFC) plays a central role. The PFC is connected to almost all sensory, motor, neocortical and subcortical structures and is often implicated in “top-down” modulation of cognitive functions (Miller, 2000). In a hierarchical model of the neurophysiology of the cortex, the PFC constitutes the highest area of cortical representations (as opposed to lower cortical structures such as sensory and motor areas) dedicated to the integration and execution of higher-order executive functions (Fuster, 2001; Breukelaar et al., 2018). As these functions are significantly affected during aging, the role of the PFC has been extensively studied, and it has been shown that greater PFC activity is associated with better cognition (Eyler et al., 2011; Fernandez-Ruiz et al., 2018) and that preservation of PFC activity contributes to the maintenance of cognitive abilities (Morcom and Henson, 2018; Vidal-Piñeiro et al., 2019).

Beyond correlational evidence from brain-behavior investigations, direct experimental data using repetitive transcranial magnetic stimulation (rTMS) to modulate older adults’ PFC function demonstrated that high-frequency rTMS delivered over the bilateral PFC can enhance cognitive functioning (e.g. Solé-Padullés et al., 2006; Cui et al., 2020). If interpreted in the framework of theoretical models of cognitive aging, this enhancement may be due to the promotion of compensatory mechanisms by rTMS (Cabeza et al., 2018).

Given the role of the PFC in cognition and its relevance in healthy aging, the characterization of its neurophysiological activity in middle-aged adults, often understudied as compared with other age brackets (Willis et al., 2010; Lachman, 2015), could represent a valuable biomarker predictive of cognitive decline in older adults (McGinnis et al., 2011). Furthermore, research in middle-aged populations is relevant because changes in brain function can occur decades prior to the onset of clinically measurable symptoms (Beason-Held et al., 2013).

Transcranial Magnetic Stimulation combined with Electroencephalography (TMS-EEG) is a non-invasive approach that allows the study of cortical reactivity via the perturbation of a cortical site and registration of the activity spread throughout the brain (Ilmoniemi and Kähkönen, 2010; Hallett et al., 2017). The spatiotemporal analysis of this reactivity and propagation allowed previous studies to explore functional network integrity in healthy and clinical populations (Pascual-Leone et al., 2011; Tremblay et al., 2019; Ozdemir et al., 2020).

Cortical reactivity has been defined as the relationship between the strength of the stimulus and the subsequent response (Komssi and Kähkönen, 2006). It is relevant because optimal excitatory and inhibitory cortical balance is needed for the correct functioning of the brain, connectivity between cortical regions, and cognitive functioning (Dehghani et al., 2016). Local and Global Mean-Field Power (GMFP/LMFP) reflect TMS-evoked brain reactivity on a specific subgroup of electrodes or throughout the entire brain, respectively (Lehmann and Skrandies, 1980; Komssi and Kähkönen, 2006; Romero-Lauro et al., 2014). Both measures can reflect the electrical field distribution on the scalp (Skrandies, 1990). They could be valuable for measuring local reactivity directly on the stimulated region and reflecting its distribution to other brain areas (Lehmann and Skrandies, 1980). The neurophysiological effect of non-invasive protocols (repetitive TMS or Transcranial Direct Current Stimulation) has been studied through these measures in healthy adults (Casarotto et al., 2010; Romero-Lauro et al., 2014; Pisoni et al., 2018; Ozdemir et al., 2021) and earlier research showed how these measures were directly related to pathological conditions, like depression (Voineskos et al., 2019). However, the relation between GMFP/LMFP and cognition in a healthy middle-aged population has not been studied before.

The goal of this study was to explore the relationship between cognition and local and global cortical reactivity after PFC stimulation using TMS-EEG in healthy middle-aged adults. Moreover, we investigated whether the effects are independent of a general measure of neuroaxonal damage and neurodegeneration as derived from plasma neurofilament light chain (NFL; Gisslén et al., 2016), a biomarker that has been associated with cognitive decline amongst elderly adults in the preclinical phase of Alzheimer’s disease (AD) (Hu et al., 2019) and potentially in healthy middle-aged adults (Beydoun et al., 2021).
MATERIALS AND METHODS
Subjects and Study Design
Fifty two middle-aged adults (36 male) between 41 and 65 years ($M = 54, SD = 6.85$) were recruited as part of the Barcelona Brain Health Initiative (Cattaneo et al., 2018). They underwent a TMS-EEG session, neuropsychological testing, a medical assessment with blood sample collection, and structural Magnetic Resonance Imaging (MRI). Participants were excluded during the medical visit if they had any neurological or psychiatric disorders or used medications that could affect brain excitability or cognitive functions. Further exclusion criteria included contraindications for TMS (Rossini et al., 2015; Rossi et al., 2021) or MRI. All participants gave written informed consent, and the local ethics committee (Comité d’Ética i Investigació Clínica de la Unió Catalana d’Hospitals) approved the study protocol, which conformed to the Declaration of Helsinki for research involving human subjects.

Neuropsychological Assessment
The neuropsychological assessment consisted of paper and pencil tests administered by two licensed neuropsychologists (VA, CP). The testing session lasted ~90 min and included 14 validated gold-standard instruments (see Cattaneo et al., 2018): Rey Auditory Verbal Learning Test (RAVLT) (Schmidt, 1996), Digit-Span Forward and Backward, Corsi block tapping test, Letter-Number Sequencing test (Peña-Casanova et al., 2012), Trail Making Test A and B (TMT) (Reitan and Wolfson, 1985; Peña-Casanova et al., 2012), Matrix Reasoning and Block design, the Digit symbol task, and the Cancellation test (Wechsler, 2012).

Raw scores of each test were transformed into z-scores and, similar to our previous reports (Vidal-Piñeiro et al., 2014; España-Irla et al., 2021), were grouped into five cognitive domains: episodic memory (RAVLT immediate recall, delayed recall, and recognition; Digit-span forward; Corsi block tapping), working memory (Digit-span backward; Letter-number sequencing), reasoning (Matrix and Block design WAIS-IV), flexibility (TMT B and B-A), and processing speed (TMT A; Digit symbol test; Cancellation test).

TMS Protocol
Participants were asked to sit in a comfortable armchair, look at a fixation cross placed at a 1.5 m distance, stay still, and keep their eyes open. The coil was placed tangentially over the scalp roughly at a 45-degree angle (relative to the mid-sagittal plane), resulting in a posterior-to-anterior current flow. A frameless stereotactic neuronavigation system (Brainsight, Rogue Research Inc., Montreal, QC Canada) was used with the subject’s T1 weighted structural MRI (obtained from a 3T Siemens Magnetom Prisma) to ensure accurate targeting of the stimulation sites throughout the session.

Participant’s Resting Motor Threshold (RMT) was assessed at the motor hotspot (M1) of the dominant hemisphere following the recommendations from the International Federation for Clinical Neurophysiology (Rossini et al., 2015; Rossi et al., 2021). Briefly, RMT was defined as the lowest stimulation intensity required to produce motor-evoked potentials (MEPs) of $\geq 50 \mu V$ in the relaxed first dorsal interosseous muscle (FDI) in five out of 10 trials. MEPs were measured using surface electromyography (EMG) with electrodes placed in a belly-tendon montage and the ground electrode on the ulnar styloid process and connected to a Biopac EMG100C amplifier (BIOPAC Systems Inc., California, USA). Handedness was assessed by the Edinburgh handedness questionnaire (Oldfield, 1971; Veale, 2014).

TMS was applied using a Medtronic Magpro X100 stimulator through a Cool-B65 figure-of-eight coil. One hundred and twenty biphasic single pulses were applied at 120% of RMT at random intervals between 3 and 6 s. Also, stimulation was applied over two target locations: the left prefrontal cortex (L-PFC) and a control target, the Inferior Parietal Lobule (L-IPL). The cohort had two different target procedures, based on the anatomy of each subject or using a cortical functional parcellation (Yeo et al., 2011) (See Supplementary Material for details on targeting procedure).

Due to time constraints during the experimental sessions, 77% of the individuals completed L-PFC stimulation (a total of 40 participants) and 67% L-IPL (35 participants), with 44% of them completing both conditions (23 participants). The complete TMS procedure lasted 2 h.

EEG Recordings
The EEG equipment used to record EEG responses to TMS was made up of a TMS-compatible EEG amplifier (ActiChamp system, Brain Products, GmbH, Munich, Germany) attached to 64 active electrodes (Acticap slim, Brain Products, GmbH, Munich, Germany), following the 10–20 international system for electrode montage. The ground was placed at the Fpz electrode site, and the signal was referenced to the AFz electrode. Electrode impedances were kept below 5 kΩ during the recording, and a continuous signal was collected, filtered DC to 500 Hz, and digitized at a sampling rate of 1,000 Hz. Besides wearing earplugs to protect from the “click” of the TMS pulse, subjects listened to white noise during stimulation to dampen the auditory evoked potential. The volume of the white noise was individually adjusted to each subjects’ tolerance, and it was played through an active noise-canceling inserted earphone (Beoplay E4, Bang&Olufsen, Denmark).

EEG Preprocessing
The EEG signal was first preprocessed offline with custom MATLAB scripts (R2020b, The MathWorks Inc., Natick, Massachusetts) that incorporate function from the EEGLAB toolbox (Delorme and Makeig, 2004) and TESA plugin (Rogasch et al., 2017). The EEG signal was epoched around the TMS pulse ($-1,000$ to $+2,000 \text{ ms}$) and baseline corrected ($-900$ to $-100 \text{ ms}$). Excessively noisy channels were removed, but no more than three channels had to be discarded for any subject. Data was zero-padded between $-2$ and $+14 \text{ ms}$ around the TMS pulse to remove the early TMS pulse artifact. Epochs were inspected visually, and excessively noisy epochs were removed ($M = 19, SD = 7$). A two-step fast Independent Component Analysis (fICA) was conducted. The first fICA, was performed with Principal Component Analysis dimension reduced to 40 to minimize overfitting and was used to remove the decay artifact,
typically 2 components were removed for each subject. Before
the second round of fICA, the zero-padded TMS pulse was
linearly interpolated, Butterworth band-pass (1 and 100 Hz) and
notch (48 and 52 Hz) filters were applied, and data were re-
terfered to the average reference. The second round of fICA
was used to remove any remaining artifacts, including eye blinks,
lateral eye movement, muscle, TMS-evoked muscle, electrode
noise, and auditory evoked potentials \((M = 28, SD = 3; a range
of 21–31 out of 38)\). Finally, initially discarded channels were
spine interpolated.

**Cortical Reactivity TMS-EEG Measures**

Global Mean-Field Power (GMFP) and Local Mean-Field Power
(LMFP) were used to quantify overall and local brain reactivity
measures, respectively.

Mean Field-Power (MFP) was calculated for both measures
using the following formula:

\[
MFP (t) = \sqrt{\frac{\sum_{i} (V_i (t) - V_{mean} (t))^2}{K}}
\]

where “\(t\)” is time, “\(V\)” is the voltage in the channel “\(i\),” “\(K\)” is the
number of channels, and “\(V_{mean}\)” the mean of the voltage across
electrodes (Lehmann and Skrandies, 1980; Esser et al., 2006).

All EEG electrodes were used to compute GMFP, whereas, for
LMFP, a subset of electrodes was chosen for L-PFC (FC1, FC3,
FC5, F1, F3, F5) and L-IPL (CP1, CP3, CP5, P1, P3, P5) (Ozdemir
et al., 2020). LMFP was used to calculate the local reactivity of the
stimulation target region.

For GMFP and LMFP, the area under the curve was calculated
using trapezoidal integration within two-time windows, before
and after the pulse (Baseline and Post-stimulation). Baseline
refers to the activity before each pulse (−500 to −3 ms), while
Post-stimulation activity includes data between 15 and 400 ms
after the TMS pulse. This time window has been selected to
minimize the TMS artifact’s impact and capture the entirety of
the TMS evoked brain response (Fuggetta et al., 2005; Van Der
Werf et al., 2006). This time window has been used in recent
and similar research (Ozdemir et al., 2020; Rocchi et al., 2020;
Vallesi et al., 2021). Furthermore, baseline data was used to
normalize the activity post-stimulation, subtracting it from the
activity post-TMS.

**NfL Measurement**

We collected blood samples using EDTA tubes during the
medical assessment, and plasma was aliquoted and stored in a
refrigerator at \(−80^\circ\)C in a biobank facility following standard
procedures usually employed for clinical purposes. Plasma NfL
concentration was measured using the Single-molecule array
(Simoa) NF-light Advantage Kit on an HD-X instrument as
described by the kit manufacturer (Quanterix, Billerica, MA).
The limit of quantification was 2.7 pg/mL, and the limit of
detection was 0.3 pg/mL. For the quality control (QC) sample
with an 11.2 pg/mL concentration, repeatability was 3.6%, and
intermediate precision was 5.0%. For a QC sample with a 115
pg/mL concentration, repeatability was 5.3%, and intermediate
precision was 6.8%. The measurements were performed at
the Clinical Neurochemistry Laboratory at the University of
Gothenburg by board-certified laboratory technicians who were
blinded to clinical data.

**Statistical Analysis**

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

First, to explore changes between local and global reactivity
before and after stimulation, we ran a repeated-measures ANOVA
using the variable “Time” (Baseline and Post-
stimulation) and “Mean-Field Type” (LMFP and GMFP) as
within-subject factors.

Then, to investigate the relation between TMS reactivity, at
local and global levels, and cognition, we ran multivariate
multiple regressions for each stimulation site (PFC, IPL). L-IPL
was used as a control condition to validate if our associations
with cognition in L-PFC results were specific to this target. Models
were run using cognitive composite scores as dependent variables
(episodic memory, working memory, reasoning, flexibility, and
processing speed) and Mean-Field Type, targeting method, NfL
levels, age, biological sex, and years of education as predictors.
Also, we run the same models without using covariates (targeting
method, NfL levels, age, biological sex, and years of education).

Finally, to specifically explore the associations between NfL
level and cognition, we first performed a bivariate correlation,
and then to see the effect of age, we ran a partial correlation
controlled by this variable.

**RESULTS**

All subjects were right-handed and tolerated well the
experimental procedures, and no adverse events were reported.
Descriptive statistics of age, educational level, RMT, and plasma
NfL levels are presented in Table 1, while cognitive scores are in
the Supplementary Material (Supplementary Table 1).

| TABLE 1 | Demographic Variables, RMT and NfL plasma values (n = 52). |
|----------------|-----------------|-----------------|-----------------|-----------------|
| Age       | 41              | 65              | 53.96           | 6.85            |
| Years of Education | 8              | 28              | 18.40           | 3.83            |
| RMT       | 43              | 82              | 59.77           | 8.76            |
| NfL levels (pg/mL) | 4.09           | 29.8            | 12.22           | 5.35            |

While LMFP showed significant differences between baseline and
Cortical Reactivity and Cognitive Functions Associations

L-PFC

Age and local reactivity resulted in statistically significant results for the multivariate regression analysis [respectively $F_{(3,28)} = 3.28$, $p < 0.019$, Wilks’ $\Lambda = 0.631$, partial $\eta^2 = 0.369$; $F_{(5,28)} = 2.91$, $p = 0.031$, Wilks’ $\Lambda = 0.658$, partial $\eta^2 = 0.342$; see Supplementary Table 2]. The analysis revealed a significant positive association between working memory and local reactivity to stimulation of the L-PFC [F(1,32) = 5.01, $p = 0.032$, partial $\eta^2 = 0.135$], as well as an association between reasoning and both age [F(1,32) = 6.76, $p = 0.014$, partial $\eta^2 = 0.174$] and local reactivity to L-PFC stimulation [F(1,32) = 4.70, $p = 0.038$, partial $\eta^2 = 0.128$] (see Figure 4). Episodic memory, processing speed, and flexibility were unrelated to the independent variables introduced in the model. Full model results including covariates can be found in Supplementary Table 3.

Conversely, no significant results were seen between cognition and cortical reactivity in models without covariates (see Supplementary Tables 4, 5).

L-IPL

For stimulation to left IPL, no statistically significant relations were found between any of the cognitive functions and either global or local TMS-EEG induced reactivity measures at baseline or post-stimulation. Model results including covariates are presented in Supplementary Tables 6, 7. Also, no significant results were seen between cognition and cortical reactivity in models without covariates (see Supplementary Tables 8, 9).

NfL Levels and Cognitive Functions

We first ran a bivariate correlation between NfL levels and cognitive variables and found that it was significantly and inversely correlated to participants’ cognitive performance in reasoning ($r = -0.373$, $p = 0.006$), processing speed ($r = -0.338$, $p = 0.014$), and cognitive flexibility ($r = -0.293$, $p = 0.035$; see Supplementary Table 10). However, when controlled for age, such associations disappeared, indicating that the age of participants largely drove the correlations. In addition, and as revealed by the multivariate regression analyses, NfL concentration was not significantly associated with cognitive status (see Supplementary Tables 3, 7).

DISCUSSION

In the present study, we explored the relationship between EEG reactivity to TMS of the PFC and IPL and cognition in healthy middle-aged adults, and the possible role of neuroaxonal damage measured by plasma NfL. Results indicate that local TMS-EEG reactivity after PFC stimulation is positively associated with executive functions, specifically...
FIGURE 3 | Butterfly plots of a subject’s TMS-EEG responses after PFC (A) and IPL (B) stimulation. Each figure time-series are plotted −100 to +400 ms around the TMS pulse.

FIGURE 4 | Multiple regression scatterplots between local cortical reactivity after PFC stimulation and working memory (A) and reasoning (B) after controlling for targeting method, NfL levels, age, biological sex, and years of education. Z-scores were used on the Y-axis and unstandardized Predicted Values on the X-axis (µV).
working memory and reasoning. However, after IPL stimulation, cortical reactivity was not related to cognitive function. Finally, it was shown that neuroaxonal damage measured by NfL did not play a role in these associations. Despite that, a significant effect was seen when we correlated directly NfL level and cognitive functions, which disappeared when we controlled by age.

The fact that the relation between TMS-EEG reactivity and cognitive were limited to the local response following PFC stimulation, and not globally or when stimulating the L-IPL, is consistent with the specific PFC role in the top-down regulation of higher-order cognitive control (Miller, 2000). These results indicate that individual differences in local cortical reactivity to TMS of the PFC could be a practical, specific, sensitive, and simple biomarker to assess cognitive functioning, independently of the global brain and axonal degeneration.

Cortical reactivity has been previously related to factors such as alcohol or medication intake (Kähkönen et al., 2003; Khedr et al., 2020) and various TMS parameters (Casula et al., 2018). A rich literature has demonstrated that activity and connectivity between PFC and IPL are associated with cognition (Lückmann et al., 2014; Friedman and Robbins, 2021). In particular, whereas PFC has been more related to executive function and cognitive control (Friedman and Robbins, 2021), IPL has been associated with language and social cognition (Numssen et al., 2021). In line with our results, Ngetich et al. (2020) showed that after a continuous theta burst stimulation over L-PFC, there was a change in executive functions like working memory and decision making (Ngetich et al., 2020). Similarly, it has been shown that abnormal higher cortical excitability in the PFC in patients with AD than healthy controls was inversely associated with global cognition/executive functions (Joseph et al., 2021), confirming the relation between cognitive functions performance and PFC evoked activity.

The role of PFC in working memory has been extensively studied in the past decade with animals and humans, suggesting that PFC is strongly related to the cognitive process of maintaining available and select information for delayed responses (see Curtis and D’Esposito, 2003 for a review). It has been proposed that while the PFC is crucial to manipulate and select relevant information, a more posterior part of PFC (e.g., Brodmann area 8) is involved in mechanisms of maintenance (Rowe et al., 2000; Glahn et al., 2002). Also, complex reasoning tasks have been consistently associated with PFC activity and integrity. It has been proposed that PFC is strongly involved in logic processing (Santarècchi et al., 2013), and specifically, its rostrolateral part is essential for relational integration and associations (Christoff et al., 2001; Krawczyk et al., 2011).

The association between cognition and PFC activity and connectivity is especially important in studying the maintenance of cognitive functioning in aging. Indeed it has been proposed that PFC activity could be related to the recruitment of compensatory mechanisms (Solé-Padullés et al., 2006; Höller-Wallscheid et al., 2017; Abellaneda-Pérez et al., 2019) that allow individuals to maintain cognition in the face of age-related brain changes.

Furthermore, NfL was shown to be negatively related to cognition, but this effect disappeared if controlled by the individual’s age, and NfL level didn’t have a significant influence on the identified relation between cortical reactivity and cognitive functions. NfL level is a marker of neuro-axonal damage in diseases such as Alzheimer’s disease, Parkinson’s disease, multiple sclerosis, or amyotrophic lateral sclerosis, where high concentrations of NfL have been reported (Gaetani et al., 2019; Dhiman et al., 2020). Recent studies (Khalil et al., 2020; Beydoun et al., 2021; Rübsamen et al., 2021) have explored in healthy individuals the relation between NfL levels, brain structures, and cognitive scores, suggesting that higher NfL levels could be associated with brain atrophy, and in consequence worse cognition. Our study sample was limited to middle-aged, cognitively-unimpaired adults, and the fact that the level of NfL didn’t influence the reactivity/cognition prediction could be because of collinearity between age and NfL level, or that most past results have focused on older adults or various patient populations. More studies in healthy middle-aged adults are needed to determine the significance and potential clinical utility of NfL plasma levels (Beydoun et al., 2021).

To conclude, our results indicate that cortical reactivity of L-PFC as characterized by TMS-EEG is related to cognition in middle-aged adults regardless of neuroaxonal damage (indicated by NfL), age, biological sex, and education. This TMS-EEG metric may represent a valuable and independent biomarker for cognition.

As with all studies, the design of the current study is subject to limitations. First, we acknowledge that our sample size was small, but still, it was in line with other studies whose objective was to associate TMS measures with cognition. Second, our sample was characterized by highly educated individuals, and there was a high prevalence of men. Furthermore, our statistical analysis was done for each stimulation site separately because of missing data. Given the small sample sizes, multiple comparisons corrections were not applied to maintain statistical power and avoid strongly increasing the probability of type II errors. Hence, further studies are needed, including more participants with both PFC and IPL stimulation data to confirm these results. Finally, a layer of foam between the coil and the electrodes was not used in this research, and despite this preventive measure could add some distance, increasing the resting motor threshold and the effect varies between subjects (ter Braack et al., 2015), it could have been beneficial for the reduction of auditory evoked potentials in the EEG analysis. Future investigations with larger and more heterogeneous samples are necessary to validate the conclusions of our study, and it would be valuable to explore if changes in cortical reactivity, measured longitudinally, may be predictive of age-related changes in cognition.

**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 Comité 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-M participated in the initial conception of the design of the BBHI project. MR-C, DB-F, AP-L, GC, and RP-A contributed to conception and design of the present study. MR-C, SD-G, GE-I, VA-S, CP-G, SA, JS-S, and TM contributed to the acquisition of data. MR-C, GC, TM, HZ, and RP-A analyzed the data. MR-C, GC, and DB-F contributed to the drafting of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2022.813444/full#supplementary-material

REFERENCES

Abellaneda-Pérez, K., Vaqué-Alcázar, L., Solé-Padullés, C., and Bartrés-Faz, D. (2019). Combining non-invasive brain stimulation with functional magnetic resonance imaging to investigate the neural substrates of cognitive aging. J. Neurosci. Res. doi: 10.1002/( Journal of Cognitive Aging. J. Neurosci. Res. doi: 10.1002/jnr.24342

Beydoun, M. A., Noren Hooten, N., Beydoun, H. A., Maldonado, A. I., Weiss, J., Beason-Held, L. L., Goh, J. O., An, Y., Kraut, M. A., O’Brien, R. J., Ferrucci, L., et al. (2013). Changes in brain function occur years before the onset of cognitive impairment. J. Neurosci. 33, 18008–18014. doi: 10.1523/JNEUROSCI.1402-13.2013

Beydoun, M. A., Noren Hooten, N., Beydoun, H. A., Maldonado, A. I., Weiss, J., Evans, M. K., et al. (2021). Plasma neurofilament light as a potential biomarker for cognitive decline in a longitudinal study of middle-aged urban adults. Transl. Psychiatry 11, 1–12. doi: 10.1038/s41398-021-01563-9

Breukelaar, I. A., Williams, L. M., Anteers, C., Grieve, S. M., Foster, S. L., Gomes, L., et al. (2018). Cognitive ability is associated with changes in the functional organization of the cognitive control brain network. Hum. Brain Mapp. 39, 5028–5038. doi: 10.1002/hbm.24342

Cabeza, R., Albert, M., Belleville, S., Craik, F. I. M., Duarte, A., Grady, C. L., et al. (2018). Maintenance, reserve and compensation: the cognitive neuroscience of healthy ageing. Nat. Rev. Neurosci. 19, 701–710. doi: 10.1038/s41583-018-0068-2

Casarotto, S., Lauro, L. J. R., Bellina, V., Casali, A. G., Rosanova, M., Pigorini, A., et al. (2010). EEG responses to TMS are sensitive to changes in the perturbation parameters and repeatable over time. PLoS One 5, e10281. doi: 10.1371/journal.pone.010281

Casula, E. P., Rocchi, L., Hannah, R., and Rothwell, J. C. (2018) . Effects of pulse width, waveform and current direction in the cortex: A combined cTMS-EEG study. Brain Stimul. 11, 1063–1070. doi: 10.1016/j.brs.2018.04.015

Cattaneo, G., Bartrés-Faz, D., Morris, T. P., Sánchez, J. S., Macià, D., Tarrero, C., et al. (2018). The Barcelona brain health initiative: a cohort study to define and promote determinants of brain health. Front. Aging Neurosci. 10, 32’. doi: 10.3389/fnagi.2018.00321

Christoff, K., Prabhakaran, V., Dorfman, J., Zhao, Z., Kroger, J. K., Holyoak, K. J., et al. (2001). Rostral lateral prefrontal cortex involvement in relational integration during reasoning. Neuroimage 14, 1136–1149. doi: 10.1006/nimg.2001.0922

Cui, X., Ren, W., Zheng, Z., and Li, J. (2020). Repetitive transcranial magnetic stimulation improved source memory and modulated recollection-based retrieval in healthy older adults. Front. Psychol. 11, 1137. doi: 10.3389/fpsyg.2020.01137

Curtis, C. E., and D’Esposito, M. (2003). Persistent activity in the prefrontal cortex during working memory. Trends Cogn. Sci. 7, 415–423. doi: 10.1016/S1364-6613(03)00197-9

Dehghani, N., Peyrache, A., Telenzckzuk, B., Le Van Quyen, M., Halgren, E., Cash, S. S., et al. (2016). Dynamic balance of excitation and inhibition in human and monkey neocortex. Sci. Rep. 6, 23176. doi: 10.1038/srep23176
Delorme, A., and Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics. J. Neurosci. Methods 134, 9–21. doi: 10.1016/j.neuroimage.2003.10.009

Dhiman, K., Gupta, V. B., Willemagne, V. L., Eratine, D., Graham, P. L., Fowler, C., et al. (2020). Cerebrospinal fluid neurofilament light concentration predicts brain atrophy and cognition in Alzheimer’s disease. Alzheimer’s Dement. 12, e12005. doi: 10.1016/j.dadst.2020.12.005

España-Irla, G., Gomes-Usman, J., Cattaneo, G., Albu, S., Cabello-Toscano, M., Solana-Sanchez, J., et al. (2021). Associations between cardiorespiratory fitness, cardiovascular risk, and cognition are mediated by structural brain health in midlife. J. Am. Heart Assoc. 10, e020688. doi: 10.1161/JAHA.120.020688

Esser, S. K., Huber, R., Massimini, M., Peterson, M. J., Ferrarelli, F., and Tononi, G. (2006). A direct demonstration of cortical LTP in humans: A combined TMS/EEG study. Brain Res. Bull. 69, 86–94. doi: 10.1016/j.brainresbull.2005.11.003

Eyster, L. T., Sherzai, A., Kaup, A. R., and Jeste, D. V. (2011). A review of functional brain imaging correlates of successful cognitive aging. Biol. Psychiatry 70, 115–122. doi: 10.1016/j.biopsych.2010.12.032

Fernandez-Ruiz, J., Pelsch, A., Alahyane, N., Brien, D. C., Coe, B. C., Garcia, A., et al. (2018). Age related prefrontal compensatory mechanisms for inhibitory control in the antisaccade task. Neuroimage 165, 92–101. doi: 10.1016/j.neuroimage.2017.10.001

Friedman, N. P., and Robbins, T. W. (2021). The role of prefrontal cortex in...
