Clinical Neurophysiology 152 (2023) 22–33

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Replicability of motor cortex-excitability modulation by intermittent theta burst stimulation

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HIGHLIGHTS

- TMS measures of cortical excitability modulation are variable and unstable across time.
- Significant facilitation was found only on the brain hemisphere where iTBS was applied.
- Cortical-excitability modulation was stable and no associations were found between psychological factors and modulation.

ARTICLE INFO

Article history:
Accepted 18 April 2023
Available online

Keywords:
Stability
Cortical excitability modulation
Intermittent theta burst stimulation
Expectation

ABSTRACT

Objective: Transcranial Magnetic Stimulation (TMS) allows for cortical-excitability (CE) assessment and its modulation has been associated with neuroplasticity-like phenomena, thought to be impaired in neuropsychiatric disorders. However, the stability of these measures has been challenged, defying their potential as biomarkers. This study aimed to test the temporal stability of cortical-excitability modulation and study the impact of individual and methodological factors in determining within- and between-subject variability.

Methods: We recruited healthy-subjects to assess motor cortex (MC) excitability modulation, collecting motor evoked potentials (MEP) from both hemispheres, before and after left-sided intermittent theta burst stimulation (iTBS), to obtain a measure of MEPs change (delta-MEPs). To assess stability across-time, the protocol was repeated after 6 weeks. Socio-demographic and psychological variables were collected to test association with delta-MEPs.

Results: We found modulatory effects on left MC and not on right hemisphere following iTBS of left MC. Left delta-MEP was stable across-time when performed immediately after iTBS (ICC = 0.69), only when obtained first in left hemisphere. We discovered similar results in a replication cohort testing only left MC (ICC = 0.68). No meaningful associations were found between demographic and psychological factors and delta-MEPs.

Conclusions: Delta-MEP is stable immediately after modulation and not impacted by different individual factors, including expectation about TMS-effect.

Significance: Motor cortex excitability modulation immediately after iTBS should be further explored as a potential biomarker for neuropsychiatric diseases.

1. Introduction

Transcranial Magnetic Stimulation (TMS) is a non-invasive brain stimulation technique which generates a magnetic field that penetrates the scalp and skull, leading to neuronal activity when reaching cortical tissue (Hallett, 2007). TMS allows for *in vivo*

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https://doi.org/10.1016/j.clinph.2023.04.014
1388-2457/

assessment, in humans, of central nervous system neurophysiology (Badawy et al., 2012; Maeda et al., 2000; Polanía et al., 2018). Application of repetitive pulses of TMS (rTMS) to an area of the cortex according to specific stimulation protocols can modulate excitability of that cortical area, lasting beyond the rTMS-protocol (Peinemann et al., 2004). Single TMS pulses can be used to assess cortical excitability (CE) and, if applied before and after rTMS, can be used to measure cortical excitability modulation (CEM) by rTMS (Badawy et al., 2012; Maeda et al., 2000; Polanía et al., 2018). Such research protocols have been widely applied in the motor cortex (MC) since the outcome of its activity is easily available through electromyography (EMG) (Groppa et al., 2012; Pascual-Leone et al., 1998a). Nevertheless, others have explored CE in other brain regions (Gosseries et al., 2015).

Measures of CEM have been considered a *proxy* of neuroplasticity (Cirillo et al., 2017), a general term describing the processes through which the brain can be modified by experience (Feldman, 2009). In fact, several neuropsychiatric disorders have been associated with deficits in neuroplastic mechanisms, including major depressive disorder (MDD) (Castricum et al., 2022; Hinchman et al., 2022; Oliveira-Maia et al., 2017; Pittenger and Duman, 2008) and neurocognitive conditions (Brem et al., 2020). Considering that CEM may be used to assess neuroplasticity *in vivo* in humans, plasticity-like phenomena assessed using TMS have been systematically explored as potential biomarkers of neuropsychiatric disorders (Player et al., 2013; Vignaud et al., 2019). Indeed, motor CEM after application of an inhibitory TMS-protocol has been shown to have a distinct interhemispheric pattern in patients with MDD when compared with healthy-volunteers (Bajwa et al., 2008). In the former, CE decreased in both hemispheres, while in healthy-volunteers the decrease was only in the hemisphere where rTMS was applied, with increases in motor CE in the other side (Bajwa et al., 2008). Moreover, we and others have shown that modulation of MC excitability has predictive value for antidepressant response to rTMS treatment (Hinchman et al., 2022; Oliveira-Maia et al., 2017). Specifically, in patients with higher MC excitability modulation before treatment, improvement of depression symptoms was also greater, after a course of rTMS treatment delivered to the prefrontal cortex (Hinchman et al., 2022; Oliveira-Maia et al., 2017).

Although CEM has potential as a biomarker of disease (Vignaud et al., 2019) and predictor of treatment response (Hinchman et al., 2022; Oliveira-Maia et al., 2017), methodological constraints to its assessment remain unsolved. Some studies have attempted to address these constraints, namely through assessment and optimization of the stability of the measure, but with conflicting results (Corp et al., 2020; Hinder et al., 2014; Jannati et al., 2019; Schilberg et al., 2017; Vallence et al., 2015). In fact, lack of stability and replicability of these measurements led some authors to question the occurrence of any modulatory effects of rTMS on CE, suggesting that most effects are simply a factor of participants' expectation regarding TMS (Perellón-Alfonso et al., 2018; Schilberg et al., 2017). However, there is significant methodological heterogeneity in studies assessing stability of CEM, namely in parameters used for rTMS neuromodulation (Vernet et al., 2014), description of materials and methods (Huang et al., 2008), use of neuronavigated *vs* non-neuronavigated TMS (Corp et al., 2020), sample sizes (Schilberg et al., 2017), or statistical testing (Fried et al., 2017). The methodology to acquire and analyse CE is also reported as a potential source of heterogeneity, specifically the number of TMS pulses used (Cuypers et al., 2014), inter-pulse intervals (De Luca, 2006; Mohr et al., 2018), and methods of electromyographic data acquisition (De Luca, 2006; Mohr et al., 2018).

Systematizing data acquisition and processing is thus a critical step to improve and adequately measure the stability of cortical excitability modulation, a fundamental characteristic for any biomarker candidate (Bernard, 1995a; Graham et al., 2017; Schuh et al., 2016). Hence, in the present study we propose to optimize and test stability of CEM assessed in the MC. Moreover, a secondary aim was to study the impact of several demographic and psychological factors on cortical excitability modulation. Given the potential relevance of inter-hemispheric effects in the context of depression, assessments were conducted in both hemispheres after left-sided stimulation with a TMS-protocol.

2. Material and methods

2.1. Population

We recruited Portuguese-speaking individuals from the local community, between 18–65 years old, and without current diagnosis of any major neuropsychiatric disorder, namely psychosis, mood disorder, substance use disorder, developmental disorder, movement disorder, neurocognitive disorder, or any other uncontrolled medical condition. Participants with previous episodes of mania/hypomania or psychosis were also excluded. Potential participants were ineligible if a contraindication for TMS was identified (Rossi et al., 2009). The study was conducted in accordance with the Declaration of Helsinki. Study procedures and protocol were reviewed and approved by the Champalimaud Foundation Ethics Committee. Written informed consent was obtained from all participants. Study procedures are included in the study protocol registered at ClinicalTrials.gov (NCT05441969).

2.2. Psychological assessment

At the screening visit, a self-report questionnaire, which included social-demographic and health related questions, as well as the Mini International Neuropsychiatric Interview (MINI) Version 5.0.0 (Sheehan et al., 1998) were used to screen for eligibility. Demographic variables such as age, sex, education level and self-reported handedness were collected. Several psychometric-instruments, translated, adapted and/or validated for the Portuguese population, were used to characterize the study population, including the Beck Depression Inventory (BDI) (Beck et al., 2011), Barratt Impulsiveness Scale (BIS-11) (Patton et al., 1995), Edinburgh Handedness Inventory (EHI) (Oldfield, 1971), Hypomania Check-List 32 (HCL-32) (Angst et al., 2005), Montgomery-Asberg Depression Rating Scale (MADRS) (Williams and Kobak, 2008), Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), Obsessive Compulsive Inventory (OCI-R) (Foa et al., 1998), State-Trait Anxiety Inventory (STAI) (Spielberger, 2012), and World Health Organization-Five Well-Being Index (WHO-5) (Topp et al., 2015). Additionally, to assess participant expectation regarding the effects of TMS, we adapted the Stanford Expectation Treatment Scale (SETS) (Younger et al., 2012) to a Transcranial Magnetic Stimulation (TMS) research setting, according to International Test Commission Guidelines for Translating and Adapting Tests (ITC Guidelines for Translating and Adapting Tests (Second Edition), 2018), thus developing a new scale, the TMS-Session Expectation Scale (TMS-EXP). Psychometric validation of the TMS-EXP Scale can be found in supplementary methods, where exploratory factor analysis confirmed two major factor loadings of positive and negative expectation, as in the original scale.

2.3. Transcranial Magnetic Stimulation and Electromyography

Transcranial Magnetic Stimulation (TMS) procedures were performed according to guidelines recommended by the International Federation of Clinical Neurophysiology (Rossini et al., 2015) using a MagVenture MagPro X100 magnetic stimulator, with a Cool-B65

figure eight coil. Electromyography (EMG) data acquisition was conducted using an in-house EMG acquisition system developed by the Champalimaud Scientific Hardware Development Platform (https://www.cf-hw.org/) in accordance with International Guidelines for TMS-EMG data collection (Groppa et al., 2012). Please see supplementary methods for further details on TMS-EMG acquisition data and pre-processing steps of neurophysiologic data.

For motor cortex (MC) excitability modulation, we used an intermittent theta burst stimulation (iTBS) protocol on left MC, applying 50 Hz pulse triplets, at 80% of the active motor threshold (AMT), delivered at 5 Hz for 2 s on and 8 s off, repeated 20 times, yielding 600 total pulses, as supported by others (Hinchman et al., 2022; Hinder et al., 2014; Huang et al., 2008). Cortical excitability modulation (CEM), i.e., measure of MEPs change (delta-MEP), at each timepoint after iTBS was computed as the difference between mean motor evoked potentials (MEP) amplitude at that time-point and at pre-iTBS, that was then expressed as a ratio of pre-iTBS mean MEP amplitude. In addition, the absolute difference of motor cortex excitability between pre-iTBS MEP and post-iTBS MEPs (pre-iTBS MEP minus post-iTBS MEP) was also analysed.

2.4. Study design

All participants were invited to perform two study visits, at baseline and after approximately 6 weeks. A first group of individuals (test cohort) was recruited to test the stability of CEM. A second group of subjects (replication cohort) was collected to confirm findings obtained in the test cohort. Each study visit started with psychological assessment, followed by the TMS-session (Fig. 1). In the test cohort two separate TMS-sessions were performed on each visit, separated by between 2 to 7 days, to assess either left or right MC excitability modulation after left-sided iTBS, with the order of left and right TMS-sessions randomized between subjects, but maintained fixed for the two visits of each subject. Considering a left TMS-session, the preparation setup included the determination of left motor hotspot, left resting motor threshold (RMT) and left active motor threshold (AMT). Then, pre-iTBS left MEPs were collected followed by left-sided iTBS. Post-modulation left MEPs were collected immediately (T0), and 10 (T10), 20 (T20), and 30 (T30) minutes after left-sided iTBS. In the right TMS-session, since iTBS was also performed on the left hemisphere, bilateral preparation setup was necessary. Such procedures included determination of left and right motor hotspot, left and right RMT and left AMT (Fig. 1A and 1B). Then, right MEPs were collected before (pre-iTBS) and after (post-iTBS) left-sided iTBS, respectively, using the same timepoints as above. Similar study procedures were conducted after 6 weeks visit. In the replication cohort, study design was simplified to include only the left TMS-session in each study visit (Fig. 1C).

2.5. Statistical analysis

All data were analysed using Statistical Package for the Social Sciences (SPSS, Version 27.0; IBM SPSS, Inc., Chicago, IL). According to visual inspection of histograms and quantile–quantile plots, we found evidence that data did not follow a normal distribution, and non-parametric statistical tests were thus conducted for data analysis. In order to compare independent samples, we used Mann-Whitney U or Kruskal–Wallis tests, when appropriate, for continuous variables, and Fisher's exact test for dichotomous variables. To test if CEM was significant, we performed one-sample Wilcoxon signed-rank tests comparing against 0. To assess CEM stability for each side and post-modulation timepoint, we computed the intraclass correlation coefficient (ICC) using a two-way mixed-effects model testing absolute agreement, between the two study visits, i.e. at baseline and after 6 weeks (Koo and Li, 2016). To test the association of different individual socio-demographic and psychological factors with CEM, we used the Spearman correlation coefficient. Unless noted otherwise, continuous variables are represented by median and minimum–maximum range, categorical variables are represented as absolute number and percentage of respective sample, and p-values are corrected for multiple comparisons using False Discovery Rate (FDR) of 0.1, according to Benjamini and Hochberg (1995).

3. Results

From an initial pool of 56 identified subjects, 47 individuals were eligible, and their resulting data was analysed (Fig. 2). These individuals were recruited into two study cohorts, test (N = 30) and replication cohort (N = 17). Socio-demographic and psychological characteristics between the two cohorts did not differ significantly (Table 1). None of the subjects experienced any major adverse effects.

In the test cohort, significant left-sided modulation, i.e., measure of MEPs change (delta-MEP), was only found at T20 (p =.04) at baseline, not surviving after multiple comparison correction, while after 6-weeks it was significant at T0 and T20 (ps < 0.03; Figs. 3-A1). No significant right-sided modulation was found at any timepoint in any of the study visits (Figs. 3-A1). Similar results were obtained when using non-normalized iTBS effects, i.e., the absolute difference of motor cortex excitability between pre-iTBS MEP and post-iTBS MEPs (pre-iTBS MEP minus post-iTBS MEP) (Table S1). Also, AMT, RMT and baseline MEP were found to be stable across time (Table S2). Motor cortex (MC) excitability modulation was not stable at any timepoint for both hemispheres (ICC $\leq$ 0.09; p $\geq$ 0.40; Figs. 3-A2, Figures S1 and S2). Due to the potential impact of performing bilateral Transcranial Magnetic Stimulation (TMS) acquisition sessions using a specific order (Bajwa et al., 2008; Di Lazzaro et al., 2008; Gilio et al., 2003; Heide et al., 2006; Stefan et al., 2008; Suppa et al., 2008), subjects randomized to perform left TMS-sessions first were separately analysed from those who performed right TMS-sessions first, obtaining two independent sub-cohorts. In the participants for whom left-sided measurements were obtained first, significant left-sided modulation was found in the baseline session only, at T0, T10 and T20 (p_s < 0.04; Figs. 3-B1). Nevertheless, left MC excitability modulation was stable at T0 (ICC = 0.69, 95% CI = 0.0 04–0.90; p =.03; Figs. 3-B2, Figure S1), but not in other timepoints. Neither significant modulation nor stability was found for measurements in the right MC (Figure S3). In subjects randomized to perform right TMS-sessions first, significant delta-MEP was not found in either side irrespective of study visit (Figure S4), and MC excitability modulation was not stable at any timepoint nor side (ICC $\leq$ 0.07; $p_s \geq 0.44$; Figure S5).

In order to confirm the results obtained in the sub-cohort with left TMS-sessions first, a second cohort was collected but only performing left MC TMS assessment sessions (replication cohort; Fig. 3-C). In this cohort, significant left-sided modulation was found at T10 at baseline (p =.02) and at all timepoints after 6 weeks (p_s < 0.01; Figs. 3-C1). Left MC excitability modulation was stable at T0 (ICC = 0.68, 95%CI = 0.12–0.89; p <.02; Figs. 3-C2, Figure S1) but not at other timepoints (ICC $\leq$ 0.34; p $\geq$ 0.24; Figure S6), replicating the findings of the previous cohort. Similar results were found when using non-normalized iTBS effects (Table S1). Also, AMT, RMT and baseline MEP were stable across time (Table S2). Since we did not find significant differences in Cortical excitability modulation (CEM) between the two cohorts with similar TMS acquisition procedures, i.e., test cohort with left TMS-sessions first and replication cohort (data not shown), they were combined for further analysis in order to increase statistical power. In the com-

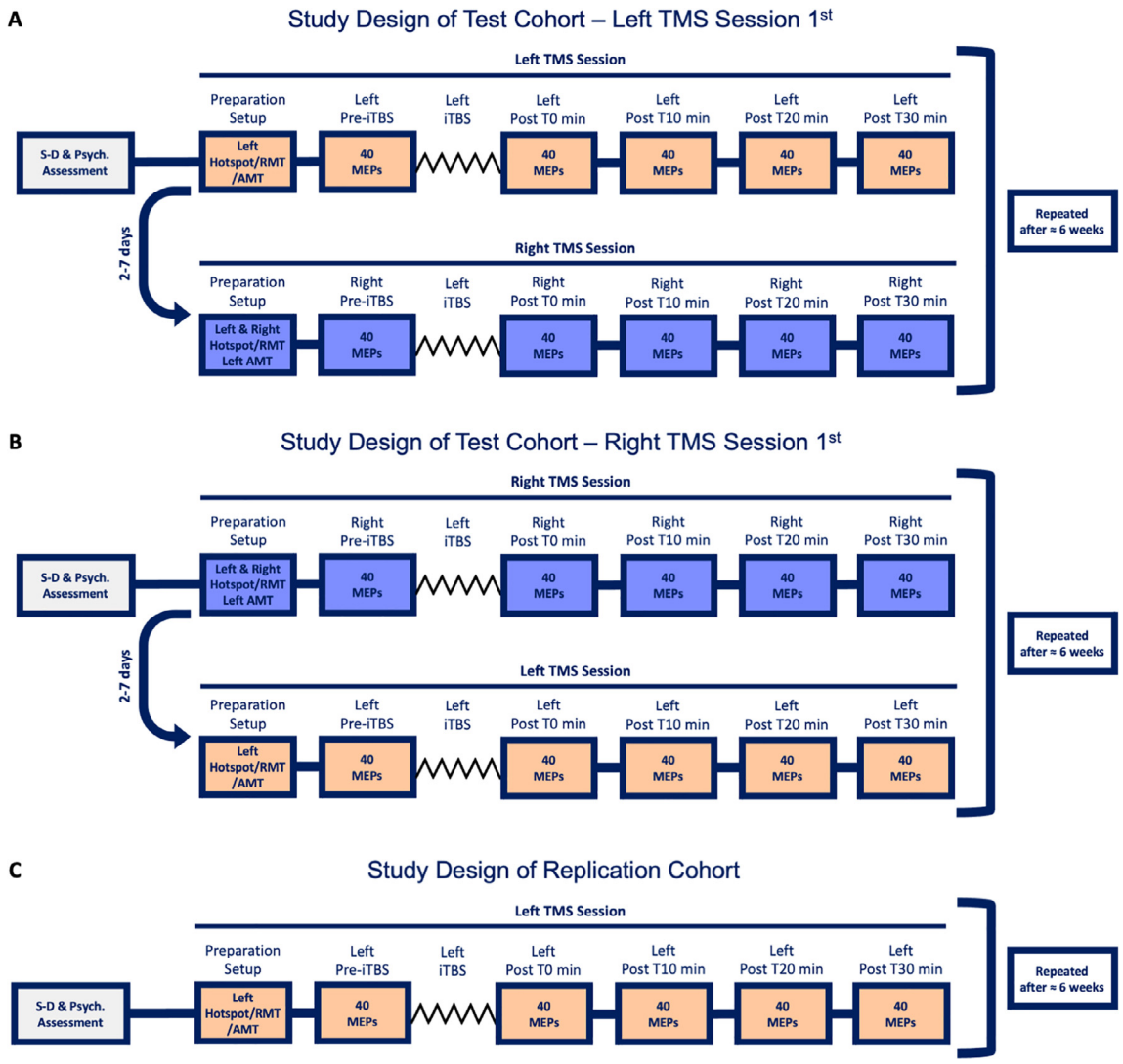


Fig. 1. Study design diagrams. Test cohort subjects were enrolled in a bilateral Transcranial Magnetic Stimulation (TMS) session study design, randomizing the order of first TMS-sessions between left (**A**) and right (**B**) hemispheres, while a simplified version of that research protocol was conducted in the replication cohort to confirm the findings obtained in the former (**C**). AMT – Active motor threshold; iTBS – Intermittent theta burst stimulation; MEPs – Motor evoked potentials; Psych. – Psychological; RMT – Resting motor threshold; S-D – Socio-demographic; T – Timepoint; TMS - Transcranial Magnetic Stimulation.

bined cohort, significant left-sided delta-MEP was found at T0, T10 and T20 at baseline ($p_s < 0.01$) and at all timepoints after 6 weeks ($p_s < 0.01$; Figs. 3-D1). Left MC excitability modulation was stable across-time at T0 (ICC = 0.67, 95%CI = 0.31–0.85; p <.01; Figs. 3-D1), but not at other timepoints (Figure S5), consistently with results in each cohort.

In order to test the potential impact of demographic and psychological factors in CEM variability, we combined all available data, since we did not find significant differences in delta-MEPs between the two study samples (data not shown). Significant associations with MC modulation were mostly not found. Only spurious significant associations with psychological variables were observed after multiple comparison correction. State-Trait Anxiety Inventory (STAI) State was weakly but significantly correlated with left delta-MEP at T0 and T30 after 6 weeks (T0: Rho = −0.29, p <.05; T30: Rho = -0.34, p =.02). Weak to moderate but significant correlation was found between Edinburgh Handedness Inventory (EHI) and left delta-MEP at T10, T20, and T30 (T10: Rho = -0.56, p <.0001; T20: Rho = -0.34, p =.02; T30: Rho = -0.41, p <.01) at baseline. Similarly, only spurious and weak significant associations were found when restricting analyses to the test cohort with left TMS-sessions first and the replication cohort. Only STAI State moderately correlated with left delta-MEP at T0 after 6 weeks (T0: Rho = -0.43, p =.02). The lack of significant associations with psychological variables included the scores for participants' expectation of TMS-effect (Fig. 4), that was also not found when restricting analyses to the test cohort with left TMS-sessions first and the replication cohort (data not shown). Multivariable linear regression models, that included handedness, anxiety state, expectation regarding TMS-effect, sex and age confirmed the absence of significant associations between socio-demographic and psychological variables and cortical excitability modulation. We included handedness and anxiety state since these two variables were found to be spuriously significant in the previous correlation analyses. We also included expectation regarding TMS-effect, since it was a variable of particular interest in this study. Finally, sex and age were also added, since they are potentially relevant demographic factors. In sum, left MC modulation immediately after left-sided iTBS (T0), where stability was found and replicated, was not impacted by any of the explored variables.

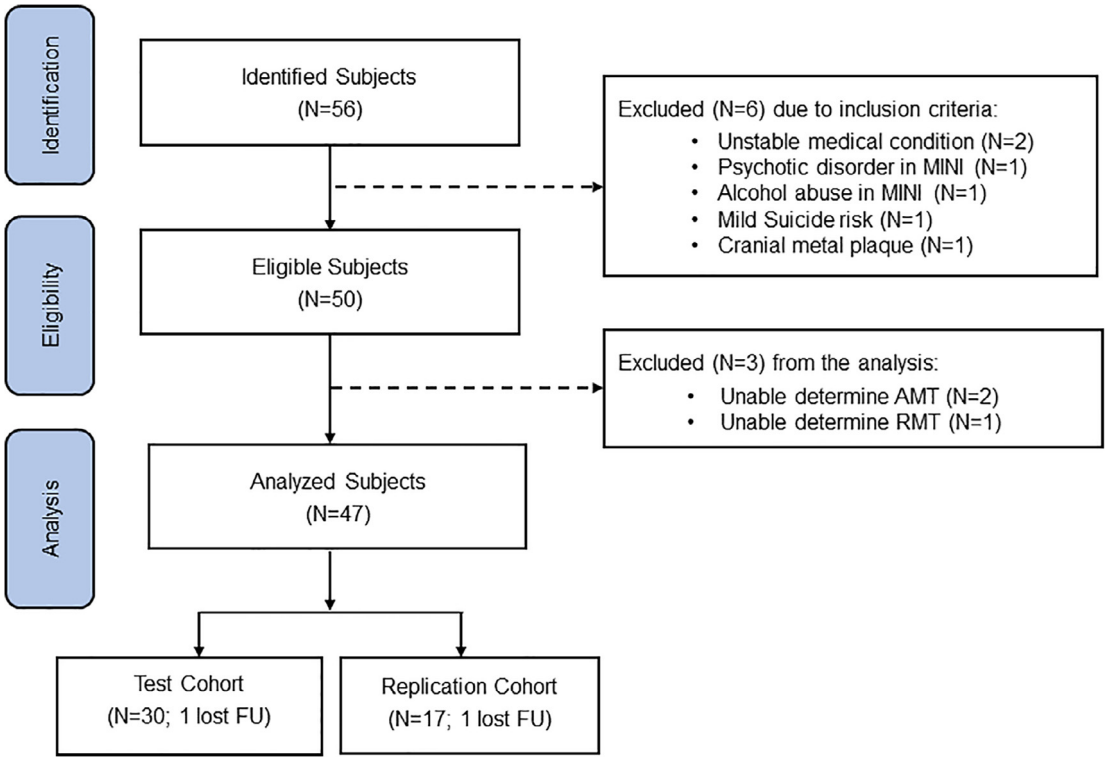


Fig. 2. Study consort diagram. From 56 identified healthy-volunteers, a total of 47 subjects were included in two separate cohorts. AMT – Active motor threshold; FU – Follow up at 6 weeks. MINI –The Mini International Neuropsychiatric Interview (MINI); N – Subject number; RMT – Resting motor threshold.

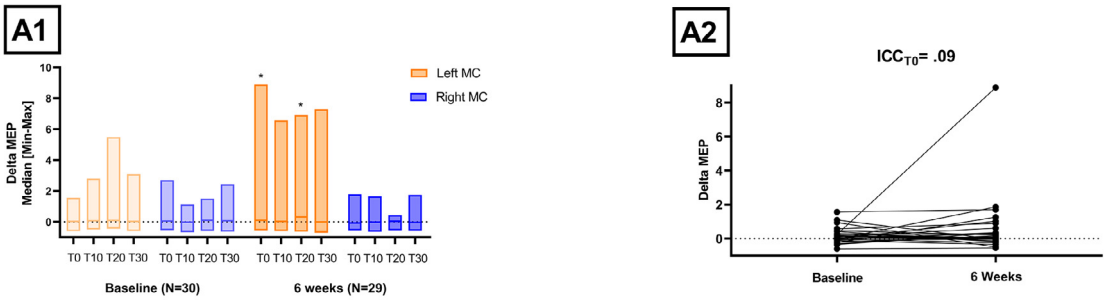
Table 1
Socio-demographic and psychological characteristics of the study sample.

	Total Sample (N = 47) Median [Min - Max]or N (%)	**Test Cohort (N = 30)** Median [Min - Max]or N (%)	**Replication Cohort (N = 17)** Median [Min - Max]or N (%)	**P Value**[a]
Age	32 [21–63]	33 [21–63]	32 [21–60]	n.s.[b]
Female	24 (51%)	15 (50%)	9 (53%)	n.s.[c]
Higher Education	40 (85%)	25 (83%)	15 (88%)	n.s.[c]
Handedness (% Right)[d]	43 (91%)	28 (93%)	15 (88%)	n.s.[c]
BDI	2 [1–22]	4 [0–22]	2 [0–13]	n.s.[b]
BIS	56 [39–76]	57 [39–76]	52 [40–68]	n.s.[b]
EHI	86 [−90–100]	89 [−90–100]	80 [−41–100]	n.s.[b]
HCL-32	14 [0–30]	15 [0–30]	11 [4–19]	n.s.[b]
MADRS	0 [0–7]	0 [0–7]	0 [0–6]	n.s.[b]
MoCA	28 [24–30]	28 [24–30]	28 [25–30]	n.s.[b]
OCI	11 [0–41]	12 [0–41]	9 [2–33]	n.s.[b]
STAI-S	29 [20–55]	29 [20–55]	29 [20–40]	n.s.[b]
T-TMS-EXP	3 [2–5]	3 [2–6]	3 [2–5]	n.s.[b]
WHO-5	18 [5–25]	18 [5–25]	18 [9–23]	n.s.[b]
Left AMT - Left TMS Session	33 [11–44]	34 [15–44]	32 [11–42]	n.s.[b]
Left AMT – Right TMS Session	30 [10–64]	30 [10–64]	n.a.	n.a.
Left RMT - Left TMS Session	45 [33–77]	45 [33–69]	44 [33–77]	n.s.[b]
Left RMT- Right TMS Session	47 [30–64]	47 [30–64]	n.a.	n.a.
Right RMT – Right TMS Session	45 [34–79]	47 [34–79]	n.a.	n.a.
Pre-iTBS Left MEP	879 [281–7788]	799 [281–6050]	1119 [371–7788]	n.s.[b]
Pre-iTBS Right MEP	1262 [265–4478]	1262 [265–4478]	n.a.	n.a.

AMT – Active motor threshold; BDI – Beck Depression Inventory; BIS-11 – Barratt Impulsiveness Scale; EHI – Edinburgh Handedness Inventory; HCL-32 – Hypomania Checklist 32; Higher Education – Education level above high school; iTBS – Intermittent theta burst stimulation; MADRS – Montgomery-Asberg Depression Rating Scale; MEP – Motor evoked potentials; Min-Max – Minimum and maximum range; MoCA - Montreal Cognitive Assessment; N – Number of subjects; n.a. – Not applicable; n.s. – Non significant; OCI-R – Obsessive Compulsive Inventory; RMT – Resting motor threshold; STAI-S – State-Trait Anxiety Inventory-State Subscale; TMS –Transcranial Magnetic Stimulation; TMS-EXP-T – Transcranial Magnetic Stimulation Expectation of Investigational Session Scale Total; WHO-5 – World Health Organization-Five Well-Being Index.

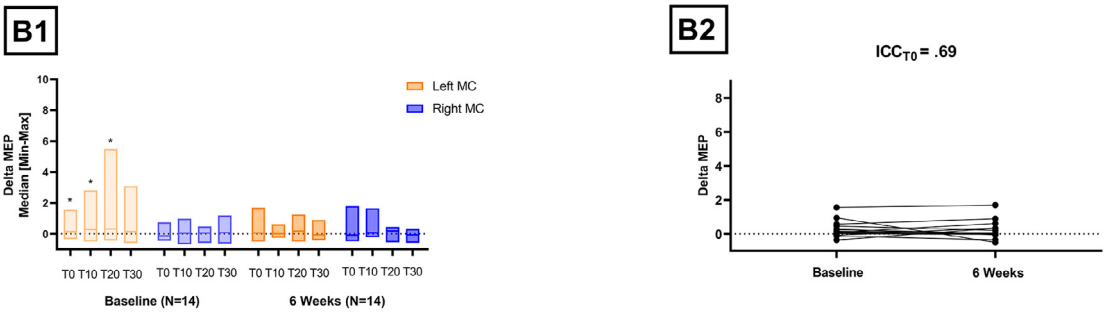
[a] Statistical significance was defined using a False Discovery Rate (FDR) of 0.1, according to Benjamini and Hochberg (1995);
[b] Mann Whitney U Independent Sample Test;
[c] Fisher's Exact Test;
[d] Self-reported handedness.

Test Cohort

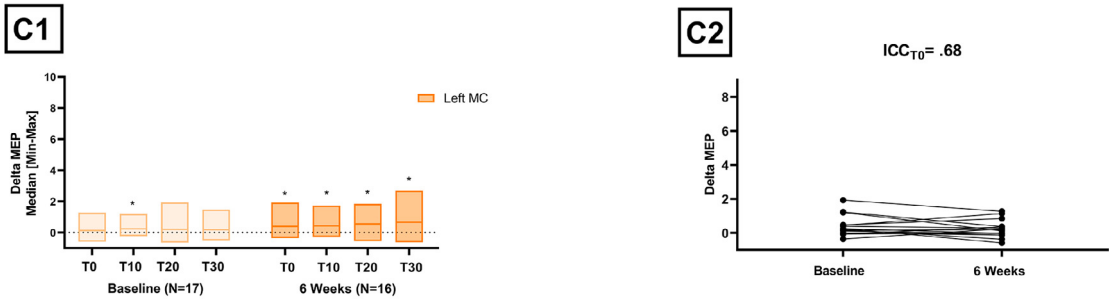


Test Cohort

Left TMS session 1st

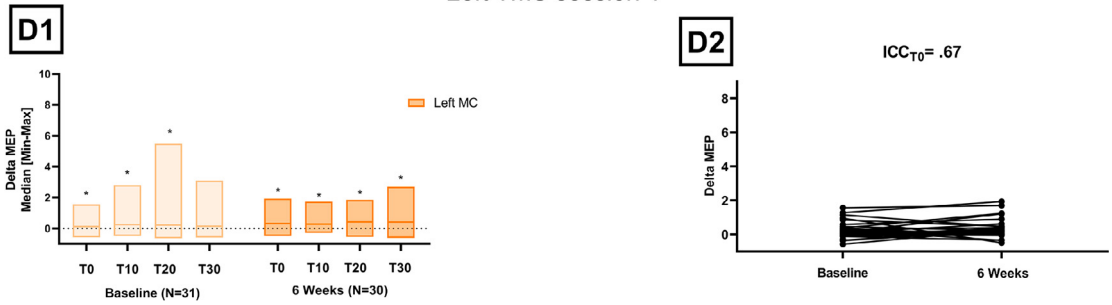


Replication Cohort



Test & Replication Cohort

Left TMS session 1st



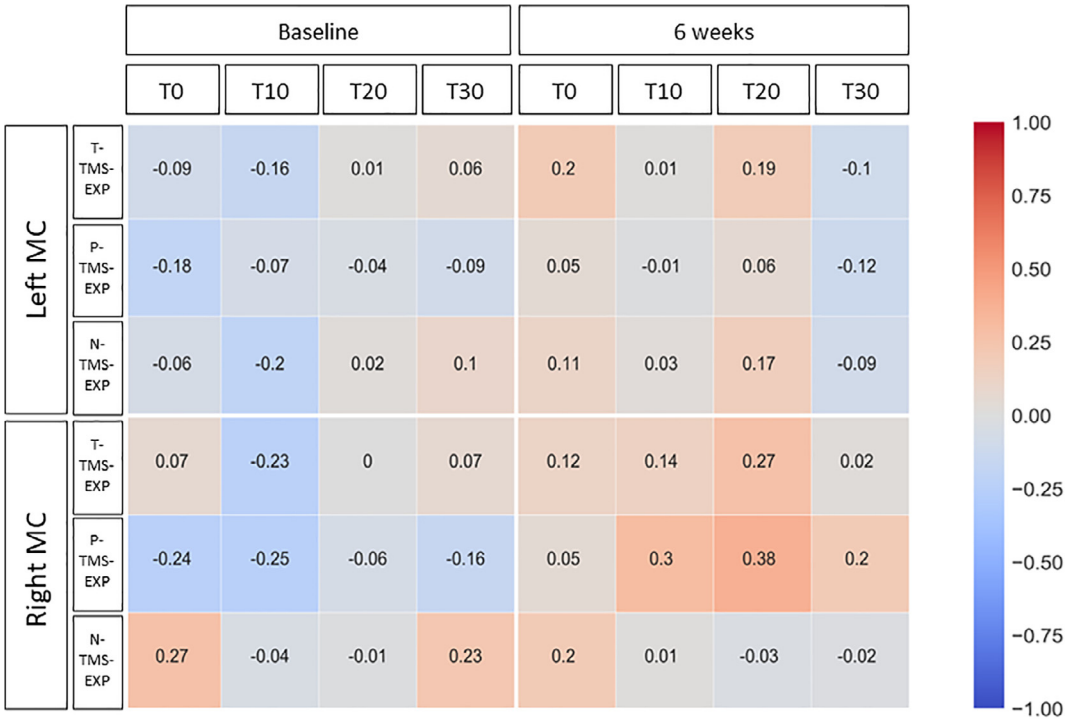


Fig. 4. Expectation of Transcranial Magnetic Stimulation (TMS) effect was not associated with cortical excitability modulation (CEM). We found low and non-significant Spearman Rank Correlation Coefficients between total, positive and negative expectation scores regarding TMS-effect in research setting and cortical excitability modulation (delta MEP) in left and right MC at T0, T10, T20, and T30, at baseline and 6 weeks. MC – Motor cortex; N-TMS-EXP – Negative Transcranial Magnetic Stimulation Expectation of Investigational Session Scale; P-TMS-EXP – Positive Transcranial Magnetic Stimulation Expectation of Investigational Session Scale; T-TMS-EXP – Total Transcranial Magnetic Stimulation Expectation of Investigational Session Scale.

4. Discussion

In the current study, we found that left cortical excitability (CE) was significantly modulated when measured immediately after left-sided motor cortex (MC) intermittent theta burst stimulation (iTBS) protocol, an effect which was not consistently found in the remaining timepoints. Moreover, this effect was stable after 6-weeks only when measured immediately after the modulatory TMS-protocol. Importantly, these results were replicated in a separate confirmatory cohort. On the other hand, no significant right-sided modulation nor stability was found after left-sided iTBS.

Cortical excitability modulation (CEM) has been explored as a biomarker in the context of neuropsychiatric disorders, such as mood (Castricum et al., 2022; Hinchman et al., 2022; Oliveira-Maia et al., 2017; Vignaud et al., 2019) and neurocognitive (Brem et al., 2020) disorders. In the past, repetitive Transcranial Magnetic Stimulation (rTMS), iTBS and continuous theta burst stimulation (cTBS) protocols have been tested as strategies to induce CEM, potentially reflecting plasticity-like phenomena (Huang et al., 2008; Oliveira-Maia et al., 2017). Nevertheless, the development of CEM measurements as diagnostic biomarkers and/or predictors of treatment response has been hindered by high levels of variability and lack of replicability (Schilberg et al., 2017). In fact, the stability of biological measures is critical when exploring potential biomarkers for any clinical condition (Bernard, 1995b; Graham et al., 2017; Schuh et al., 2016). When stability was tested using rTMS, iTBS and cTBS protocols, prior evidence was inconsistent. While some have shown lack of stability (Schilberg et al., 2017) others have found moderate replicability of these measures (Hinder et al., 2014; Jannati et al., 2019). Specifically, when stability of CEM after iTBS was tested, Hinder and colleagues (Hinder et al., 2014) found moderate to poor reliability. However, previous studies assessing MC modulation stability either do not describe their methods in detail and/or present heterogeneous methodological procedures, making them difficult to reproduce in a different research setting. Moreover, such constraints may increase intra

Fig. 3. Motor cortex excitability modulation amplitude and stability. In the test cohort, while left motor cortex (MC) excitability modulation (delta-MEP) at T20 was significant (Wilcoxon Rank Test; p =.04), it did not survive multiple comparison correction, at baseline. Delta-MEP in the left MC was significant at T0 and T20 (p_s < 0.03) at 6 weeks (A1). Delta-MEP was not stable across-time (baseline and 6 weeks) at T0 (ICC = 0.09, 95% CI = 0.90–0.57; F [28,28] = 1.10; p =.40; A2), nor at other timepoints (please see Figure S2). In the test cohort, in subjects randomized to perform left Transcranial Magnetic Stimulation (TMS) sessions first, delta-MEP in left MC was significant at T0, T10, T20 (p_s < 0.04), at baseline (B1). Delta-MEP in left MC was stable across-time at T0 (ICC = 0.69, 95%CI = 0.004–0.90; F [13,13] = 3.11; p =.03; B2), but not in other timepoints (see Figure S2). One subject randomized to perform left TMS-sessions first was excluded from these analyses due to non-compliance to the randomization order at 6 weeks. In the replication cohort, delta-MEP in left MC was significant T10 min (p =.02) at baseline, and at all timepoints (p_s < 0.01) at 6 weeks (C1). Delta-MEP was stable across-time at T0 (ICC = 0.68, 95% CI = 0.12–0.89; F [15,15] = 3.17; p <.02; C2), but not at other timepoints (please see Figure S6). In the test and replication cohort combined, in subjects randomized to perform the left TMS-sessions first, delta-MEP in left MC was significant at T0, T10 and T20 (p_s < 0.01) at baseline, and at all timepoints (p_s < 0.01) at 6 weeks (D1). Delta-MEP in left MC was stable across-time at T0 (ICC = 0.67, 95% CI = 0.31–0.85; F [29,29] = 3.01; p <.01; D2), but not at other timepoints (see Figure S7). As mentioned above, one subject was excluded from these analyses. Overall, delta-MEP in the right MC in the test cohort was not significant (A1 and B1) nor stable across time at all timepoints (see Figures S3 and S4). Friedmańs analysis of variance was equally performed and significant differences between Delta-MEP at all timepoints was not found ($p \geq 0.13$). 1st – First; Delta MEP – Delta motor evoked potential; ICC - Intraclass correlation coefficient; MC – Motor cortex; Min-Max – Minimum and maximum range; N – Number of subjects; T – Timepoint 0, 10, 20 and 30 minutes after left-sided iTBS; TMS – Transcranial Magnetic Stimulation. *Wilcoxon Signed Rank Test corrected for multiple comparisons. Statistical significance was defined using a False Discovery Rate (FDR) of 0.1, according to Benjamini and Hochberg (1995).

and inter-subject variability and limit stability of CEM measures (Roy Choudhury et al., 2011; Schilberg et al., 2017). In this study, in order to decrease the potential impact of methodological heterogeneity we followed a systematic approach of best available evidence in the field (Groppa et al., 2012; Rossini et al., 2015), including adequate Electromyography (EMG) acquisition procedures (De Luca, 2006), the use of neuronavigation (Herwig et al., 2001), collection of appropriate number of motor evoked potentials (MEPs) (Chang et al., 2016), adequate inter-pulse-intervals (Massé-Alarie et al., 2016) and detailed report of acquisition procedures and signal processing (De Luca, 2006). While we did not test the impact of each specific proceedure in CE variability, our results showed improved stability when compared to the best available current literature (Hinder et al., 2014). Future studies, conducted in other TMS research centres, may further validate this approach as a strategy to reduce intra and inter-subject variability of CEM measures.

While we found that left MC excitability modulation is stable immediately after left-sided iTBS, this was not present at other timepoints after modulation. This probably reflects an increase of intra-subject variability in the remaining timepoints (Corp et al., 2020; Fried et al., 2017; Sui et al., 2020). Such results suggest that assessing CE after longer periods post-modulation will more likely be impacted by other factors, resulting in increased variability of these measures (Corp et al., 2020; Fried et al., 2017; Sui et al., 2020). Hence, our results suggest that when exploring CEM as a potential biomarker, the moment of its assessment is critical. In fact, the timepoint post left iTBS where we found most stability differs from the timepoint where differences were found between healthy-subjects and a clinical population, specifically in depressed subjects (Castricum et al., 2022; Vignaud et al., 2019). Since there is inherent variability of CEM in these later timepoints, future studies using our systematized methodology should be conducted to clarify if these findings are consistent. Moreover, such studies should also explore if CEM immediately after left-sided iTBS as measured by our protocol may also reveal differences between healthy and clinical populations, further confirming their role as potential biomarkers in neuropsychiatric disorders.

Additionally, we did not find any consistent modulation on the right hemisphere after applying iTBS to the left MC, even when focusing on individuals who were randomized to right TMS-sessions first. Other studies have explored the modulatory effects of facilitatory and inhibitory TMS-protocols in both hemispheres with mixed results. After an inhibitory TMS-protocol, i.e., low frequency rTMS (LF-rTMS) (Gangitano et al., 2002) or continuous TBS (cTBS) (Huang et al., 2008), decreased and increased CE was found in ipsilateral and contra-lateral motor cortices, respectively (Bajwa et al., 2008; Heide et al., 2006; Stefan et al., 2008; Suppa et al., 2008). On the other hand, the opposite effect was described after a facilitatory protocol (iTBS) (Huang et al., 2008), i.e., increased and decreased CE was found in ipsilateral and contra-lateral hemispheres, respectively (Di Lazzaro et al., 2008; Suppa et al., 2008). While these results favour a trans-hemispheric impact of TMS modulatory protocols (Trompetto et al., 2004), aforementioned studies did not randomize the order and side of assessment. In fact, in studies where randomization was performed, the contra-lateral effect of TMS was absent (Di Lazzaro et al., 2011; Plewnia et al., 2003), as we have shown in the current study after performing a facilitatory protocol. These findings suggest that the order of assessment may impact contra-lateral TMS-effects. However, to unequivocally clarify the effects of TMS modulatory protocols in bilateral CE, future studies measuring ipsilateral and contra-lateral impact of rTMS should be conducted in a single sample, in different TMS-sessions, while randomizing the order of hemispheric assessment.

Finally, we were interested in studying the possible impact of socio-demographic and psychological variables on MC excitability modulation. Previous studies have shown that sex had no effect on MEP stability (Vernet et al., 2014), while physical activity was not associated with CEM when assessed using TMS-protocols (Vallence et al., 2015). Conversely, body weight (Sui et al., 2020) and age (Fried et al., 2017) were found to potentially influence the level of CE. In our study, we found that when CE modulation was present it was not consistently associated with any of the explored variables, except for significant yet spurious, poor to moderate, correlation between handedness (assessed with Edinburgh Handedness Inventory, EHI) and CEM. Specifically, higher degree of right-handedness was correlated with lower CEM, only on the left hemisphere 10, 20, and 30 min after left-sided iTBS at baseline visit, which was not observed at 6 weeks, making this result difficult to interpret. Cahn and colleagues did not find significant differences between right and left-handed subjects regarding CE (Cahn et al., 2003), further suggesting that there are mixed results regarding handedness that should be clarified in future research.

We were particularly interested in assessing if expectation regarding TMS, similar to a placebo-like-effect, was a potential predictor of CEM. The role of placebo-effect in TMS treatment for depression has been studied in clinical research (Razza et al., 2018). Interestingly, a recent study explored how placebo-effect modulates brain activity through similar neuronal networks to those stimulated in TMS treatment for depression (Burke et al., 2019). Considering current evidence, we hypothesized that individual expectation towards TMS could act as a placebo-like-effect and consequently impact CEM. In fact, in a neurophysiological TMS research context, Perellón-Alfonso and colleagues (Perellón-Alfonso et al., 2018) have suggested that placebo-like TMS, i.e. sham TMS, had similar effects when compared to active modulatory protocols, after informing all subjects that a temporal increase of CE was expected (Perellón-Alfonso et al., 2018). In another study, lower levels of modulation were observed in a second study visit, i.e., when subjects had already performed a TMS-session (Schilberg et al., 2017). This result may suggest that being familiar with a modulatory TMS-protocol may impact CEM due to changes in expectation towards the TMS-effect (Schilberg et al., 2017). In fact, clinical response to a first TMS treatment cycle for depression is considered a good predictor for antidepressant response in a second treatment cycle (Kelly et al., 2017), suggesting that positive expectation may have an impact on subsequent TMS experience. Nevertheless, our results showed that CEM was not impacted by total, positive or negative expectations towards TMS-effect. We believe that these results should motivate future research exploring the impact of individual expectation on CEM variability in operationalized settings (Enck et al., 2011). Overall, while we found spurious associations between potential socio-demographic and psychological predictors and CEM, namely handedness or levels of state anxiety, they were not consistent nor present when considering the most stable timepoint, i.e., immediately after modulation. These results suggest that CEM immediately after left-sided iTBS is stable and not likely impacted by external factors. Nevertheless, the low variability of severity across psychometric assessments, such as symptoms of anxiety or depression, in this study sample of healthy volunteers, is a limitation regarding interpretability of the spurious correlations found between these variables and delta MEP. Indeed, the fact that we analyzed these association only considering healthy individuals may limit the meaning of this finding. Future studies, including clinical populations, should confirm or disprove these findings.

Importantly, current results were obtained from CE measures acquired on the MC, which may not truly reflect other brain regions activity (Boroojerdi et al., 2002). This is particularly important when considering such measures as potential biomarkers of

neuropsychiatric disorders (Brem et al., 2020; Oliveira-Maia et al., 2017) or when studying the mechanism of action of therapeutic TMS (Pascual-Leone et al., 1998b). Hence, different authors have been exploring CE measures in other brain regions using different methods (Gosseries et al., 2015; Voineskos et al., 2019). In fact, Voineskos and colleagues found differences between patients diagnosed with depression and healthy-subjects in CE measures acquired with electroencephalography (EEG) on left dorsolateral prefrontal cortex (DLPFC (Voineskos et al., 2019), a clinical effective TMS target to treat depression (Mutz et al., 2019). However, while they are promising clinical and neurophysiological tools (Thut and Pascual-Leone, 2010), TMS-EEG measures are still under development, with several authors claiming for technical improvement of the acquisition protocols (Siebner et al., 2019; Thut and Pascual-Leone, 2010).

There are limitations that need to be considered in the present work. First, the combined methodological procedures used in this study to assess MC excitability modulation lack external validation. Nevertheless, while the methods used in our study need to be tested in other research centres and contexts, they were selected according to best available evidence and are described in detail, further supporting its overall use. Even if MC excitability modulation was not consistent across all sessions and not well established in all study cohorts, despite stable AMT, RMT and pre iTBS MEPs, when using the same methods, we were able to replicate our results in a subsequent and separate cohort, suggesting that this methodology can be a valid and promising improvement to the field. Second, our study follows a complex design, including a total of four TMS research sessions, i.e., two study visits, baseline and after 6 weeks, with two sessions in each visit to assess the two hemispheres. In addition, right TMS-sessions included additional procedures that were not performed in left TMS-sessions, such as right-hand skin preparation, localization of right-hand motor hotspot, and assessment of right RMT. Such complexity might interfere in CEM due to potential impact of TMS carry-over effects. In fact, we hypothesised that long-lasting changes after performing a first TMS-session on the right side may impact CEM on the left hemisphere in a subsequent left TMS-session, particularly because left hemisphere was modulated in both sessions. While this may not be concerning for right sided measures, since modulation was not consistently observed, this might be the reason why left CEM was less reproducible when measured shortly after a previous TMS-session. Further pursuing this hypothesis, in an exploratory approach, we assessed possible carry over effects, using within-subjects comparisons of RMT measured in the left MC at the start of the first and second TMS sessions, and of pre-iTBS MEP, also assessed in the first and second sessions. In both comparisons, we found no significant differences (p =.07-0.93). Whilst these results suggest the absence of carry over effects, this hypothesis should be further explored in a study specifically designed to clarify this question. For example, by assessing MEPs post iTBS in sequential later time-points (days or weeks) at the same hemisphere and using pre-iTBS stimulation intensity (RMT). While the complex study design in the test cohort might have impacted our results, our main findings were confirmed when we simplified research design to only assess left side CEM. Nevertheless, more research is needed to validate the implemented measurement procedures. While we have attempted to minimize the potential carry-over effects between TMS-sessions according to current evidence (Pellicciari et al., 2016; Vallence et al., 2015), namely by separating each session by at least 48 hours, this effect might still be present. Future studies, specifically addressing this question, with similar design as presented above, may help to further confirm the hypothesis of long-lasting effect of TMS. Moreover, in the replication cohort, when restricting the assessment to left TMS-sessions, we were able to replicate CEM stability immediately after left-sided iTBS. Importantly, this study design was less complex, limiting the potential impact of TMS between the two sessions. Third, our study did not consider other biological variables that might contribute to CEM variability. In fact, previous studies found that genetic polymorphisms, e.g. Val66Met (Harvey et al., 2021), and immunomarkers (Mori et al., 2016; Rossi et al., 2011) impacted CEM. Hence, we cannot exclude similar effects in our cohorts. However, as a secondary focus we also intended to explore socio-demographic and psychological variables, which were not found to have any meaningful association with CEM. The fact that we did analyse this association only in a healthy population so far might limit the interpretation of this finding. Finally, in order to investigate the possible association between participants' expectation towards TMS and CEM in our study, we did not manipulate participant's expectation towards TMS-effects. The most adequate research design to answer this question would be a randomized control trial with manipulation of expectations. While this can be considered a potential limitation, our study was the first to formally explore the impact of individual expectation in neurophysiological measures. To the best of our knowledge, there was no appropriate self-report instrument available for this purpose. Accordingly, while acknowledging the limitations of self-report scales (Prasad et al., 2004; Rolley et al., 2008), we followed the most appropriate psychometric procedures (ITC Guidelines for Translating and Adapting Tests (Second Edition), 2018) to increase assessment accuracy. Specifically, we have adapted a validated treatment expectation instrument (Younger et al., 2012) to the TMS research context. While our results should not be viewed as definitive, they may prompt future studies, using appropriate experimental designs, to answer if expectation impacts CEM.

5. Conclusion

In conclusion, in this study we found that left-sided intermittent theta burst stimulation (iTBS) had a significant effect on left but not on right cortical excitability (CE). Noteworthy, left cortical excitability modulation (CEM) was stable when assessed immediately after left-sided iTBS. However, stability was not observed in other post-modulation timepoints nor at any timepoint on the right hemisphere. Additionally, we found that CEM was not impacted by different individual socio-demographic and psychological factors, including participants expectation about the Transcranial Magnetic Stimulation effect itself. This was particularly consistent for left CEM immediately after left-sided iTBS, which was also the measurement with most stability.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

GC was funded by Fundação para a Ciência e Tecnologia (FCT; Portugal) through a PhD Scholarship (SFRH/BD/130210/2017. CS, GC and AJO-M were supported by grant PTDC/MED-NEU/31331/2017. AJO-M by grant PTDC/MEC-PSQ/30302/2017-I C&DT-LISBOA-01–0145-FEDER, funded by national funds from FCT/MCTES and co-funded by FEDER, under the Partnership Agreement Lisboa 2020 - Programa Operacional Regional de Lisboa, and by a Starting Grant from the European Research Council under the European Union's Horizon 2020 research and innovation programme (grant agreement no. 950357). The content of this study is solely the responsibility of the authors and does not necessarily

represent the official views of the Fundação para a Ciência e Tecnologia or the European Research Council.

AJO-M was national coordinator for Portugal of a non-interventional study (EDMS-ERI-143085581, 4.0) to characterize a Treatment-Resistant Depression Cohort in Europe, sponsored by Janssen-Cilag, Ltd (2019–2020), national coordinator for Portugal of trials of psilocybin therapy for treatment-resistant depression, sponsored by Compass Pathways, Ltd (EudraCT number 2017–003288-36), and of esketamine for treatment-resistant depression, sponsored by Janssen-Cilag, Ltd (EudraCT NUMBER: 2019–002992-33), and is recipient of a grant from Schuhfried GmBH for norming and validation of cognitive tests.

None of the aforementioned agencies had a role in the design and conduct of the study, in the collection, management, analysis, and interpretation of the data, in the preparation, review, or approval of the manuscript, nor in the decision to submit the manuscript for publication. The remaining authors have declared that they have no potential conflicts of interest involving this work, including relevant financial activities outside the submitted work and any other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing what is written.

Acknowledgments

CS, GC, FFV, DRS and AJO-M conceived and designed the work; CS, GC, FFV, DRS, PP and AJO-M acquired the data; CS, GC, FV, DRS, PP and AJO-M analyzed and interpreted data; CS, GC and AJO-M drafted the manuscript, that was critically revised by the remaining authors for important intellectual content. All authors approved the final version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. AJO-M had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Order of co-first authors was decided by consensus.

The authors would like to thank Raquel Lemos and Anna Hobbiss, Catarina Fonseca, Daniel Houghton, Diana Frasquilho and Silvia Almeida for their contribution in the adaptation process of TMS Expectation of Investigational Session Scale.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2023.04.014.

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