Investigation of LTP-like plasticity, memory and prefrontal cortical thickness: a TMS-EEG and brain imaging study

Jessica Drodge

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Department of Cellular and Molecular Medicine
Faculty of Medicine
University of Ottawa

Abstract

Introduction. Memory is a complex cognitive process formerly linked to mechanisms of brain plasticity that can be estimated in the left dorsolateral prefrontal cortex (DLPFC) using transcranial magnetic stimulation and electroencephalography (TMS-EEG). Also, cortical thickness in the DLPFC may be a potential proxy measure of brain plasticity as previous literature reports a link between better memory and thicker cortex. However, the link between brain plasticity and memory performance as well as DLPFC thickness remains to be clarified.

Methods. Intermittent theta burst stimulation (iTBS) probed plasticity-like mechanisms in the left DLPFC in 17 cognitively healthy participants. TMS-EEG recordings were performed before and after sham and active iTBS to quantify plasticity via transcranial magnetic stimulation-evoked potentials (TEPs). Composite memory scores for each domain (verbal episodic, visual episodic and working memory) were obtained using the Cambridge Neuropsychological Test Automated Battery. Anatomical T1 images were acquired by magnetic resonance imaging and processed by open-source software (CIVET) and the Automated Anatomical Labeling atlas to extract cortical thickness of the DLPFC. All statistical analyses (linear mixed model, Tukey's post hoc test and Pearson's correlations) were completed in R Studio.

Results. iTBS resulted in increased TEP amplitude P30 ($F= 5.239$, $p = 0.029$), as shown by a significant interaction between condition (iTBS, sham) and time (pre- and post-condition). Specifically, Tukey's post hoc test revealed that the P30 increase was near trending significant post-iTBS compared to pre-iTBS for the active condition ($p = 0.166$) but not for the sham condition ($p = 0.294$). A trending significant relationship was observed between the magnitude of P30 change post-iTBS and thicker left DLPFC ($r = 0.488$; $p = 0.108$). Lastly, no significant relationships between P30 change and memory performance were observed.

Conclusion. These preliminary findings suggest there could be a relationship between increased capacity for brain plasticity and a thicker left DLPFC. To further investigate these relationships, we plan to recruit additional cognitively healthy participants. Our preliminary findings support the foundation for future clinical studies in which DLPFC thickness could be explored as a predictive factor for response to plasticity-targeting iTBS treatment.

Dedication & Acknowledgments

Firstly, I thank my family and close friends for their unwavering support and encouragement throughout my graduate studies.

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List of Abbreviations

3D	Three dimensional
AAL	Automated Anatomical Labeling
AMT	Active motor potential
ANOVA	Analysis of variance
CANTAB	Cambridge Neuropsychological Test Automated Battery
CI	Confidence interval
COVID-19	Coronavirus disease 2019
DLPFC	Dorsolateral prefrontal cortex
DMS	Delayed matching to sample
EEG	Electroencephalography
EMG	Electromyography
EPSP	Excitatory post-synaptic potential
fMRI	Functional magnetic resonance imaging
GABA	Gamma-aminobutyric acid
ICA	Independent component analysis
IQ	Intelligence quotient
IQR	Interquartile range
iTBS	Intermittent theta burst stimulation
LTP	Long-term potentiation
MATLAB	MATrix LABoratory
MEP	Motor-evoked potential
MINI	Mini International Neuropsychiatric Interview

MNI152	Montreal Neurological Institute Template
MPRAGE	Magnetization-prepared rapid gradient-echo
MRI	Magnetic resonance imaging
PAL	Paired associate learning
PET	Positron emission tomography
PFC	Prefrontal cortex
RMT	Resting motor potential
ROI	Region of interest
SWM	Spatial working memory
TEP	Transcranial magnetic stimulation evoked potential
TMS	Transcranial magnetic stimulation
VRM	Verbal recognition memory
WASI	Wechsler Abbreviated Scale of Intelligence

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1 Introduction

The human brain is a complex organ which can develop and adapt over time in ways still not fully understood. Scientists have spent years studying the brain to understand its capacity for adaptation. However, it was not until the late 1800s that researchers such as Santiago Ramón y Cajal and Donald Olding Hebb first used terms such as the "neuron doctrine" and "brain plasticity" to describe adaptive neural communication and cell re-organization found in the central nervous system (Fuchs & Flügge, 2014). Brain plasticity refers to the process of neural network modification and adaptation in response to repeated network activation with actions like thought, behaviour, and other external stimuli (Gillick & Zirpel, 2012). Without brain plasticity, adaptive processes such as learning would be impossible (T. V. P. Bliss & Collingridge, 1993b; Lashley, 1920; Oberman & Pascual-Leone, 2013; Stanley & Jaynes, 1949).

1.1 Mechanism of brain plasticity

The Hebbian Theory of Learning was one of the first published theories to explain the core cellular mechanisms underlying brain plasticity (Hebb, 1949; Tees, 2003). The famous citation, "neurons that fire together wire together," credited to Carla Shatz highlights the foundation of the Hebbian Theory (Hebb, 1949). This theory proposes that repeatedly activated neurons and their associated synaptic connections will create an association between the experience, creating cell memory. When cell memory occurs, efficient neural communication at the synapse level can occur during processes involved in learning and memory. Neuroscientists Terji Lømo and Timothy Bliss published some of the first evidence of cell memory and synaptic plasticity in the hippocampus of rabbits, in which repetitive stimulation of perforant path fibres in the hippocampus produced a lasting potentiated cellular response (T. V. P. Bliss & Gardner-Medwin, 1973; T. V. P. Bliss & Lømo, 1973). As a result of research such as this, long-term potentiation (LTP) may be used to

describe the synaptic mechanisms facilitating strengthened synaptic connections (Andersen & Lømo, 1967; T. V. P. Bliss & Lømo, 1973; Lømo, 2003, 2018).

1.2 Long-term potentiation (LTP)

The process of LTP has been observed to produce a long-lasting increase in neuron-to-neuron signal transmission between two or more neurons (Cooke & Bliss, 2006). Tetanic stimulation (i.e., a high-frequency series of pre-synaptic neuron stimulation) can induce LTP *in vivo,* which produces an excess of ion fluctuation that can trigger various cellular processes, including changes in neurotransmitter and synaptic receptor function that may alter synaptic activity (T. V. Bliss & Collingridge, 2013; T. V. P. Bliss et al., 1968; Cooke & Bliss, 2006; Madison et al., 1991; Maren, 1999). Activity-dependent synaptic modifications are essential for ongoing neural communication, as they can influence and reinforce molecular and electrical properties of neural networks (Citri & Malenka, 2008). Such modifications may include increased excitability and sustained excitatory postsynaptic potentials (T. V. P. Bliss & Gardner-Medwin, 1973). When neural networks are reinforced, brain function and behaviour may change. For this reason, LTP is one of the potential mechanisms of brain plasticity. Previous research suggests that LTP may produce adaptive functional change within the brain, which can have an essential role in learning and memory (Eccles, 1983; Lynch, 2004).

1.3 Transcranial magnetic stimulation and brain plasticity

LTP has been extensively studied in animal models using electrophysiological stimulation techniques (Anderson et al., 2016; Eccles, 1983; Vulovic et al., 2018). However, such invasive techniques cannot be replicated *in vivo*; thus, human research requires different stimulation techniques. The development of brain stimulation methods from animal studies, such as transcranial magnetic stimulation (TMS), has provided researchers with a new tool to examine human brain plasticity mechanisms (Bashir et al., 2010). TMS is a neurostimulation tool based on

Faraday's law of electromagnetic induction, in which a magnetic pulse is applied to the cortex to induce electrical activity in neurons of the targeted cortical region (Rossi et al., 2021; Rossini et al., 2015). TMS is non-invasive, painless, and can be used to stimulate any cortical area (Rossi et al., 2009, 2021). When applied repeatedly, TMS can modulate brain activity beyond the duration of the stimulation (Huang et al., 2005; Hui et al., 2019). A specific form of TMS called intermittent theta burst stimulation (iTBS) was developed based on LTP induction protocols in animal studies (Guerra et al., 2018; Huang et al., 2005). ITBS uses a pattern of stimulation (i.e., two trains of 50Hz burst pulses repeated at 5Hz frequency every 10s for a total of 600 pulses), in which the timing and frequency of stimulation may modify brain activity. When applied to cortical regions, the iTBS protocol modulates cortical activity (Struckmann et al., 2019). In previous LTP induction studies, researchers have observed a similar change in neural activity between stimulation of the hippocampus in rodents compared to iTBS-dependant modulation of the human cortex (Capocchi et al., 1992; J & G, 1986, 1989). For this reason, similar brain plasticity mechanisms are suggested to underlie each process (Suppa et al., 2016). The TMS research field refers to "LTP-like" brain plasticity when discussing iTBS (Pell et al., 2011) since it is believed that iTBS-dependent neural modulation may represent a change in synaptic strength.

1.4 LTP-like brain plasticity in the human cortex

The primary motor cortex was the first cortical site targeted to quantify the LTP-like effects of iTBS for human application (Huang et al., 2005). When single TMS pulses were applied to the primary motor cortex, the stimulation activated the corticospinal tract, producing quantifiable muscle activity in the targeted muscle (Rossini et al., 2015). The induced muscle activity, known as motor-evoked potentials (MEPs), can be measured with electromyography (EMG) which provides a marker of cortical excitability (Rossini et al., 2015). Previous literature has linked changes in MEP amplitude to changes in local brain activity (Huang et al., 2005; Premoli et al.,

2014). With one 3-minute session of iTBS to the motor cortex, a sustained increase in cortical excitability was obtained and quantified by an increase in MEP amplitude up to 90 minutes after stimulation (Chung et al., 2017; Guerra et al., 2018; Hui et al., 2019). The sustained increase in cortical excitability due to iTBS is suggested to mirror the process of LTP in brain plasticity (Chung et al., 2019; Chung, Rogasch, Hoy, & Fitzgerald, 2018; Chung, Rogasch, Hoy, Sullivan, et al., 2018). However, brain regions outside the primary motor cortex require additional electrophysiological monitoring technology to measure iTBS-induced changes in cortical excitability.

A combination of electroencephalography (EEG) and concurrent TMS may be used to monitor iTBS-induced changes to cortical excitability in non-motor regions, such as in the prefrontal cortex (see Figure 1; PFC) (Hui et al., 2019; Tremblay et al., 2019). More specifically, EEG was used to measure changes in cortical electrical activity through summated excitatory postsynaptic potential (EPSP) evaluation from recording electrodes built into the EEG cap (Tremblay et al., 2019). Research groups have recently combined both methods (TMS-EEG) due to advancements in EEG amplifier technology and data processing techniques. The electrical current generated by TMS in neural tissue produces a measurable waveform pattern of neural electrical activity in the cortex known as TMS-evoked potentials (TEPs), which can be further examined with EEG before and after iTBS application (Hui et al., 2019; Siebner et al., 2019). The standard TEP waveform response exhibits specific patterns in amplitude (positive peaks (P) or negative troughs (N)) at five-time points after a TMS pulse (i.e., P30, N45, P60, N100, P200) as shown in Figure 2. The number associated with these components represents the time in ms when they present after TMS stimulation.

Each peak or trough observed in the TEP waveform listed above has been linked to either excitatory or inhibitory neural communication and can be monitored to estimate LTP-like brain plasticity in response to repeated brain stimulation (Casarotto et al., 2010; Huang et al., 2005; Ilmoniemi et al., 1997). To better understand the TEP waveform's excitatory and inhibitory mechanistic nature, research groups have employed a method termed pharmaco-TMS in which pharmacological agents, such as GABAergic receptors agonists, are administered before TMS-EEG recordings to assess their effects on TEP waveform amplitudes (Tremblay et al., 2019). Specifically, previous literature suggests that early positive TEP components (i.e., P30, P60) may reflect excitatory activity through glutamatergic receptors, and negative TEP components (i.e., N45 and N100) may reflect inhibitory activity via GABAergic receptors (Tremblay et al., 2019). For example, TEP component P30 was shown to be modulated by a novel anti-epileptic drug known to reduce cortical excitability (Premoli et al., 2019), while P60 was modulated by an anti-glutamatergic drug (Belardinelli et al., 2021). Conversely, TEP components N100 and N45 recorded in the left primary motor cortex have significantly changed in response to GABA-B and GABA-A receptor action (Premoli et al., 2014, 2018; Darmani et al., 2016). Although the majority of pharmaco-TMS-EEG studies to date have been conducted in the left primary motor cortex, results can be translated to other cortical regions in which similar TEP waveforms are observed. Altogether, these studies provide important insights into the independent mechanisms involved in TEP component presentation and modulation following iTBS in cortical regions like the left DLPFC.

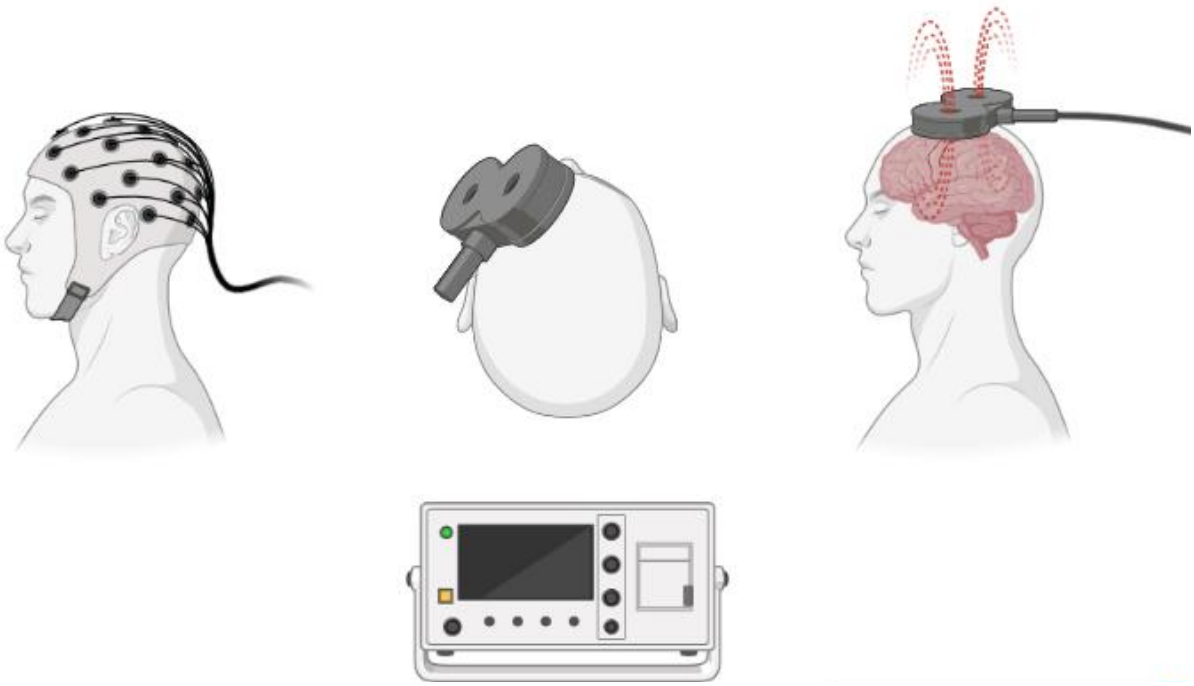

Figure 1. Schematic of TMS coil and EEG cap placement, created with BioRender.com.

TMS = transcranial magnetic stimulation; EEG = electroencephalography.

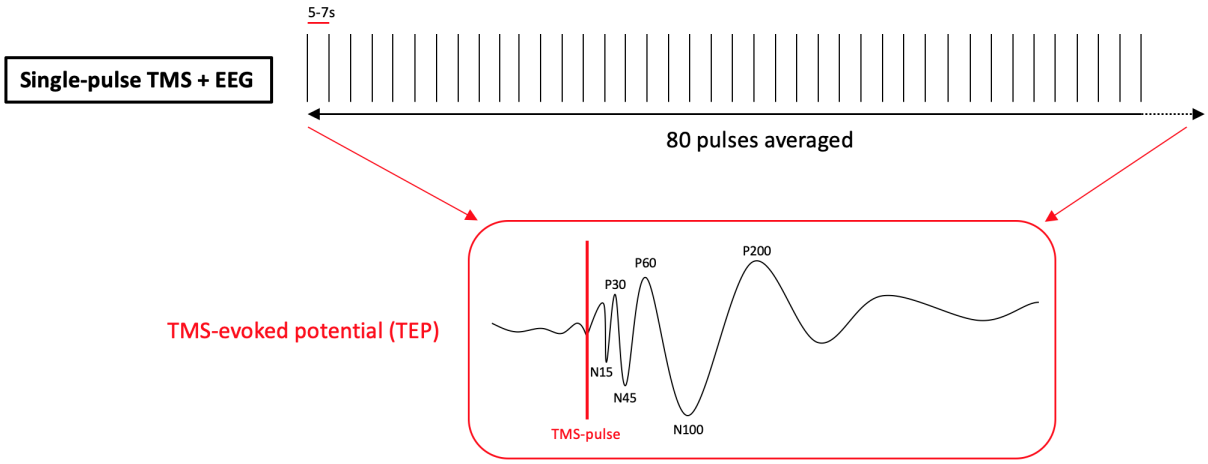

Figure 2. Transcranial magnetic stimulation evoked potential waveform.

In 2017, the first demonstration of iTBS-induced LTP-like brain plasticity in the human dorsolateral prefrontal cortex (DLPFC) was shown (Chung et al., 2017). This study used TMS-

EEG to measure brain plasticity in healthy participants before and after iTBS and sham stimulation were applied to the left DLPFC. A significant change in cortical excitability was reported following active iTBS compared to the sham condition. Specifically, mean amplitudes of components N100 and P200 significantly increased post iTBS, in which N100 became more negative in amplitude and P200 became more positive in amplitude. This finding is crucial as it provides evidence to support plastic-like cortical activity in the DLPFC due to iTBS (Chung et al., 2017). Following this evidence of LTP-like plasticity in the DLPFC, iTBS-induced changes to TEP amplitudes in the DLPFC were partially replicated in a series of studies from the same group (Chung et al. 2018a, b; 2019), as well as from other groups. A summary of TMS-EEG studies assessing the impact of iTBS on DLPFC activity in healthy individuals is presented in Table 1.

Table 1. TMS-EEG protocols at left DLPFC in healthy individuals only.

Authors & Date	Sample size	TEP	Sham (y/n)	Neuronavigation & MRI	Results post-iTBS	EEG electrodes
Chung et al., 2017	10	N40, P60, N100, P200	yes	none	Increased N100 and P200 amplitude	F3, F1, FC3, FC1
Chung el al., 2018a	18	N45, P60, N100, P200	yes	none	Increased N100 and P200 amplitudes	FC1, FCz, FC2
Chung et al., 2018b	16	N45, P60, N100, P200	no	none	Increased N100 amplitude	FC1, FCz, FC2
Chung et al., 2019	20	N45, P60, N100, P200	no	none	No change	FC1, FCz, FC2
Goldsworthy et al., 2020	33	N45, P60, N100,	yes	none	Increased P60 amplitude	AF3, F5, F3, F1, FC5, FC3, FC1
Desforges et al., 2022	14	P30, N45, P60, N100, P200	no	MRI (none), Neuronavigation (yes)	Decreased P30, P60 and P200 amplitude; Increased N45 amplitude	AF3, F1, F3, FC1, FC3

Six out of seven studies in Table 1 showed significant modulation of TEP amplitudes after iTBS. However, the effect and direction of TEP amplitude change in the DLPFC due to iTBS are generally inconsistent across the studies. The most consistent finding by Chung and collaborators was an increase in the amplitude of the N100 component, reflecting increased inhibition following iTBS. Even so, this result was not replicated by recent studies conducted by other groups (Chung et al., 2017, 2019; Chung, Rogasch, Hoy, & Fitzgerald, 2018; Chung, Rogasch, Hoy, Sullivan, et al., 2018). In addition, four out of seven studies showed a modulation of the amplitude of the P200 component although the direction of the change has been inconsistent, with three studies showing an increase (Chung et al., 2017; Chung, Rogasch, Hoy, & Fitzgerald, 2018) and one showing a decrease in its amplitude (Desforges et al., 2022). Finally, two studies showed an increase in N45 amplitude (Desforges et al., 2022; Noda et al., 2021) while the P60 amplitude was modulated in two studies. Nonetheless, discrepancies occurred in these studies (Table 1) regarding the direction of effect (Desforges et al., 2022; Goldsworthy et al., 2020). Of note, one study did not show any significant group effects of iTBS on TEP compared to sham (Chung et al., 2019). Moreover, this group showed a significant impact on TEP amplitude when the frequency of iTBS was individually adjusted to participants' EEG. The above result could reflect inter-individual variability in the after-effects of iTBS, a topic previously highlighted by TMS-EEG studies in the motor cortex (Corp et al., 2020).

Apart from interindividual variability, multiple factors could account for these variable findings. One example could be the use or lack of MRI data to produce individualized stimulation targets or the lack of advanced neuro-navigational software for consistent coil positioning pre- and post- iTBS (Casarotto et al., 2022). Another factor could be related to the small sample sizes in TMS-EEG studies. In addition to these factors, EEG electrode selection for the region of interest

in which TEP amplitude is assessed also vary among studies due to differences in EEG systems used. In addition, environmental noise and TMS-linked artifacts could have impacted amplitudes in EEG recordings. Therefore, appropriately designed studies with sufficient statistical power are required to help elucidate the direction of LTP-like effects on the TEP waveforms. As such, the current study aims to replicate and improve on recent studies in the field. We will do this by 1) examining the same five TEP components as Desforges et al., 2022, and 2) including a sham condition in a 3) larger healthy population sample. Altogether, further examinations of the impact of iTBS on prefrontal cortical activity will help define the role of LTP-like mechanisms in DLPFC function and provide more clarity on the relationship between LTP-like brain plasticity and the direction (i.e., increase or decrease) of cortical changes post-iTBS.

1.5 Memory and brain plasticity in the dorsolateral prefrontal cortex

Memory is a complex cognitive process linked to mechanisms of LTP brain plasticity. For instance, previous research has investigated patterns of synaptic activity within the hippocampus; a brain region suggested to be essential for memory processes (Bruel-Jungerman et al., 2007). Important mechanisms such as LTP in regions like the hippocampus have been associated with enhanced synaptic efficiency (Andersen, 1982; T. V. P. Bliss & Collingridge, 1993a; Eccles, 1983; Lømo, 2003). Both *in vivo* and *in vitro* studies have identified a relationship between hippocampus activity and memory processes (Neves et al., 2008).

While most research focused on the LTP in the hippocampus underlying memory ability, other brain regions, such as the PFC, have been identified as important for memory processes (Anderson et al., 2016; Guimond et al., 2016; Luu et al., 2014; McEwen & Morrison, 2013; Wierzba et al., 2018). Elevated PFC activity during retention intervals of delayed response-type neuroimaging tasks has been observed, which has linked this region to cognitive processes like working memory (Curtis & D'Esposito, 2003). In other related studies, the DLPFC was shown to be highly involved

in episodic and working memory processes (Barbey et al., 2013; Hui et al., 2019; Isaacson & Scanziani, 2011; Sanches et al., 2009). Functional magnetic resonance (fMRI) imaging has provided further evidence to support the activation and role of the DLPFC in memory ability (Curtis & D'Esposito, 2003). More specifically, increased DLPFC activation was obtained in fMRI tasks targeting working memory processes such as memory manipulation (Kluen et al., 2019), preparation of action using short-term memory (Pochon, 2001) and delay-related selection and maintenance of items from memory (Rowe et al., 2000; Turnbull et al., 2019) to name a few. In the context of memory deficits, neuroimaging-based studies investigating the implication of altered DLPFC activity or structure in psychiatric disorders like depression and schizophrenia supports the role of abnormal DLPFC activity in impaired memory performance (Guimond et al., 2018; Meyer et al., 2019; Wheeler et al., 2014). In essence, previous neuroimaging studies have identified the DLPFC as a key region linked to human memory ability. To further explore the role of DLPFC activity in memory in healthy human populations, additional evidence is required to clarify the link between memory processes and plasticity-like mechanisms in humans.

A recent study has gone one step further and provided some of the first evidence linking LTP-like brain plasticity to better memory performance (Goldsworthy et al., 2020). In this study, the authors investigated the link between memory performance in two groups (healthy young adults (n=33) and older adults (n=33)) and their differences in TEP amplitude modulation post-iTBS in the left lateral PFC. Increased TEP amplitude post-iTBS was observed at timepoint P60 in the young adult group with better memory performance compared to the older adult group with poorer memory performance. The older adult group revealed no significant change in TEP amplitude P60 post-iTBS. The older adult group also showed a link between reduced memory performance and smaller changes in P60 peak amplitude post-iTBS. This result is important as it is the first to

suggest a relationship between reduced brain plasticity (i.e., no significant TEP modulation post-iTBS) and reduced memory ability.

To date, the scientific community has suggested that brain regions like the left DLPFC display LTP-like mechanisms that may be linked to memory ability. Research requires further investigation and replication of current findings related to the complex LTP-like brain plasticity processes involved in memory for healthy populations. With more evidence, the effect and direction of iTBS on left DLPFC LTP-like brain plasticity mechanisms can be clarified, which may help us to elucidate the relationship between brain plasticity in the DLPFC and memory performance.

1.6 Brain plasticity, memory and brain structure

Previous studies using iTBS and assessing memory performance suggest that potential changes in brain plasticity are linked with memory ability (Goldsworthy et al., 2020). Furthermore, a link between memory performance and brain structure, like cortical thickness, has also been observed (Emami et al., 2016; Guimond et al., 2016; Jiang et al., 2016). Cortical thickness is a measure of brain structure that is suggested to be sensitive to changes in brain plasticity (List et al., 2013). Cortical thickness is a structural MRI morphometric measure used to quantify the thickness or width of grey matter segmentation from white matter within the cortex (Hutton et al., 2008). Since an association between LTP-like brain plasticity and better memory performance has occurred in TMS-EEG and iTBS literature (Goldsworthy et al., 2020), other studies have further explored the relationship between cortical thickness and memory ability. Brain imaging evidence generally supports that an overall thicker cortex is linked with better cognitive functioning and memory performance (Engvig et al., 2010; Jiang et al., 2016; Yuan & Raz, 2014). In a 2010 study, a group of researchers observed that middle-aged adults and elderly healthy individuals who participated in memory training showed improved memory performance and a regional increase in cortical

thickness, further linking structural brain plasticity, memory and cortical thickness (Engvig et al., 2010). In another study with a younger population, better cognitive performance was also linked with greater regional grey matter density in the PFC, specifically the left DLPFC (Wang et al., 2017). In comparing differences in PFC cortical thickness and memory ability in individuals exhibiting memory deficits, individuals with schizophrenia showed lower levels of working memory ability in addition to reductions in both left and right DLPFC cortical thickness (Guimond et al., 2018; Wheeler et al., 2014). Overall, greater cortical thickness in the PFC has been linked to better memory and cognitive performance. This relation may suggest a larger link between the neural processes involved in learning and memory, in which LTP-like brain plasticity mechanisms have an important contribution to brain structure. However, no study to our knowledge has explored whether LTP-like brain plasticity in the left DLPFC (via TMS-EEG) is linked to its cortical thickness.

2 Study objectives

Thus far, only a handful of studies have investigated LTP-like brain plasticity in the left DLPFC using iTBS and TMS-EEG. More research is needed to examine these measures of LTP-like plasticity concerning memory ability and cortical thickness in the left DLPFC. This thesis aims to better understand the mechanisms surrounding brain plasticity, cognitive function, and brain structure in humans. Firstly, I identified the TEP amplitude deflections most sensitive to iTBS in the left DLPFC in a sample of cognitively healthy adults as a baseline of LTP-like brain plasticity in the left DLPFC (Aim 0). I also determined whether there is a relationship between differences in TEP amplitude post-iTBS (i.e., LTP-like brain plasticity) in the left DLPFC and overall memory performance (Aim 1) and whether there is a relationship between differences in TEP amplitude post-iTBS (i.e., LTP-like brain plasticity) and cortical thickness of the left DLPFC (Aim 2).

Based on previous TMS-EEG and iTBS application to the left DLPFC, I hypothesized that iTBS would modify cortical excitability (LTP-like plasticity) by altering amplitudes of any of the five TEP components examined in previous literature (i.e., P30, N45, P60, N100 and P200) in the left DLPFC, while sham iTBS would not induce any significant change in amplitudes (Chung et al., 2017; Chung, Rogasch, Hoy, & Fitzgerald, 2018; Desforges et al., 2022; Goldsworthy et al., 2020) (Aim 0). Based on previous trends in the literature, I expected to observe an increase in at least one of the five TEP amplitudes post-iTBS. I also hypothesized that better memory performance would be associated with a greater increase in at least one of the five TEP amplitudes sensitive to iTBS, reflecting LTP-like brain plasticity in the left DLPFC as previously shown in healthy controls (Goldsworthy et al., 2020) (Aim 1). Since there is little evidence investigating the relationship between the direction of amplitude change post-iTBS and better memory performance, I foresaw a possible positive relationship between larger TEP change and higher memory score. Finally, I hypothesized that participants with greater cortical thickness in the left DLPFC would have a greater increase in TEP amplitude post-iTBS (i.e., increased LTP-like brain plasticity) (Aim 2).

3 Methods

3.1 Participants

Seventeen participants were recruited through community flyers and online advertisements (Kijiji, Reddit). Participants gave written content before participation commenced. Participants were in the study if they were between 18 to 45 years of age, had an IQ $\geq$ 70 as measured by the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 2008), and could read and speak fluent English. Participants were excluded if they had; a current or past history of health-related or neuropsychiatric disorders producing cognitive impairment; a current or past history of severe brain injury; a recent history (< 3 months) of substance abuse or dependence; any magnetic

resonance imaging (MRI) or transcranial magnetic stimulation (TMS) contraindications (e.g. metallic head implant, history of seizure, pacemaker) as defined by (Rossi et al., 2009, 2021); decisional incapacity requiring a guardian; taking benzodiazepine and/or anticholinergic medication; and if they have a first-degree relative who received a diagnosis of major depression, schizophrenia or schizoaffective disorder.

3.2 Procedure

The current study was an optional portion of a larger ongoing cognitive remediation trial (NCT04159662) at the Royal Ottawa Institute of Mental Health Research (IMHR), where all participants were invited to participate if they were interested. Informed written consent was obtained for study participation prior to the evaluation of participant eligibility. All study visits took place at the IMHR. The current study had a randomized crossover double-blinded sham-controlled design, consisting of five visits over one month. Before participants were enrolled, an initial telephone screening was conducted to assess initial eligibility. Participants were then invited for two in-lab visits where written consent was obtained, and eligibility was evaluated. Cognitive assessments using clinical and cognitive tests were completed during these visits. Participants were invited for a third visit, where they completed an MRI imaging session. Brain stimulation (i.e., active iTBS condition, sham iTBS condition) occurred at visits 4 and 5. During each stimulation session, cortical excitability was measured before and after active/sham iTBS using concurrent TMS and EEG. The order of iTBS and sham was randomized (one visit was sham, and the other was active iTBS). Furthermore, the two stimulation sessions were separated by more than five days to eliminate potential carryover effects of iTBS stimulation.

3.2.1 Clinical assessments

Mini International Neuropsychiatric Interview (M.I.N.I) (Sheehan et al., 1998) administration confirmed that participants did not show signs of a psychiatric illness. This

interview assessment controlled undiagnosed psychiatric illnesses that may represent altered neural functioning. Therefore, neural functioning associated with psychiatric illness was controlled for in the current study.

3.2.2 Cognitive assessments

The Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 2008) is an IQ test used to measure each participant's intelligence and general cognitive ability. The WASI assessed eligibility and excluded individuals with potential intellectual disabilities.

The Cambridge Neuropsychological Test Automated Battery (CANTAB) (Cambridge Cognition Ltd.) is a computerized cognitive assessment that targets cognitive functions linked to specific neural processes. The CANTAB tests used to assess memory ability in the current study were; paired associate learning (PAL), spatial working memory (SWM), verbal recognition memory (VRM) and delayed matching to sample (DMS) (Figure. 2). Following the CANTAB recommendation for aggregating scores, a composite memory score was created for each participant using their combined raw scores from the tasks listed above. In addition, memory subdomain scores were created: DMS and PAL were used to represent visual episodic memory, SWM for working memory, and VRM for verbal episodic memory. Raw task scores were averaged for each participant and compared to the norm of the same CANTAB tests completed by other healthy controls in three other research experiments at the IMHR, including the current study (n = 82). Z-scores defined participant performance for each task and memory subdomain. Finally, a composite overall memory score was used for each participant by averaging all memory z-scores. See Table S4 and Table S5 for measure details.

3.2.3 Neuroimaging

A 3T Siemens MR-PET system Siemens Biograph mMR, (Siemens, Germany) at the Royal Ottawa Brain Imaging Centre was used for participant MRI acquisition for a total of 50 mins. For

the current study, localizer sequences (3 mins) and high-resolution three-dimensional (3D) magnetization-prepared rapid gradient-echo (MPRAGE) sagittal sequences (5 mins) produced T1-weighted structural brain imaging data for cortical thickness assessment. Additional imaging sequences were acquired during this visit as a part of a larger study but were not used for the current project.

3.2.4 TMS-EEG procedures

3.2.4.1 EEG preparation

At the start of each session, a TMS- compatible 64-channel EEG cap (64Ch actiCAP slim or BrainCap, BrainVision, EASYCAP GmbH, Germany; Figure 3) was positioned on the head of the participant and connected to a TMS-compatible amplifier (ActiCHamp or BrainAmp, BrainVision Gmb). First, head measurements were conducted to determine the EEG cap size and placement. To guide sham electrode placement, electrode locations 3(F3)-4(F1)-7(FC3)-7(FC1) and 6(FC5)-7(FC3)-9(C5)-8(C3) were marked with washable eyeliner on the scalp. These electrodes were used during the iTBS and sham to mask the stimulation condition. Conductive gel was inserted using a small syringe on the EEG cap electrode to improve conductance. Impedance levels were kept under 5-10 kΩ throughout the three recording sessions (baseline, iTBS/sham, post).

For the first 6 participants (pre-covid, 2019), the first model of a TMS- compatible 64-channel EEG cap (64Ch-Standard-BrainCap for TMS with Multitrodes, BrainVision EASYCAP GmbH, Germany) and amplifier (BrainAmp, Brainvision Gmb) were used. A new EEG system was obtained during the covid-19 research halt at the IMHR (64Ch actiCAP slim, BrainVision, EASYCAP GmbH, Germany (cap); ActiCHamp, BrainVision Gmb, Germany (amplifier)). When research resumed in June 2021, recruitment continued. The purpose of the new EEG system was to enable faster EEG preparation and data collection than the previous system.

3.2.4.2 Neuronavigation

Neuronavigation guided TMS coil placement with an infrared camera system that displayed coil location on the structural MRI of the participant in real time (Brainsight, Rogue Research, Canada; Figure 4). The TMS coil was spatially co-registered with the participant's structural MRI image as follows: prior to applying TMS, a headband with an attached 3-dimensional tracker was placed on the head of the participant and away from the left dorsolateral prefrontal cortex (DLPFC) target, a 3D digitizer marked fiduciary landmarks and additional scalp points, after which TMS coil was displayed in real-time. The left DLPFC was identified for each participant using reversed co-registration with the following MNI152 stereotaxic coordinates: x = -38, y = 44, z = 26 (D. Blumberger, 2019; D. M. Blumberger et al., 2018).

3.2.4.3 Threshold determination

Resting and active motor threshold (RMT, AMT) intensities were determined using a MagPro X100-MagOption Stimulator with a 70 mm figure-of-eight MC-B70 coil and a 70 mm figure-of-eight CB-60 coil (MagVenture, Denmark) respectively. Electromyographic (EMG) surface electrodes were placed on the right first dorsal interosseous muscle as well as a reference electrode on the right elbow joint. Before RMT and AMT determination, the left motor cortex hotspot was targeted to determine stimulation intensity. To define the motor hotspot, the TMS coil was positioned (handle pointing 45° away from the midline) where the TMS produced the largest motor-evoked potential (MEP) amplitude. To determine RMT, the TMS coil was placed at the defined motor hotspot while stimulation intensity was decreased until the EMG recorded an average 50μV motor-evoked potential (MEP) amplitude response in 5 out of 10 trials, while the target muscle was at rest. To determine AMT, stimulation was decreased until about a 200μV MEP amplitude response was obtained in 5 out of 10 trials, while the participant maintained a minimal contraction (10% of maximal contraction) in the target muscle. Once RMT and AMT were

obtained at the beginning of visit five, these threshold intensities were used for TMS intensity selection for iTBS and single-pulse TMS.

3.2.4.4 Single-pulse TMS-EEG recording

Baseline and post-iTBS cortical excitability in the left DLPFC were measured using TMS-EEG recording blocks of 80 single pulses at 120% RMT sent every 5-7 seconds (see Figure. 2) using a cooled B70 coil (MagVenture, Denmark). A TMS-compatible amplifier (Brain Amp DC or ActiCHamp, Brain Vision, Gmb) recorded EEG signals at a sample rate of 5000Hz during each TMS-EEG block. During EEG, participants wore noise-cancelling earphones which produced white noise to help mask auditory potentials derived from single-pulse TMS delivery (Rocchi et al., 2021). Participants also wore ear defenders on top of the earphones, and a piece of 1mm foam was attached to the coil to minimize confounding auditory and sensory potentials, respectively (Conde et al., 2019; Gordon et al., 2018; Mancuso et al., 2021; Rocchi et al., 2021)

3.2.4.5 Plasticity-inducing procedure

iTBS was applied to the left DLPFC with a cool-B65 coil (MagVenture, Denmark) using the standard iTBS procedure (i.e., triple pulse bursts at a frequency of 50Hz and a rate of 5Hz, at 2-second intermittent trains, repeated every 10 seconds) for a total of 600 pulses in 190 seconds at 80% of the AMT (Huang et al., 2005) (see Figure. 6). The symmetrical appearance of this coil blinded the investigators to the active or placebo side of the coil. Unique and randomized identification codes were entered into the TMS machine, which indicated coil orientation on the scalp through internal sensors. The identification codes directed the TMS machine to select either active (iTBS) or sham stimulation.

3.2.4.6 Sham procedure

When the identification code signalled sham, the placebo side of the coil was positioned against the scalp of the participant. Similar tactile sensations experienced during active iTBS condition were produced by synchronous electrical pulses delivered by two scalp electrodes

attached to the TMS machine. Identification codes were randomized by a member outside of the research team who had no participation in the TMS application or data analysis. Participants were told that they would receive one active and one placebo condition, but both the research team and participants were blinded to the stimulation condition. At the end of each stimulation visit, participants were asked which stimulation condition they believed they received. The purpose of the sham stimulation condition was to control for potential placebo response and to provide reliable TMS-EEG cortical measurements.

3.2.5 Data preprocessing

3.2.5.1 MRI data processing & DLPFC selection

The T1 weighted images were pre-processed using B-PIPE (https://github.com/CoBrALab/minc-bpipe-library). B-PIPE is an advanced processing pipeline available online for free. Upon image input, the pipeline performed various pre-processing steps: N4 correction, neck removal, head/brain masks and registration to MNI space. The CIVET processing pipeline (Montreal Neurological Institute at McGill University, Montreal, Quebec, Canada) was used to measure participants' left DLPFC cortical thickness (https://github.com/CobraLab/documentation/wiki/Cortical-Thickness-&-Surface-Analysis-with-CIVET). CIVET (version 2.1.0) performed multiple tasks: N3 correction to correct for nonuniformity in imaging data (Sled et al., 1998), mask and interpolation to template (0.5mm voxel resolution stereotaxic MNI152 space), tissue classification (i.e., white matter, grey matter, cerebral spinal fluid, subcortical), hippocampus masking and exclusion, hemisphere separation, surface parcellations using the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002). In the end, CIVET produced cortical thickness information (Bhagwat et al., 2020; Sled et al., 1998) (see Table S4-S5). The images were visually inspected for motion and issues with

image capture (i.e., distorted image, missing portions in image). No participants were excluded during this quality control assessment.

Cortical thickness is defined as the distance between grey matter and white matter cortical surface boundaries, a measure indicating the size integrity of the cerebral cortex. The average cortical thickness value of the left dorsolateral superior frontal gyrus (SFGdor.L_CT) and the left middle frontal gyrus (MFG.L_CT) were combined to provide an average left DLPFC thickness measure (mm).

3.2.5.2 EEG data preprocessing

EEG signals were recorded at a sample rate of 5000Hz, filtered, digitized and recorded offline for analysis. Transcranial magnetic stimulation-evoked potentials (TEPs) were processed in MATLAB (Version R2021a, The MathWorks Inc., USA) using the EEGLAB toolbox (Delorme et al., 2003; Delorme & Makeig, 2004), FieldTrip toolbox (Oostenveld et al., 2011) and the FastICA MATLAB program (Aapo Hyvarinen et al.; https://research.ics.aalto.fi/ica/fastica/about.shtml, 2022).

First, if present, unneeded channels (TP9, TP10, Iz and FT10) were removed. Next, noisy impedance channels were removed using the pop_rejchan function in the EEGLAB Toolbox with absolute values (non-ROI threshold 2.5σ, ROI threshold 3.5σ). After channel and epoch removal, data from -2ms to 15ms (large-amplitude TMS artifact) were removed, epoched around the TMS pulse (-2000 to 2000 ms), then interpolated. To remove potential distortion in the data, epochs were detrended and data were baseline corrected (0 mV). EEG data were down-sampled to 1000Hz from 5000 Hz. A custom MATLAB script completed the initial processing steps described above. Next, residual TMS-provoked muscular artifacts (i.e., voltage decay, eye blinks, jaw clenching, head muscle activation) were removed via two rounds of independent component analysis (ICA) using the FastICA MATLAB algorithm (Desforges et al., 2022; Rogasch et al., 2014). If artifact-

like activity was visually detected, it was manually removed during ICA analysis. Following ICA component analysis, data filters were applied (band-pass filter 0.2-80Hz and notch filter 0.2-60Hz) and data were referenced to the average of all electrodes. Finally, all previously removed channels were interpolated from the average of surrounding electrodes.

Overall, the pre-and post- 80 single-pulse TMS-EEG recording sessions were averaged to extract TEP amplitudes at time points specific to DLPFC activity. The window for TEP extraction was slightly adjusted to match the current sample: P30 (30-48 ms), N45 (60-78 ms), P60 (80-98 ms), N100 (105-133 ms) and P200 (200-250 ms) (Figure 3-4, highlighted gray regions) (Tremblay et al., 2019). TEP amplitudes were visually identified, and then a +/- 9 ms time window was selected to capture the peak for the first three components. For later TEP components N100 and P200, time windows were adjusted by visual inspection of the TEP waveform. This step follows similar peak identification methods, yet the time windows (ms) were adjusted compared to previous research (Desforges et al., 2022; Goldsworthy et al., 2020). TEP amplitudes were extracted over the left DLPFC region of interest from electrodes containing the least amount of noise located under the coil (FC1, F1, AFz) and averaged for each participant pre- and post-EEG recording session. Lastly, all participant grand averaged TEP data were organized into files for each TEP amplitude value and unblinded stimulation condition. To effectively compare EEG recordings from two different EEG systems, differing electrodes for each group were removed to include the same 58 electrodes for all participants.

In conclusion, iTBS-induced LTP-like brain plasticity was measured by comparing the magnitude of amplitude change at each TEP amplitude before (baseline/pre) and after (post) iTBS stimulation in the left DLPFC.

4 Statistical analysis

Potential outliers were removed prior to statistical analysis (see Table S3). Memory performance left DLPFC cortical thickness and TEP component amplitude outliers were identified based on the interquartile range (IQR) criterion displayed using a boxplot in R studio, which flagged a total of 13 values. Scores for visual episodic and working memory were missing for one participant, which caused some inconsistencies in the degrees of freedom (see Table 2 and S3). Secondly, average TEP waveforms for each participant were inspected and removed if they exceeded 10μV amplitude to minimize the influence of the TMS artifact further. Altogether, 12 out of 17 participants were included in statistical analyses due to outlier removal.

All statistical analyses were conducted in R studio (v. 2021.09.0). Positive and negative TEP amplitude values were extracted for each participant, giving five sets of amplitude values per individual (i.e., pre- and post-active iTBS and sham). Each set consisted of 5 amplitude values within a select time window (P30, N45, P60, N100, P200).

Firstly, linear mixed model ANOVAs, with an alpha of 0.05 as the threshold of significance, were performed to assess the TEP amplitude change before (time = pre) and after (time = post) the active iTBS condition and the sham stimulation condition for each TEP component, then Tukey's Post Hoc tests were conducted to explore for multiple comparisons (Aim 0). Time (i.e., pre-, post-) was the dependent variable, and condition (i.e., iTBS, sham) was the independent variable. Age, sex and the difference in EEG cap type were evaluated as covariates in this model. Secondly, two-tailed Pearson's product-moment correlations were conducted to assess the linear relationship between the differences in TEP amplitude (μV) over time (ms) for each stimulation condition and the overall memory z-score for each participant (Aim 1). Thirdly, one-tailed Pearson's product-moment correlations were performed to assess the linear relationship between the differences in TEP amplitude (μV) over time (ms) for each stimulation condition and

participant left DLPFC thickness (mm). Results were significant if p values were < 0.05 and trending significant if ≤ 0.15, considering our relatively small sample size. Given the small sample size, we did not apply a correction for multiple comparisons for Pearson's correlation. Such comparisons will be performed on the final sample when the larger study will be completed.

5 Results

5.1 Demographics

In total, 3 of the 17 participants were female and 14 were male, and they were between 18 and 43 (29 +/- 7.16). Concerning race and ethnicity, the participants identified as Asian (7), Caucasian (6), Aboriginal (1), African (1), Mestizo (1), and one did not specify. All participants were right-handed except one. In addition, all participants completed high school and completed or partially completed college/undergraduate programs.

5.2 Aim 0: Difference between active iTBS and sham TEPs

Linear mixed model with condition and time (ms) as fixed factors revealed a significant interaction for component P30 ($F= 5.238$, $p = 0.029$) (Figure. 5). An averaged single-pulse TEP waveform for the active iTBS condition is shown in Figure. 3. An average single-pulse TEP waveform for the sham condition is shown in Figure. 4. Single-subject TEP waveforms and topographies for the active iTBS and sham conditions are shown in Supplementary Maternal (Figure S1-S6). Detailed results for interactions between stimulation condition and pre-, and post-stimulation differences in TEP amplitude (μV) are outlined in Supplementary Material (Table S1). See Table S6 for participant information. No significant interactions were observed for the other components.

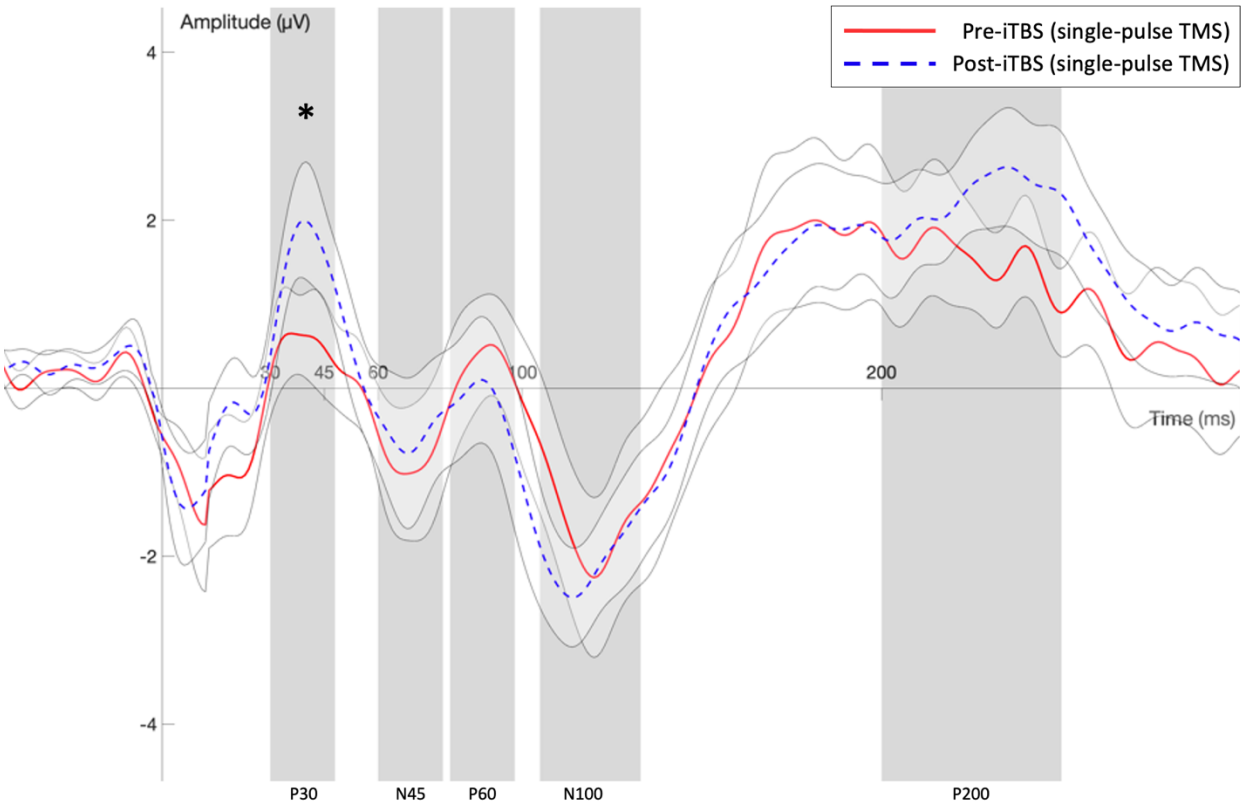

Figure 3: Active iTBS Condition – Averaged single-pulse TEP waveform obtained from ROI (FC1, F1, AFZ). *The single solid red line displays the grand average waveform pre-iTBS, whereas the dotted blue line displays the grand average waveform post-iTBS. iTBS = intermittent theta burst stimulation; TEP = transcranial magnetic stimulation evoked potential; ROI = region of interest; **p < 0.05; *p < 0.15.*

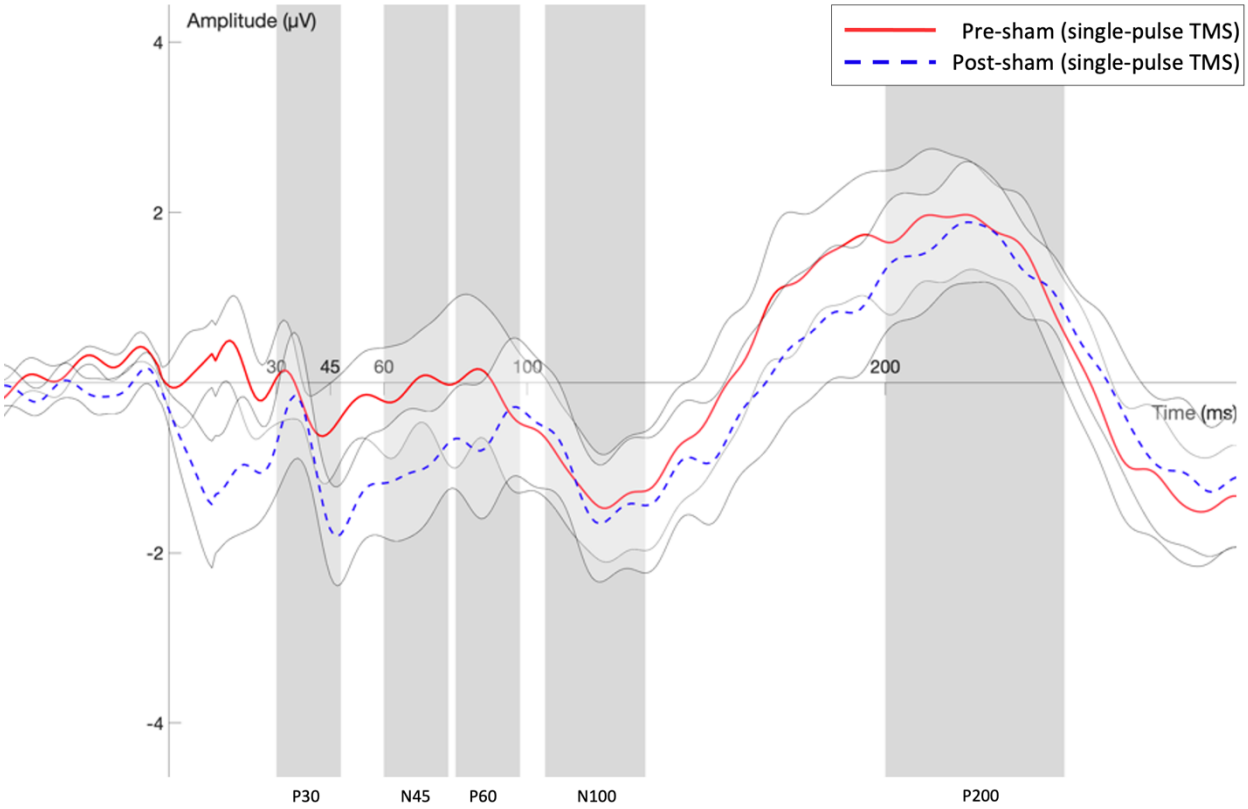

Figure 4: SHAM Condition – Averaged single-pulse TEP waveform obtained from ROI (FC1, F1, AFZ). *The single solid red line displays the grand average waveform pre-sham, whereas the dotted blue line displays the grand average waveform post-sham. iTBS = intermittent theta burst stimulation; TEP = transcranial magnetic stimulation evoked potential; ROI = region of interest; **p < 0.05; *p < 0.15.*

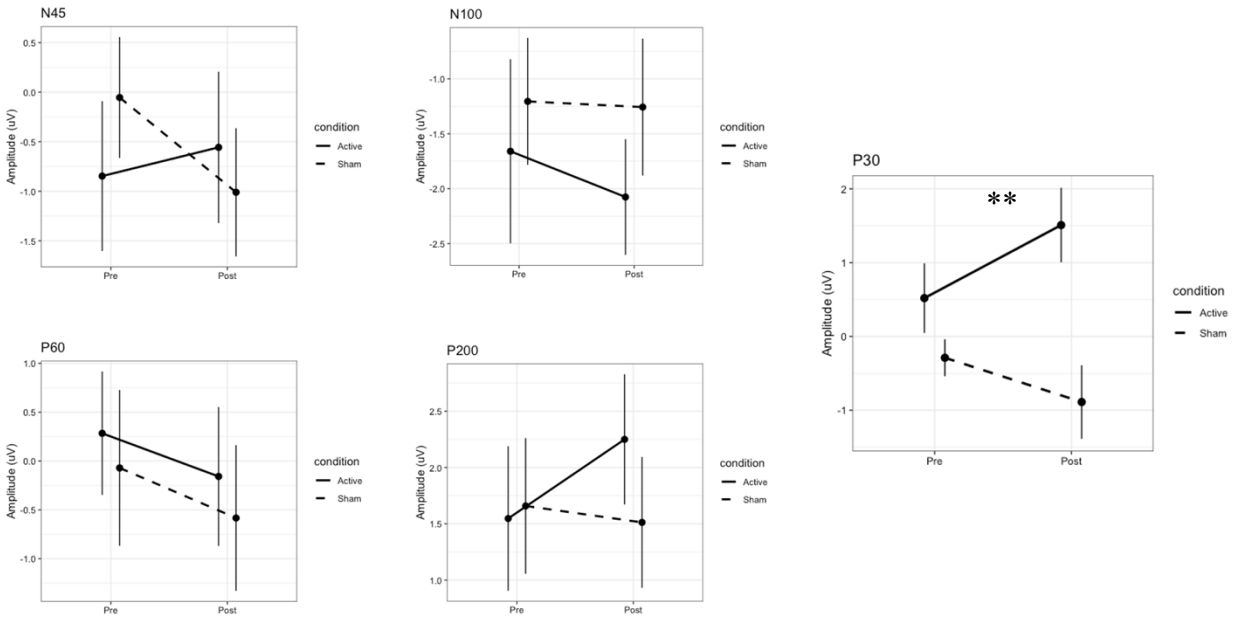

Figure 5: Single-pulse TEP amplitudes (μV) pre- and post-iTBS and sham from ROI (FC1, F1, AFZ) for each TEP peak of interest*. iTBS increased the amplitude of the P30 component. Error bars represent the standard error of the mean. iTBS = intermittent theta burst stimulation; TEP = transcranial magnetic stimulation evoked potential; ROI = region of interest; **p < 0.05; *p < 0.15.*

Tukey's post hoc for multiple comparisons revealed that the mean value of amplitude (μV) for component P30 was near trending significant between pre- and post- iTBS (P30: p-value = 0.166, 95% C.I.), but not in the sham condition (P30: p-value = 0.294, 95% C.I.; see Table S2).

5.3 Aim 1: Relationship between baseline memory scores and TEP amplitudes

A Pearson's product-moment correlation coefficient revealed no significant relationships between the differences in TEP amplitude for component P30 (μV) over time (ms) for each stimulation condition and overall memory z-score for each participant (Table 2). See Table S4-S5 for additional participant information.

Table 2: Pearson's product-moment correlation for memory domain z-score vs difference in P30 amplitude

Active iTBS condition – P30				
Memory domain	**t**	**df**	**p-value**	**cor**
Overall memory	-1.134	9	0.286	-0.354
Visual episodic	-0.390	9	0.706	-0.129
Working memory	-1.379	9	0.201	-0.418
Verbal episodic	-1.004	9	0.342	-0.317
Sham condition – P30				
Memory domain	**t**	**df**	**p-value**	**cor**
Overall memory	0.388	10	0.706	0.121
Visual episodic	0.572	9	0.581	0.187
Working memory	0.291	9	0.777	0.097
Verbal episodic	0.438	10	0.670	0.137

*Note: iTBS = intermittent theta burst stimulation. **p < 0.05; *p < 0.15. Inconsistencies in the degrees of freedom (df) occur due to missing data or outlier data which were removed (see Table S3 for details).*

5.4 Aim 2: Relationship between left DLPFC thickness and TEP amplitudes

A one-tailed Pearson's product-moment correlation coefficient was computed to assess the linear relationship between the differences in TEP amplitude (μV) over time (ms) for component P30 for each stimulation condition and participant left DLPFC thickness. A trending significant relationship was observed between the change in TEP component P30 amplitude and left DLPFC thickness (r = 0.488; Figure 6; Table 3). The below scatterplot displays the strength and direction of correlation between left DLPFC thickness and the difference in TEP amplitude (μV) for the active iTBS is shown in Figure 10. See Table S4-S5 for additional participant information.

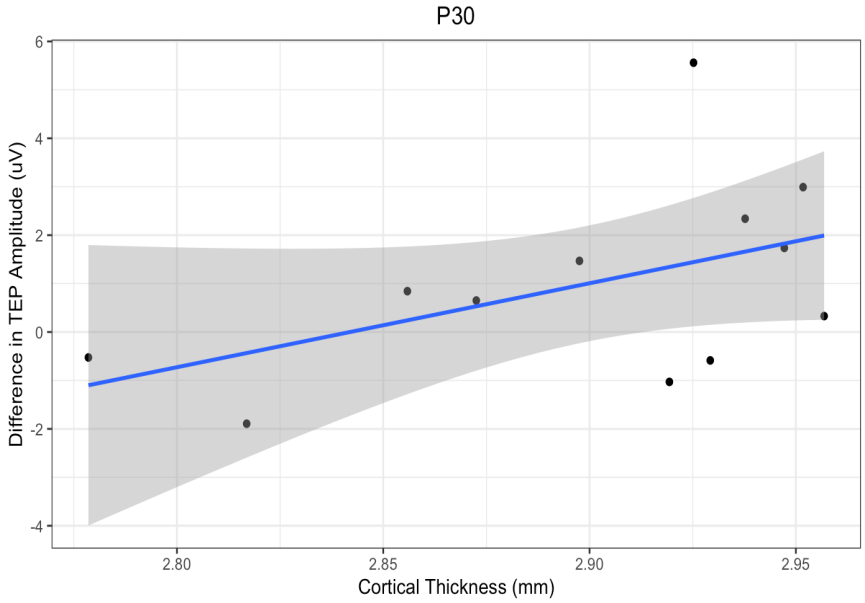

Figure 6: Active iTBS condition - Difference in single-pulse TEP amplitudes (μV) post-sham from ROI (FC1, F1, AFZ) for TEP peak P30 and left DLPFC thickness (mm) (Pearson's correlation). *Trending significance observed. iTBS = intermittent theta burst stimulation; TEP = transcranial magnetic stimulation evoked potential; ROI = region of interest.*

Table 3: Pearson's product-moment correlation for left DLPFC thickness vs difference in P30 amplitude.

Active iTBS condition – P30				
	t	**df**	**p-value**	**cor**
Left DLPFC thickness '*'	1.766	10	0.108	0.488
Sham condition – P30				
	t	**df**	**p-value**	**cor**
Left DLPFC thickness	0.403	10	0.695	0.126

*Note: iTBS = intermittent theta burst stimulation. **p < 0.05; *p < 0.15.*

6 Discussion

In the current sample, LTP-like plasticity was examined in the left DLPFC through a direct comparison of neurophysiological effects pre- and post-iTBS. To do this, we investigated the direction and magnitude of TEP amplitude change post-iTBS at time windows P30, N45, P60, N100 and P200. Furthermore, we looked for interactions of TEP amplitudes post-iTBS between

two stimulation conditions (active iTBS, sham iTBS). We also assessed whether there was a relationship between iTBS-induced LTP-like plasticity in the left DLPFC to both memory performance and left DLPFC cortical thickness. The current study showed a significant increase in amplitude post-iTBS for time window P30. This increase in amplitude is suggested to reflect LTP-like plastic effects in the left DLPFC, whereby cortical excitability was temporarily modified. We also observed a significant trending relationship between the change in P30 amplitude post-iTBS and a thicker left DLPFC. No trending nor significant relationship was observed between change in P30 amplitude post-iTBS and overall memory performance. Although the sample is rather small, the data suggest a link between LTP-like brain plasticity and a thicker left DLPFC.

6.1 Prevalence of P30 modulation & iTBS

6.1.1 Motor cortex

The motor cortex is a region examined by electromyography and single-pulse TMS-EEG techniques to assess cortical excitation and inhibition, and is the key region in which iTBS was developed. With iTBS application to the motor cortex, sustained increases in MEP amplitudes have occurred post-iTBS (Gedankien et al., 2017; Suppa et al., 2016). In a 2017 study, MEP amplitudes significantly increased post-iTBS delivery to the left motor cortex (Gedankien et al., 2017). In the same study, MEP amplitude change post-iTBS significantly correlated with changes in early TEP amplitude at P30 post-iTBS. This result followed an earlier study from 2010, which also observed significantly correlated amplitudes for both MEP change and TEP component P30 in the left motor cortex (Mäki & Ilmoniemi, 2010). Moreover, it is well known that TEP component amplitude responses post-iTBS in the motor cortex show a greater magnitude of amplitude change compared to other cortical regions (Kähkönen et al., 2004, 2005; Lioumis et al., 2009; Tremblay et al., 2019). To further understand the similarities and differences between the

motor cortex and non-motor cortical regions, additional studies are needed to compare TEP amplitude modification post-ITBS between motor and non-motor regions.

6.1.2 Left DLPFC

Motor cortex studies, such as the ones listed above, have explored and highlighted the use of TMS-EEG and iTBS to target LTP-like plasticity and modulate cortical activity successfully. Even though this evidence occurs in the motor cortex, similar trends of altered cortical activity following iTBS have occurred in the DLPFC (see Table 1). In the current study, our results showed that active iTBS increased TEP component P30 amplitude and was not significantly altered in the sham stimulation condition. Other TEP components of interest (i.e., N45, P60, N100 and P200) remained unchanged following both active iTBS and sham. Our results replicated a previous 2019 study in which no significant change in TEP amplitudes post-iTBS in the left DLPFC were revealed in time windows N45, P60, N100 or P200, while P30 was not quantified (Chung et al., 2019). Three different iTBS frequencies were examined in this study (30 Hz bursts repeated at 6 Hz; 50 Hz bursts repeated at 5 Hz, and individualized iTBS), where no significant differences in TEP components post-iTBS occurred following both the 30Hz and 50Hz iTBS conditions. This group only observed an effect of iTBS when the frequency was individualized based on cross-frequency coupling between frontal theta (phase) and parietal gamma (amplitude) oscillations during an EEG memory task (3-back). With individualized iTBS, TEP component P60 significantly increased post-iTBS, whereas components P100 and P200 significantly decreased in amplitude post-iTBS (Chung et al., 2019). Although some features were not replicated in the current study (i.e., individualized iTBS, 30 Hz at 6Hz iTBS, two post-iTBS time measurements (5 and 30 minutes post-iTBS)), both the current study and the Chung et al., 2019 study did not produce a significant change in TEP component P60 amplitude in response to 50Hz iTBS. In a more recent TMS-EEG study, and the only one that quantified the P30 component following

DLPFC iTBS, three different dosages of active iTBS at the same 50Hz frequency (i.e., 600 pulses, 1200 pulses, 1800 pulses) were performed, which produced a significant change in P30 amplitude post-iTBS in the left DLPFC; however, the direction of this change did not relate to the current study (Desforges et al., 2022). Although we observed a discrepancy in the direction of P30 change post iTBS compared to the study by Desforges and colleagues, it is important to note that only this study revealed a significant decrease in TEP P30 amplitude after iTBS application (Desforges et al., 2022). In addition, significant modulation of TEP components post-iTBS (active) was not compared to a sham condition; therefore, the overall significance and direction of TEP component modulation in this study may have been fueled by external factors such as procedural or placebo effect. To further clarify the significance of TEP amplitude P30 change following iTBS, additional studies must include TEP component P30 as an amplitude of interest.

6.1.3 Pharmaco-TMS-EEG evidence

Based on the increased TEP amplitude at P30 post-iTBS, the direction and significance of amplitude changes suggest increased cortical excitability in the left DLPFC following iTBS. The specific neural mechanisms involved in LTP-like plastic changes in cortical excitability at P30 were not explored in the current study, but previous pharmaco-TMS-EEG studies suggest a possible role of glutamatergic neurotransmission and excitatory cell mechanisms for the change in early positive TEP amplitude components P30 and P60, which are thought to be linked to similar mechanisms (Belardinelli et al., 2021; Premoli et al., 2019). More specifically, a 2019 study assessed TMS parameters of cortical excitability (TEPs) in the left motor cortex before and administering a novel potassium channel opener which is being developed for treatment of epilepsy, XEN1101, using TMS-EEG (Premoli et al., 2019). After drug intake, which is known to reduce cortical excitability, a decrease in TEP component P30 amplitude was observed. This result indicated that P30 is sensitive to pharmaco-modulation of cortical excitability (Premoli et

al., 2019). Again pointing towards the link between early positive TEP components and excitatory mechanisms, another study observed a decrease in TEP component P60 after anti-epileptic drug intake (Perampanel), known to modulate glutamatergic transmission, following TMS stimulation in the left motor cortex (Belardinelli et al., 2021). Although the P60 component was not modulated by iTBS in the current study, these results help better understand the underlying mechanisms of early TEP components such as the P30 and P60. Of note, both studies by Belardinelli et al., 2021 and Premoli et al., 2019 are limited to left motor cortex TMS stimulation and smaller sample sizes ($n < 20$), highlighting the need of DLPFC-specific studies in larger samples. Pharmaco-TMS-EEG studies are vital for exploring the relationship between neurotransmission and neuroelectrophysiological patterns in cortical activity in the human cortex. More pharmaco-TMS-EEG studies looking at the sensitivity and direction of significant TEP amplitude change post-iTBS for TEP component P30 are critically required to further clarify the mechanism of action in non-motor regions like the DLPFC.

6.1.4 TEP component exclusion

Altogether, the current study is one of two projects to have explored TEP component P30 in the left DLPFC with TMS-EEG and iTBS (see Table 1). One reason underlying P30 exclusion is due to the component's proximity to the TMS single pulse trigger, which has made the component harder to isolate and visualize if a large TMS artifact is observed. Overtime, research groups have provided detailed descriptions and methods to support effective TMS and other artifact removal allowing for isolated artifact-free brain signals (Bertazzoli et al., 2021; Rocchi et al., 2021; Rogasch et al., 2014). For example, advancements in EEG active recording electrodes and TMS-compatible amplifiers equipment over the years have contributed to improved data collection and a better signal-to-noise ratio during EEG recording (Farzan & Bortoletto et al., 2022; Mancuso et al., 2021; Varone et al., 2021). Improved recording methods have resulted in

improved data cleaning for final signal analyses. In time, replication and fine-tuning of TMS and EEG procedures will provide a more reliable and accurate assessment of cortical neurophysiology and, therefore, LTP-like brain plasticity in the DLPFC.

6.2 Memory performance and cortical excitability

As discussed in the introduction, memory performance has been associated with brain plasticity mechanisms in animal models for many years. However, this relationship has not been directly explored in humans. Previous research has used TEP amplitude in the DLPFC as a proxy of cortical excitatory and inhibitory mechanisms to explore its relationship with memory. Although the increase in TEP P30 amplitude post-iTBS was not significantly correlated with overall memory performance assessed at baseline in the current sample, cortical excitability (i.e., TEP amplitude monitoring without iTBS) has been previously linked to memory performance in the DLPFC in other groups using TMS-EEG. In 2019, a group of researchers explored whether cortical excitability/inhibition, as measured by TEP amplitudes in the left DLPFC, could predict memory performance in patients with Alzheimer's disease (Bagattini et al., 2019). To do this, they delivered single TMS pulses to the left DLPFC and measured TEP amplitudes locally (i.e., region of interest located around the left DLPFC), as well as using a whole-brain analysis method which allowed this group to measure the spread of activity induced by TMS in other cortical regions. Results showed that component P30 amplitude shared a relationship with memory performance. Specifically, the P30 amplitude located in the right parietal region predicted poorer memory performance in these patients (a control sample was not included). In another TMS-EEG study, cortical excitability was examined via TEP amplitudes from the left motor cortex and left DLPFC in three different groups: (1) younger, (2) older and (3) schizophrenia (Noda et al., 2021). The purpose of this study was to explore the relationship between patterns of cortical excitability in individuals with altered cognition and memory performance due to aging and schizophrenia

disease progression compared to cognitively healthy younger individuals. Although no significant differences in P30 TEP amplitude were shown among the three groups, the authors revealed a significant interaction between TEP component P30 and the groups based on a multiple regression analysis. The significant interaction between P30 amplitude and the groups examined in this study suggests that TEP P30 amplitude predicted group classification; however, this result is unclear and requires further exploration into the relationship between TEP P30 amplitude and additional quantifiable information about cognitive and memory performance for each group.

Previous literature observed a link between poorer memory performance and differences in baseline cortical excitability in Alzheimer's disease (Bagattini et al., 2019), other studies with more groups (i.e., controls, older, schizophrenia) showed similar trends (Noda et al., 2021). However, these studies did not assess LTP-like brain plasticity as they only examined baseline measures of cortical excitability without iTBS. In line with these discrepancies, the current study exhibited no significant relationship between overall memory performance and change in TEP component P30 amplitude post-iTBS. It is important to note that baseline TEP amplitudes (i.e., pre-iTBS) were not statistically compared to the overall memory scores between participants in the current study, but this could be explored in the final sample with more participants. In addition, whole-brain analyses could also be included in the final sample. The addition of these steps could provide further insight into the overall relationship between memory performance and baseline cortical excitability in cognitively healthy individuals.

There are a few potential reasons why the current study showed no significant relationships between memory performance and LTP-like brain plasticity in the left DLPFC (as measured by the difference in TEP P30 amplitude post-iTBS). One possibility for the lack of relationship could be due to the healthy control population assessed in the current sample. A small group of

cognitively healthy individuals may not exhibit the same differences in memory performance observed between clinical populations with cognitive features (i.e., Alzheimer's disease, schizophrenia.) or in older participants compared to healthy control samples. Similarly, the overall memory scores for the current small healthy control sample may not be sensitive enough to compare to our measure of LTP-like brain plasticity in the left DLPFC. This lack of sensitivity could be related to the overall intelligence of our healthy control sample. Since our participant sample generally performed well in the memory tasks (i.e., the majority of overall memory z-scores fall >0), it may be harder to differentiate the impact of their performance. Overall, a larger and more generalizable sample size may help to differentiate the impact of memory performance concerning our LTP-like brain plasticity measure. The addition of a clinical group displaying cognitive impairments might also help shed light into this potential relationship.

6.3 Left DLPFC thickness and plasticity

In the current study, a trending significant relationship was shown between a thicker left DLPFC and our measure of LTP-like brain plasticity in the left DLPFC. To our knowledge, TEP amplitude components in the left DLPFC have not been examined with left DLPFC thickness before; therefore, our study has provided preliminary evidence for this topic. Interpretation of these preliminary and novel results has required careful examination of applicable work.

Firstly, most of the research to date have investigated overall cortical thickness instead of specific regions like the left DLPFC. In such literature, it is suggested that experience-dependent plasticity (also known as brain plasticity) has been linked with the specific brain structure involved in the experience (Zatorre et al., 2012). A famous London taxi-driver experiment examined the general trend of this relationship, whereby larger regional brain volume (specifically in the posterior hippocampus) was reported in individuals who expressed a high level of spatial navigation and spatial memory (Maguire et al., 2000). Studies like this have revealed a link

between knowledge or prowess in a specific task or cognitive function and a larger activity-dependent brain structure, reflecting a link between structural brain plasticity and experience-dependent brain plasticity. Since the literature has also shown a link between better cognitive and memory performance with a higher degree of cortical excitation in the left DLPFC, we expected to observe a link between thicker DLPFC and increased cortical excitability in the same region following an effective stimulus for LTP-like brain plasticity (i.e., iTBS) in the current study. Other studies have explored the proposed relationship between better cognitive and memory performance, which is suggested to be linked with experience-dependent brain plasticity in both the prefrontal cortex as well as the entirety of the cortex. For example, a thicker cortex was observed in young middle-aged adults with better cognitive functioning, reflected by higher intelligence quotients (IQ) (Schnack et al., 2015). In contrast, a thinner cortex was reported in older adult populations who exhibited a decline in cognition with age (Engvig et al., 2010). This negative relationship is suggested to reflect altered or loss of plastic effects in the cortex.

With respect to clinical populations such as schizophrenia, previous groups have reported a link between a thinner cortex in the left frontal lobe and parahippocampal gyri and reduced verbal memory ability (Guimond et al., 2016), which may also indicate altered plasticity mechanisms in these regions. Further investigation of experience-dependent plasticity (via skill/cognitive assessment), LTP-like brain plasticity (via TMS) and activity-dependent cortical regions of interest, like the DLPFC, are required to examine the overarching relationship between cortical thickness and brain plasticity. Future exploration of these relationships in clinical populations would yield relevant and important information for this topic.

7 Limitations

The current study should be reviewed considering its limitations. With a small final sample of 12 participants, the results from our correlational analyses may have undermined the internal

and external validity of the project, for which the strength of relationships (or lack thereof) may be exaggerated by a biased sample with inadequate power. Small sample size is a recurrent and relevant problem in TMS-EEG literature, even before the halt of research activities during the first couple of years of the covid-19 pandemic. The current study will continue to recruit participants until 25 participants can be included for statistical analyses.

Secondly, our raw TMS-EEG data exhibited different TMS artifacts that were difficult to remove during EEG post-processing. For example, each TMS pulse produced a TMS pulse artifact (i.e., time-linked spike in neural activity that extends beyond the pulse), auditory and somatosensory artifacts (i.e., activation of sensory axons) and muscle artifacts (i.e., activation of motor axons and cranial nerves) that may corrupt EEG recorded brain signal. These artifacts produced electromagnetic activity that is larger in amplitude than typical brain activity, which was observed in the entirety of the raw TEP waveform (Farzan et al., 2016; Ilmoniemi et al., 1997; Ilmoniemi & Kičić, 2010; Rossi et al., 2009, 2021; Tremblay et al., 2019). Participants were removed from analyses if these artifacts were not completely removed, which would have contributed to noisy or distorted or shifted EEG data. Five participants were removed as a result (Table S6).

With a small sample, each participant's data contributes a great deal to the overall trend, and those distortions could have prevented us from observing generalizable results for our population of interest. A solution for this obstacle for future studies would be to implement real-time TEP visualization software to minimize artifacts and fine-tune TMS parameters for optimal cortical stimulation during TMS-EEG recordings (Casarotto et al., 2022; Varone et al., 2021). Future studies could also include whole-brain analyses to minimize the influence of TMS artifacts

on regional EEG signals as not all brain regions show the same artifacts (Bertazzoli et al., 2021; Mutanen et al., 2013; Rocchi et al., 2021).

Another limitation of the current study was the use of two different EEG caps and amplifiers for the current sample. Although this limitation was ruled out by entering this as a covariate in our analyses, it is never good practice to alter recording methods once a study begins. We justified the change in EEG equipment during the COVID-19 pandemic since the initial EEG equipment was older compared to newer and updated EEG equipment.

Lastly, a large limitation of the current study was, and still is, the covid-19 pandemic (Alsiri et al., 2021; Bikson et al., 2020; Luck & Kappenman, 2020; Perellón-Alfonso et al., 2021). Participant recruitment and assessment halted from March 2020 to June 2021, causing this project to lose potential participants who would have increased statistical test power and lowered the standard error of sample distribution. Recruitment continues to run at a slower pace than before the covid-19 pandemic; moreover, the current project will continue into 2023 to compensate for lost time.

8 Conclusion and future directions

By combining MRI, an increased number of TEP components and memory assessment, our team were provided with key measures to explore brain plasticity in a greater capacity. Nonetheless, even with a small sample, we observed a significant change in TEP component P30 post-iTBS. Overall, our results suggest that we can successfully combine TMS-EEG and iTBS to estimate LTP-like brain plasticity in the left DLPFC. Our data also suggest cortical excitability post-iTBS may be associated with a thicker left DLPFC, which has not been explored before in the literature. Our team will continue to recruit participants to gain a more generalizable sample for future study publication.

Future studies could supplement our findings by including resting-state connectivity to further individualize left DLPFC targeting with iTBS (Cash et al., 2021). In conjunction, future studies could also include TEP component P30 during post-iTBS TEP waveform analysis to clarify our results. It is also important to note that the current study focused on a small healthy control sample. Furthermore, the inclusion of a clinical population sample could provide additional insight into the relationship between LTP-like brain plasticity, cognition and brain structure. Based on our results relating to LTP-like brain plasticity and left DLPFC thickness, the current study opens a new door for future studies to use TMS-EEG, iTBS and brain imaging to explore disease pathology and predict illness severity in different groups and at individualized cortical targets. Future studies should continue to include measures of LTP-plasticity (via TMS-EEG and iTBS) and cortical thickness in cognitively healthy individuals as well as in clinical populations to establish these measures as indicative factors in disease progression. With more evidence, TMS-EEG methods could become common practice along disease pathophysiology, just as brain imaging or prescribed blood panels are used to indicate and monitor signs of disease. Additionally, it would be of interest to apply real-time visualization tools to monitor TEPs during EEG recording to minimize artifacts and signal noise (Casarotto et al., 2022; Varone et al., 2021). With more TMS-EEG, brain imaging studies, and fine-tuned standard procedures using newer and adaptive visualization tools mentioned above, research groups will continue to effectively replicate, accurately compare and interpret the overarching synthesis of evidence. Overall, the current study supports the combination of TMS-EEG and iTBS as a safe and effective tool to examine brain plasticity in the cortex. Lastly, our preliminary findings support the foundation for future clinical studies in which DLPFC thickness could be explored as a predictive factor for response to plasticity-targeting iTBS treatment.

9 References

Alsiri, N. F., Alhadhoud, M. A., & Palmer, S. (2021). The impact of the COVID-19 on research. *Journal of Clinical Epidemiology*, *129*, 124–125. https://doi.org/10.1016/j.jclinepi.2020.09.040

Andersen, P. (1982). Physiological and Chemical Control of Hippocampal Neurones. In *Neurotransmitter Interaction and Compartmentation* (pp. 601–616). Springer US. https://doi.org/10.1007/978-1-4684-1140-9_38

Andersen, P., & Lømo, T. (1967). Control of Hippocampal Output by Afferent Volley Frequency. *Progress in Brain Research*, *27*(C), 400–412. https://doi.org/10.1016/S0079-6123(08)63112-X

Anderson, M. C., Bunce, J. G., & Barbas, H. (2016). Prefrontal–hippocampal pathways underlying inhibitory control over memory. In *Neurobiology of Learning and Memory* (Vol. 134, pp. 145–161). https://doi.org/10.1016/j.nlm.2015.11.008

Bagattini, C., Mutanen, T. P., Fracassi, C., Manenti, R., Cotelli, M., Ilmoniemi, R. J., Miniussi, C., & Bortoletto, M. (2019). *Predicting Alzheimer's disease severity by means of TMSeEEG coregistration*. https://doi.org/10.1016/j.neurobiolaging.2019.04.008

Barbey, A. K., Koenigs, M., & Grafman, J. (2013). Dorsolateral prefrontal contributions to human working memory. *Cortex*, *49*(5), 1195–1205. https://doi.org/10.1016/j.cortex.2012.05.022

Bashir, S., Mizrahi, I., Weaver, K., Fregni, F., & Pascual-Leone, A. (2010). Assessment and modulation of neural plasticity in rehabilitation with transcranial magnetic stimulation. *PM and R*, *2*(12 SUPPL), 253–268. https://doi.org/10.1016/j.pmrj.2010.10.015

Belardinelli, P., König, F., Liang, C., Premoli, I., Desideri, D., Müller-Dahlhaus, F., Gordon, P. C., Zipser, C., Zrenner, C., & Ziemann, U. (2021). TMS-EEG signatures of glutamatergic neurotransmission in human cortex. *Scientific Reports*, *11*(1), 8159. https://doi.org/10.1038/s41598-021-87533-z

Bertazzoli, G., Esposito, R., Mutanen, T. P., Ferrari, C., Ilmoniemi, R. J., Miniussi, C., & Bortoletto, M. (2021). The impact of artifact removal approaches on TMS–EEG signal. *NeuroImage*, *239*. https://doi.org/10.1016/j.neuroimage.2021.118272

Bhagwat, N., Barry, A., Dickie, E., Brown, S., Devenyi, G., Hatano, K., DuPre, E., Dagher, A., Chakravarty, M. M., Greenwood, C., Misic, B., Kennedy, D., & Poline, J.-B. (2020). Understanding the impact of preprocessing pipelines on neuroimaging cortical surface analyses. *BioRxiv*, 2020.05.22.100180. https://doi.org/10.1101/2020.05.22.100180

Bikson, M., Hanlon, C. A., Woods, A. J., Gillick, B. T., Charvet, L., Lamm, C., Madeo, G., Holczer, A., Almeida, J., Antal, A., Ay, M. R., Baeken, C., Blumberger, D. M., Campanella, S., Camprodon, J. A., Christiansen, L., Loo, C., Crinion, J. T., Fitzgerald, P., … Ekhtiari, H. (2020). Guidelines for TMS/tES clinical services and research through the COVID-19 pandemic. *Brain Stimulation*, *13*(4), 1124–1149. https://doi.org/10.1016/j.brs.2020.05.010

Bliss, T. V., & Collingridge, G. L. (2013). Expression of NMDA receptor-dependent LTP in the hippocampus: bridging the divide. In *Molecular brain* (Vol. 6). https://doi.org/10.1186/1756-6606-6-5

Bliss, T. V. P., Burns, B. D., & Uttley, A. M. (1968). Factors affecting the conductivity of pathways in the cerebral cortex. *The Journal of Physiology*, *195*(2), 339–367. https://doi.org/10.1113/jphysiol.1968.sp008462

Bliss, T. V. P., & Collingridge, G. L. (1993a). A synaptic model of memory: Long-term potentiation in the hippocampus. In *Nature* (Vol. 361, Issue 6407, pp. 31–39). https://doi.org/10.1038/361031a0

Bliss, T. V. P., & Collingridge, G. L. (1993b). A synaptic model of memory: long-term potentiation in the hippocampus. *Nature*, *361*(6407), 31–39. https://doi.org/10.1038/361031a0

Bliss, T. V. P., Collingridge, G. L., Morris, R. G. M., & Reymann, K. G. (2018). Long-term potentiation in the hippocampus: Discovery, mechanisms and function. *Neuroforum*, *24*(3), A103–A120. https://doi.org/10.1515/nf-2017-A059

Bliss, T. V. P., & Gardner-Medwin, A. R. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the unanaesthetized rabbit following stimulation of the perforant path. *The Journal of Physiology*, *232*(2), 357–374. https://doi.org/10.1113/jphysiol.1973.sp010274

Bliss, T. V. P., & Lømo, T. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *The Journal of Physiology*, *232*(2), 331–356. https://doi.org/10.1113/jphysiol.1973.sp010273

Blumberger, D. (2019). Can combined TMS-EEG to the dorsolateral prefrontal cortex help guide therapeutic rTMS? *Brain Stimulation*, *12*(2), 479. https://doi.org/10.1016/j.brs.2018.12.563

Blumberger, D. M., Vila-Rodriguez, F., Thorpe, K. E., Feffer, K., Noda, Y., Giacobbe, P., Knyahnytska, Y., Kennedy, S. H., Lam, R. W., Daskalakis, Z. J., & Downar, J. (2018). Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. *The Lancet*, *391*(10131), 1683–1692. https://doi.org/10.1016/S0140-6736(18)30295-2

Bruel-Jungerman, E., Davis, S., & Laroche, S. (2007). Brain Plasticity Mechanisms and Memory: A Party of Four. *The Neuroscientist*, *13*(5), 492–505. https://doi.org/10.1177/1073858407302725

Capocchi, G., Zampolini, M., & Larson, J. (1992). Theta burst stimulation is optimal for induction of LTP at both apical and basal dendritic synapses on hippocampal CA1 neurons. *Brain Research*, *591*(2), 332–336. https://doi.org/10.1016/0006-8993(92)91715-Q

Casarotto, S., Fecchio, M., Rosanova, M., Varone, G., D'Ambrosio, S., Sarasso, S., Pigorini, A., Russo, S., Comanducci, A., Ilmoniemi, R. J., & Massimini, M. (2022). The rt-TEP tool: real-time visualization of TMS-Evoked Potentials to maximize cortical activation and minimize artifacts. *Journal of Neuroscience Methods*, *370*, 109486. https://doi.org/10.1016/J.JNEUMETH.2022.109486

Casarotto, S., Lauro, L. J. R., Bellina, V., Casali, A. G., Rosanova, M., Pigorini, A., Defendi, S., Mariotti, M., & Massimini, M. (2010). EEG responses to TMS are sensitive to changes in the perturbation parameters and repeatable over time. *PLoS ONE*, *5*(4), e10281. https://doi.org/10.1371/journal.pone.0010281

Casarotto, S., Määttä, S., Herukka, S. K., Pigorini, A., Napolitani, M., Gosseries, O., Niskanen, E., Könönen, M., Mervaala, E., Rosanova, M., Soininen, H., & Massimini, M. (2012). Transcranial magnetic stimulation-evoked EEG/cortical potentials in physiological and pathological aging. *Neuroreport*, *22*(12), 592–597. https://doi.org/10.1097/WNR.0B013E328349433A

Cash, R. F. H., Cocchi, L., Lv, J., Wu, Y., Fitzgerald, P. B., & Zalesky, A. (2021). Personalized connectivity-guided DLPFC-TMS for depression: Advancing computational feasibility, precision and reproducibility. *Human Brain Mapping*, *42*(13), 4155–4172. https://doi.org/10.1002/HBM.25330

Chung, S. W., Lewis, B. P., Rogasch, N. C., Saeki, T., Thomson, R. H., Hoy, K. E., Bailey, N. W., & Fitzgerald, P. B. (2017). Demonstration of short-term plasticity in the dorsolateral prefrontal cortex with theta burst stimulation: A TMS-EEG study. *Clinical Neurophysiology*, *128*(7), 1117–1126. https://doi.org/10.1016/j.clinph.2017.04.005

Chung, S. W., Rogasch, N. C., Hoy, K. E., & Fitzgerald, P. B. (2018). The effect of single and repeated prefrontal intermittent theta burst stimulation on cortical reactivity and working memory. *Brain Stimulation*, *11*(3), 566–574. https://doi.org/10.1016/j.brs.2018.01.002

Chung, S. W., Rogasch, N. C., Hoy, K. E., Sullivan, C. M., Cash, R. F. H., & Fitzgerald, P. B. (2018). Impact of different intensities of intermittent theta burst stimulation on the cortical properties during TMS-EEG and working memory performance. *Human Brain Mapping*, *39*(2), 783. https://doi.org/10.1002/HBM.23882

Chung, S. W., Sullivan, C. M., Rogasch, N. C., Hoy, K. E., Bailey, N. W., Cash, R. F. H., & Fitzgerald, P. B. (2019). The effects of individualised intermittent theta burst stimulation in the prefrontal cortex: A TMS-EEG study. *Human Brain Mapping*, *40*(2), 608–627. https://doi.org/10.1002/hbm.24398

Citri, A., & Malenka, R. C. (2008). Synaptic plasticity: Multiple forms, functions, and mechanisms. In *Neuropsychopharmacology* (Vol. 33, Issue 1, pp. 18–41). Nature Publishing Group. https://doi.org/10.1038/sj.npp.1301559

Conde, V., Tomasevic, L., Akopian, I., Stanek, K., Saturnino, G. B., Thielscher, A., Bergmann, T. O., & Siebner, H. R. (2019). The non-transcranial TMS-evoked potential is an inherent source of ambiguity in TMS-EEG studies. *NeuroImage*, *185*, 300–312. https://doi.org/10.1016/j.neuroimage.2018.10.052

Cooke, S. F., & Bliss, T. V. P. (2006). Plasticity in the human central nervous system. In *Brain* (Vol. 129, Issue 7, pp. 1659–1673). https://doi.org/10.1093/brain/awl082

Corp, D. T., Bereznicki, H. G. K., Clark, G. M., Youssef, G. J., Fried, P. J., Jannati, A., Davies, C. B., Gomes-Osman, J., Stamm, J., Chung, S. W., Bowe, S. J., Rogasch, N. C., Fitzgerald, P. B., Koch, G., di Lazzaro, V., Pascual-Leone, A., & Enticott, P. G. (2020). Large-scale analysis of interindividual variability in theta-burst stimulation data: Results from the "Big TMS Data Collaboration." *Brain Stimulation*, *13*(5), 1476–1488. https://doi.org/10.1016/J.BRS.2020.07.018

Curtis, C. E., & D'Esposito, M. (2003). Persistent activity in the prefrontal cortex during working memory. In *Trends in Cognitive Sciences* (Vol. 7, Issue 9, pp. 415–423). https://doi.org/10.1016/S1364-6613(03)00197-9

Darmani, G., Zipser, C. M., Böhmer, G. M., Deschet, K., Müller-Dahlhaus, F., Belardinelli, P., Schwab, M., & Ziemann, U. (2016). Effects of the Selective α5-GABAAR Antagonist S44819 on Excitability in the Human Brain: A TMS–EMG and TMS–EEG Phase I Study. *The Journal of Neuroscience*, *36*(49), 12312–12320. https://doi.org/10.1523/JNEUROSCI.1689-16.2016

Desforges, M., Hadas, I., Mihov, B., Morin, Y., Rochette Braün, M., Lioumis, P., Zomorrodi, R., Théoret, H., Lepage, M., Daskalakis, Z. J., & Tremblay, S. (2022). Dose-response of intermittent theta burst stimulation of the prefrontal cortex: A TMS-EEG study. *Clinical Neurophysiology*, *136*, 158–172. https://doi.org/10.1016/j.clinph.2021.12.018

Diamond, D. M., Dunwiddie, T. v, & Rose, G. M. (1988). Characteristics of Hippocampal Primed Burst Potentiation in vitro and in the Awake Rat. *The Journal of Neuroscience*, *8*(11), 4079–4088.

Eccles, J. C. (1983). Calcium in long-term potentiation as a model for memory. *Neuroscience*, *10*(4), 1071–1081. https://doi.org/10.1016/0306-4522(83)90100-8

Emami, S., Guimond, S., Mallar Chakravarty, M., & Lepage, M. (2016). Cortical thickness and low insight into symptoms in enduring schizophrenia. *Schizophrenia Research*, *170*(1), 66–72. https://doi.org/10.1016/j.schres.2015.10.016

Engvig, A., Fjell, A. M., Westlye, L. T., Moberget, T., Sundseth, O., Larsen, V. A., & Walhovd, K. B. (2010). Effects of memory training on cortical thickness in the elderly. *NeuroImage*, *52*(4), 1667–1676. https://doi.org/10.1016/j.neuroimage.2010.05.041

Farzan, F., & Bortoletto, M. (2022). Identification and verification of a “true” TMS evoked potential in TMS-EEG. *Journal of Neuroscience Methods*, *378*, 109651. https://doi.org/10.1016/j.jneumeth.2022.109651

Farzan, F., Vernet, M., Shafi, M. M. D., Rotenberg, A., Daskalakis, Z. J., & Pascual-Leone, A. (2016). Characterizing and modulating brain circuitry through transcranial magnetic stimulation combined with electroencephalography. *Frontiers in Neural Circuits*, *10*(SEP). https://doi.org/10.3389/fncir.2016.00073

Fuchs, E., & Flügge, G. (2014). Adult neuroplasticity: More than 40 years of research. In *Neural Plasticity* (Vol. 2014, p. 541870). Hindawi Limited. https://doi.org/10.1155/2014/541870

Gedankien, T., Fried, P. J., Pascual-Leone, A., & Shafi, M. M. (2017). Intermittent theta-burst stimulation induces correlated changes in cortical and corticospinal excitability in healthy older subjects. *Clinical Neurophysiology*, *128*(12), 2419–2427. https://doi.org/10.1016/j.clinph.2017.08.034

Gillick, B. T., & Zirpel, L. (2012). Neuroplasticity: An appreciation from synapse to system. *Archives of Physical Medicine and Rehabilitation*, *93*(10), 1846–1855. https://doi.org/10.1016/j.apmr.2012.04.026

Goldsworthy, M. R., Rogasch, N. C., Ballinger, S., Graetz, L., van Dam, J. M., Harris, R., Yu, S., Pitcher, J. B., Baune, B. T., & Ridding, M. C. (2020). Age-related decline of neuroplasticity to intermittent theta burst stimulation of the lateral prefrontal cortex and its relationship with late-life memory performance. *Clinical Neurophysiology*, *131*(9), 2181–2191. https://doi.org/10.1016/j.clinph.2020.06.015

Gordon, P. C., Desideri, D., Belardinelli, P., Zrenner, C., & Ziemann, U. (2018). Comparison of cortical EEG responses to realistic sham versus real TMS of human motor cortex. *Brain Stimulation*, *11*(6), 1322–1330. https://doi.org/10.1016/j.brs.2018.08.003

Guerra, A., Suppa, A., Bologna, M., D’Onofrio, V., Bianchini, E., Brown, P., di Lazzaro, V., & Berardelli, A. (2018). Boosting the LTP-like plasticity effect of intermittent theta-burst stimulation using gamma transcranial alternating current stimulation. *Brain Stimulation*, *11*(4), 734–742. https://doi.org/10.1016/j.brs.2018.03.015

Guimond, S., Béland, S., & Lepage, M. (2018). Strategy for Semantic Association Memory (SESAME) training: Effects on brain functioning in schizophrenia. *Psychiatry Research - Neuroimaging*, *271*, 50–58. https://doi.org/10.1016/j.pscychresns.2017.10.010

Guimond, S., Chakravarty, M. M., Bergeron-Gagnon, L., Patel, R., & Lepage, M. (2016). Verbal memory impairments in schizophrenia associated with cortical thinning. *NeuroImage: Clinical*, *11*, 20–29. https://doi.org/10.1016/j.nicl.2015.12.010

Hebb, D. 0. (1949). *The Organization of Behavior A NEUROPSYCHOLOGICAL THEORY*. John Wiley & Sons. Inc. http://s-f-walker.org.uk/pubsebooks/pdfs/The_Organization_of_Behavior-Donald_O._Hebb.pdf

Huang, Y. Z., Edwards, M. J., Rounis, E., Bhatia, K. P., & Rothwell, J. C. (2005). Theta burst stimulation of the human motor cortex. *Neuron*, *45*(2), 201–206. https://doi.org/10.1016/j.neuron.2004.12.033

Hui, J., Tremblay, S., & Daskalakis, Z. J. (2019). The Current and Future Potential of Transcranial Magnetic Stimulation With Electroencephalography in Psychiatry. *Clinical Pharmacology & Therapeutics*, *106*(4), 734–746. https://doi.org/10.1002/cpt.1541

Hutton, C., De Vita, E., Ashburner, J., Deichmann, R., & Turner, R. (2008). Voxel-based cortical thickness measurements in MRI. *NeuroImage*, *40*(4), 1701–1710. https://doi.org/10.1016/j.neuroimage.2008.01.027

Ilmoniemi, R. J., & Kičić, D. (2010). Methodology for combined TMS and EEG. *Brain Topography*, *22*(4), 233–248. https://doi.org/10.1007/s10548-009-0123-4

Ilmoniemi, R. J., Virtanen, J., Ruohonen, J., Karhu, J., Aronen, H. J., Näätänen, R., & Katila, T. (1997). Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity. *NeuroReport*, *8*(16), 3537–3540. https://doi.org/10.1097/00001756-199711100-00024

Isaacson, J. S., & Scanziani, M. (2011). How inhibition shapes cortical activity. In *Neuron* (Vol. 72, Issue 2, pp. 231–243). https://doi.org/10.1016/j.neuron.2011.09.027

J, L., & G, L. (1986). Induction of synaptic potentiation in hippocampus by patterned stimulation involves two events. *Science (New York, N.Y.)*, *232*(4753), 985–988. https://doi.org/10.1126/SCIENCE.3704635

J, L., & G, L. (1989). Theta pattern stimulation and the induction of LTP: the sequence in which synapses are stimulated determines the degree to which they potentiate. *Brain Research*, *489*(1), 49–58. https://doi.org/10.1016/0006-8993(89)90007-3

Jiang, L., Cao, X., Li, T., Tang, Y., Li, W., Wang, J., Chan, R. C., & Li, C. (2016). Cortical thickness changes correlate with cognition changes after cognitive training: Evidence from a Chinese community study. *Frontiers in Aging Neuroscience*, *8*(MAY), 118. https://doi.org/10.3389/fnagi.2016.00118

Kähkönen, S., Komssi, S., Wilenius, J., & Ilmoniemi, R. J. (2005). Prefrontal TMS produces smaller EEG responses than motor-cortex TMS: Implications for rTMS treatment in depression. *Psychopharmacology*, *181*(1), 16–20. https://doi.org/10.1007/s00213-005-2197-3

Kähkönen, S., Wilenius, J., Komssi, S., & Ilmoniemi, R. J. (2004). Distinct differences in cortical reactivity of motor and prefrontal cortices to magnetic stimulation. *Clinical Neurophysiology*, *115*(3), 583–588. https://doi.org/10.1016/j.clinph.2003.10.032

Kallioniemi, E., & Daskalakis, Z. J. (2022). Identifying novel biomarkers with TMS-EEG-Methodological possibilities and challenges. *Journal of Neuroscience Methods*, *377*, 109631. https://doi.org/10.1016/j.jneumeth.2022.109631

Kluen, L. M., Dandolo, L. C., Jocham, G., & Schwabe, L. (2019). Dorsolateral Prefrontal Cortex Enables Updating of Established Memories. *Cerebral Cortex*, *29*(10), 4154–4168. https://doi.org/10.1093/cercor/bhy298

Lashley, K. S. (1920). Studies of cerebral function in learning. *Psychobiology*, *2*(1), 55–135. https://doi.org/10.1037/h0071866

Lioumis, P., Kičić, D., Savolainen, P., Mäkelä, J. P., & Kähkönen, S. (2009). Reproducibility of TMS - Evoked EEG responses. *Human Brain Mapping*, *30*(4), 1387–1396. https://doi.org/10.1002/hbm.20608

Lioumis, P., & Rosanova, M. (2022). The role of neuronavigation in TMS–EEG studies: Current applications and future perspectives. *Journal of Neuroscience Methods*, *380*. https://doi.org/10.1016/J.JNEUMETH.2022.109677

List, J., Kübke, J. C., Lindenberg, R., Külzow, N., Kerti, L., Witte, V., & Flöel, A. (2013). Relationship between excitability, plasticity and thickness of the motor cortex in older adults. *NeuroImage*, *83*, 809–816. https://doi.org/10.1016/j.neuroimage.2013.07.033

Lømo, T. (2003). The discovery of long-term potentiation. In *Philosophical Transactions of the Royal Society B: Biological Sciences* (Vol. 358, Issue 1432, pp. 617–620). https://doi.org/10.1098/rstb.2002.1226

Lømo, T. (2018). Discovering long-term potentiation (LTP) – recollections and reflections on what came after. In *Acta Physiologica* (Vol. 222, Issue 2, p. e12921). John Wiley & Sons, Ltd. https://doi.org/10.1111/apha.12921

Luck, S. J., & Kappenman, E. S. (2020). Resources to assist EEG/ERP researchers during the COVID-19 pandemic. In *Psychophysiology* (Vol. 57, Issue 9). https://doi.org/10.1111/psyp.13659

Luu, P., Caggiano, D. M., Geyer, A., Lewis, J., Cohn, J., & Tucker, D. M. (2014). Time-course of cortical networks involved in working memory. *Frontiers in Human Neuroscience*, *8*(JAN), 4. https://doi.org/10.3389/fnhum.2014.00004

Lynch, M. A. (2004). Long-Term Potentiation and Memory. In *Physiological Reviews* (Vol. 84, Issue 1, pp. 87–136). American Physiological Society. https://doi.org/10.1152/physrev.00014.2003

Madison, D. v, Malenka, R. C., & Nicoll, R. A. (1991). Mechanisms underlying long-term potentiation of synaptic transmission. In *Annual Review of Neuroscience* (Vol. 14, Issue 1, pp. 379–397). Annual Reviews 4139 El Camino Way, P.O. Box 10139, Palo Alto, CA 94303-0139, USA. https://doi.org/10.1146/annurev.ne.14.030191.002115

Maguire, E. A., Gadian, D. G., Johnsrude, I. S., Good, C. D., Ashburner, J., Frackowiak, R. S. J., & Frith, C. D. (2000). Navigation-related structural change in the hippocampi of taxi drivers. *Proceedings of the National Academy of Sciences of the United States of America*, *97*(8), 4398–4403. https://doi.org/10.1073/pnas.070039597

Mäki, H., & Ilmoniemi, R. J. (2010). The relationship between peripheral and early cortical activation induced by transcranial magnetic stimulation. *Neuroscience Letters*, *478*(1), 24–28. https://doi.org/10.1016/j.neulet.2010.04.059

Mancuso, M., Sveva, V., Cruciani, A., Brown, K., Ibáñez, J., Rawji, V., Casula, E., Premoli, I., D'Ambrosio, S., Rothwell, J., & Rocchi, L. (2021). Transcranial Evoked Potentials Can Be Reliably Recorded with Active Electrodes. *Brain Sciences*, *11*(2), 1–16. https://doi.org/10.3390/brainsci11020145

Maren, S. (1999). Long-term potentiation in the amygdala: A mechanism for emotional learning and memory. In *Trends in Neurosciences* (Vol. 22, Issue 12, pp. 561–567). https://doi.org/10.1016/S0166-2236(99)01465-4

McEwen, B. S., & Morrison, J. H. (2013). The Brain on Stress: Vulnerability and Plasticity of the Prefrontal Cortex over the Life Course. In *Neuron* (Vol. 79, Issue 1, pp. 16–29). NIH Public Access. https://doi.org/10.1016/j.neuron.2013.06.028

Meyer, K., Garzón, B., Lövdén, M., & Hildebrandt, A. (2019). Are global and specific interindividual differences in cortical thickness associated with facets of cognitive abilities, including face cognition? *Royal Society Open Science*, *6*(7), 180857. https://doi.org/10.1098/rsos.180857

Mutanen, T., Mäki, H., & Ilmoniemi, R. J. (2013). The effect of stimulus parameters on TMS-EEG muscle artifacts. *Brain Stimulation*, *6*(3), 371–376. https://doi.org/10.1016/j.brs.2012.07.005

Neves, G., Cooke, S. F., & Bliss, T. V. P. (2008). Synaptic plasticity, memory and the hippocampus: A neural network approach to causality. In *Nature Reviews Neuroscience* (Vol. 9, Issue 1, pp. 65–75). https://doi.org/10.1038/nrn2303

Noda, Y., Barr, M. S., Zomorrodi, R., Cash, R. F. H., Lioumis, P., Chen, R., Daskalakis, Z. J., & Blumberger, D. M. (2021). Single-pulse transcranial magnetic stimulation-evoked potential amplitudes and latencies in the motor and dorsolateral prefrontal cortex among young, older healthy participants, and schizophrenia patients. *Journal of Personalized Medicine*, *11*(1), 1–12. https://doi.org/10.3390/jpm11010054

Oberman, L., & Pascual-Leone, A. (2013). Changes in plasticity across the lifespan: Cause of disease and target for intervention. In *Progress in Brain Research* (Vol. 207, pp. 91–120). NIH Public Access. https://doi.org/10.1016/B978-0-444-63327-9.00016-3

Oostenveld, R., Fries, P., Maris, E., & Schoffelen, J. M. (2011). FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Computational Intelligence and Neuroscience*, *2011*, 156869. https://doi.org/10.1155/2011/156869

Pell, G. S., Roth, Y., & Zangen, A. (2011). Modulation of cortical excitability induced by repetitive transcranial magnetic stimulation: Influence of timing and geometrical parameters and underlying mechanisms. In *Progress in Neurobiology* (Vol. 93, Issue 1, pp. 59–98). https://doi.org/10.1016/j.pneurobio.2010.10.003

Perellón-Alfonso, R., Redondo-Camós, M., Abellaneda-Pérez, K., Cattaneo, G., Delgado-Gallén, S., España-Irla, G., Sánchez, J. S., Tormos-Muñoz, J. M., Pascual-Leone, A., & Bartrés-Faz, D. (2021). TMS-induced EEG perturbation as a marker of psychological resilience to deleterious mental health effects during the COVID-19 pandemic. *Alzheimer's & Dementia*, *17*(S5), e056179. https://doi.org/10.1002/ALZ.056179

Pochon, J.-B. (2001). The Role of Dorsolateral Prefrontal Cortex in the Preparation of Forthcoming Actions: an fMRI Study. *Cerebral Cortex*, *11*(3), 260–266. https://doi.org/10.1093/cercor/11.3.260

Premoli, I., Castellanos, N., Rivolta, D., Belardinelli, P., Bajo, R., Zipser, C., Espenhahn, S., Heidegger, T., Müller-Dahlhaus, F., & Ziemann, U. (2014). TMS-EEG signatures of GABAergic neurotransmission in the human cortex. *Journal of Neuroscience*, *34*(16), 5603–5612. https://doi.org/10.1523/JNEUROSCI.5089-13.2014

Premoli, I., Király, J., Müller-Dahlhaus, F., Zipser, C. M., Rossini, P., Zrenner, C., Ziemann, U., & Belardinelli, P. (2018). Short-interval and long-interval intracortical inhibition of TMS-evoked EEG potentials. *Brain Stimulation*, *11*(4), 818–827. https://doi.org/10.1016/J.BRS.2018.03.008

Premoli, I., Rossini, P. G., Goldberg, P. Y., Posadas, K., Green, L., Yogo, N., Pimstone, S., Abela, E., Beatch, G. N., & Richardson, M. P. (2019). TMS as a pharmacodynamic indicator of cortical activity of a novel anti-epileptic drug, XEN1101. *Annals of Clinical and Translational Neurology*, *6*(11), 2164–2174. https://doi.org/10.1002/acn3.50896

Rocchi, L., di Santo, A., Brown, K., Ibáñez, J., Casula, E., Rawji, V., di Lazzaro, V., Koch, G., & Rothwell, J. (2021). Disentangling EEG responses to TMS due to cortical and peripheral activations. *Brain Stimulation*, *14*(1), 4–18. https://doi.org/10.1016/j.brs.2020.10.011

Rogasch, N. C., Thomson, R. H., Farzan, F., Fitzgibbon, B. M., Bailey, N. W., Hernandez-Pavon, J. C., Daskalakis, Z. J., & Fitzgerald, P. B. (2014). Removing artefacts from TMS-EEG recordings using independent component analysis: Importance for assessing prefrontal and motor cortex network properties. *NeuroImage*, *101*, 425–439. https://doi.org/10.1016/j.neuroimage.2014.07.037

Rossi, S., Antal, A., Bestmann, S., Bikson, M., Brewer, C., Brockmöller, J., Carpenter, L. L., Cincotta, M., Chen, R., Daskalakis, J. D., di Lazzaro, V., Fox, M. D., George, M. S., Gilbert, D., Kimiskidis, V. K., Koch, G., Ilmoniemi, R. J., Pascal Lefaucheur, J., Leocani, L., … Hallett, M. (2021). Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. In *Clinical Neurophysiology* (Vol. 132, Issue 1, pp. 269–306). Elsevier. https://doi.org/10.1016/j.clinph.2020.10.003

Rossi, S., Hallett, M., Rossini, P. M., Pascual-Leone, A., Avanzini, G., Bestmann, S., Berardelli, A., Brewer, C., Canli, T., Cantello, R., Chen, R., Classen, J., Demitrack, M., di Lazzaro, V., Epstein, C. M., George, M. S., Fregni, F., Ilmoniemi, R., Jalinous, R., … Ziemann, U. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. In *Clinical Neurophysiology* (Vol. 120, Issue 12, pp. 2008–2039). https://doi.org/10.1016/j.clinph.2009.08.016

Rossini, P. M., Burke, D., Chen, R., Cohen, L. G., Daskalakis, Z., di Iorio, R., di Lazzaro, V., Ferreri, F., Fitzgerald, P. B., George, M. S., Hallett, M., Lefaucheur, J. P., Langguth, B., Matsumoto, H., Miniussi, C., Nitsche, M. A., Pascual-Leone, A., Paulus, W., Rossi, S., … Ziemann, U. (2015). Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application: An updated report from an I.F.C.N. Committee. In *Clinical Neurophysiology*(Vol. 126, Issue 6, pp. 1071–1107). NIH Public Access. https://doi.org/10.1016/j.clinph.2015.02.001

Rowe, J. B., Toni, I., Josephs, O., Frackowiak, R. S. J., & Passingham, R. E. (2000). The prefrontal cortex: Response selection or maintenance within working memory? *Science*, *288*(5471), 1656–1660. https://doi.org/10.1126/science.288.5471.1656

Sanches, M., Caetano, S., Nicoletti, M., Monkul, E. S., Chen, H. H., Hatch, J. P., Yeh, P. H., Mullis, R. L., Keshavan, M. S., Rajowska, G., & Soares, J. C. (2009). An MRI-based approach for the measurement of the dorsolateral prefrontal cortex in humans. *Psychiatry Research - Neuroimaging*, *173*(2), 150–154. https://doi.org/10.1016/j.pscychresns.2009.02.007

Schnack, H. G., van Haren, N. E. M., Brouwer, R. M., Evans, A., Durston, S., Boomsma, D. I., Kahn, R. S., & Hulshoff Pol, H. E. (2015). Changes in thickness and surface area of the human cortex and their relationship with intelligence. *Cerebral Cortex*, *25*(6), 1608–1617. https://doi.org/10.1093/cercor/bht357

Sheehan, D. v., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., & Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry*, *59*(SUPPL. 20), 22–33. https://www.psychiatrist.com/JCP/article/Pages/mini-international-neuropsychiatric-interview-mini.aspx

Siebner, H. R., Conde, V., Tomasevic, L., Thielscher, A., & Bergmann, T. O. (2019). Distilling the essence of TMS-evoked EEG potentials (TEPs): A call for securing mechanistic specificity and experimental rigor. In *Brain Stimulation* (Vol. 12, Issue 4, pp. 1051–1054). Elsevier. https://doi.org/10.1016/j.brs.2019.03.076

Sled, J. G., Zijdenbos, A. P., & Evans, A. C. (1998). A nonparametric method for automatic correction of intensity nonuniformity in mri data. *IEEE Transactions on Medical Imaging*, *17*(1), 87–97. https://doi.org/10.1109/42.668698

Stanley, W. C., & Jaynes, J. (1949). The function of the frontal cortex. *Psychological Review*, *56*(1), 18–32. https://doi.org/10.1037/h0062790

Struckmann, W., Persson, J., Gingnell, M., & Bodén, R. (2019). The effect of intermittent theta-burst stimulation on the depressed brain: a sham controlled study with near-infrared spectroscopy. *Brain Stimulation*, *12*(2), 504. https://doi.org/10.1016/j.brs.2018.12.651

Suppa, A., Huang, Y. Z., Funke, K., Ridding, M. C., Cheeran, B., di Lazzaro, V., Ziemann, U., & Rothwell, J. C. (2016). Ten Years of Theta Burst Stimulation in Humans: Established Knowledge, Unknowns and Prospects. In *Brain Stimulation* (Vol. 9, Issue 3, pp. 323–335). https://doi.org/10.1016/j.brs.2016.01.006

Tees, R. C. (2003). Review of The organization of behavior: A neuropsychological theory. *Canadian Psychology*, *44*(1), 74–76. https://doi.org/10.1037/h0088061

Tremblay, S., Rogasch, N. C., Premoli, I., Blumberger, D. M., Casarotto, S., Chen, R., di Lazzaro, V., Farzan, F., Ferrarelli, F., Fitzgerald, P. B., Hui, J., Ilmoniemi, R. J., Kimiskidis, V. K., Kugiumtzis, D., Lioumis, P., Pascual-Leone, A., Pellicciari, M. C., Rajji, T., Thut, G., …

Daskalakis, Z. J. (2019). Clinical utility and prospective of TMS–EEG. In *Clinical Neurophysiology* (Vol. 130, Issue 5, pp. 802–844). https://doi.org/10.1016/j.clinph.2019.01.001

Turnbull, A., Wang, H. T., Murphy, C., Ho, N. S. P., Wang, X., Sormaz, M., Karapanagiotidis, T., Leech, R. M., Bernhardt, B., Margulies, D. S., Vatansever, D., Jefferies, E., & Smallwood, J. (2019). Left dorsolateral prefrontal cortex supports context-dependent prioritisation of off-task thought. *Nature Communications*, *10*(1). https://doi.org/10.1038/s41467-019-11764-y

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., & Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage*, *15*(1), 273–289. https://doi.org/10.1006/nimg.2001.0978

Varone, G., Hussain, Z., Sheikh, Z., Howard, A., Boulila, W., Mahmud, M., Howard, N., Morabito, F. C., & Hussain, A. (2021). Real-Time Artifacts Reduction during TMS-EEG Co-Registration: A Comprehensive Review on Technologies and Procedures. *Sensors (Basel, Switzerland)*, *21*(2), 1–23. https://doi.org/10.3390/S21020637

Vulovic, M., Divac, N., & Jakovcevski, I. (2018). Confocal Synaptology: Synaptic Rearrangements in Neurodegenerative Disorders and upon Nervous System Injury. *Frontiers in Neuroanatomy*, *12*, 11. https://doi.org/10.3389/fnana.2018.00011

Wang, S., Zhou, M., Chen, T., Yang, X., Chen, G., Wang, M., & Gong, Q. (2017). Examining gray matter structure associated with academic performance in a large sample of Chinese high school students. *Scientific Reports*, *7*(1), 893. https://doi.org/10.1038/s41598-017-00677-9

Wheeler, A. L., Chakravarty, M. M., Lerch, J. P., Pipitone, J., Daskalakis, Z. J., Rajji, T. K., Mulsant, B. H., & Voineskos, A. N. (2014). Disrupted prefrontal interhemispheric structural coupling in Schizophrenia related to working memory performance. *Schizophrenia Bulletin*, *40*(4), 914–924. https://doi.org/10.1093/schbul/sbt100

Wierzba, M., Riegel, M., Wypych, M., Jednoróg, K., Grabowska, A., & Marchewka, A. (2018). Cognitive control over memory-individual differences in memory performance for emotional and neutral material. *Scientific Reports*, *8*(1), 3808. https://doi.org/10.1038/s41598-018-21857-1

Yuan, P., & Raz, N. (2014). Prefrontal cortex and executive functions in healthy adults: A meta-analysis of structural neuroimaging studies. In *Neuroscience and Biobehavioral Reviews* (Vol. 42, pp. 180–192). NIH Public Access. https://doi.org/10.1016/j.neubiorev.2014.02.005

Zatorre, R. J., Fields, R. D., & Johansen-Berg, H. (2012). Plasticity in Gray and White: Neuroimaging changes in brain structure during learning. *Nature Neuroscience*, *15*(4), 528. https://doi.org/10.1038/NN.3045

10 Supplementary Material

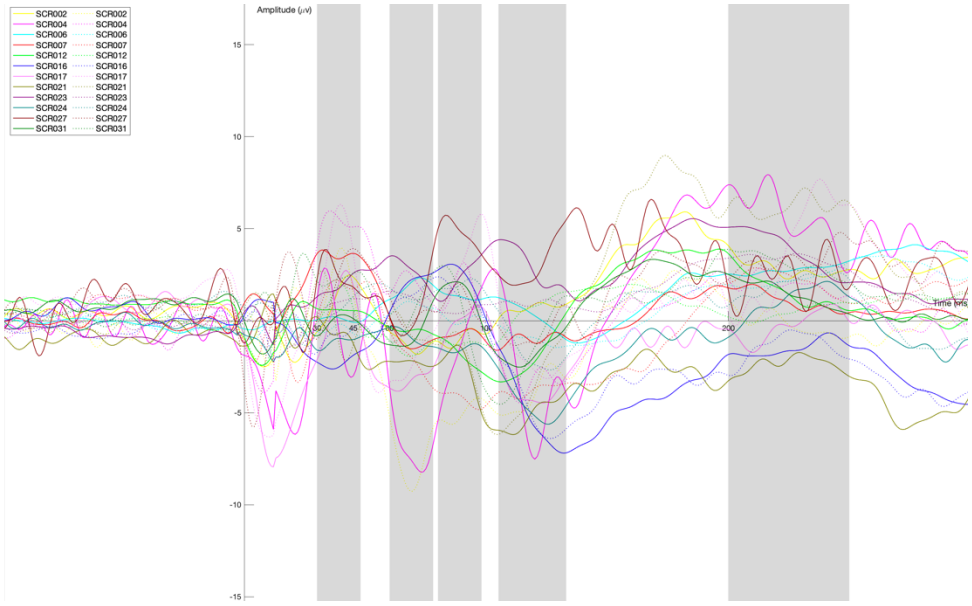

Figure S1: Active iTBS condition – Averaged single-pulse TEP waveform for each participant at ROI (FC1, F1, AFZ). *The shaded gray areas denote the time window for each peak of interest. iTBS = intermittent theta burst stimulation; TEP = transcranial magnetic stimulation evoked potential; ROI = region of interest.*

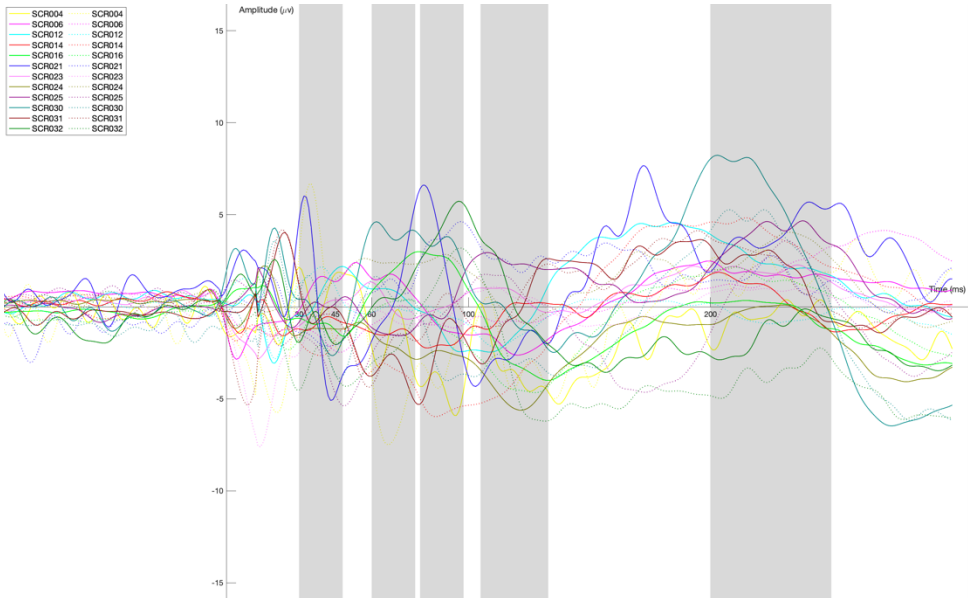

Figure S2. Sham iTBS condition – Averaged single-pulse TEP waveform for each participant at ROI (FC1, F1, AFZ). *The shaded gray areas denote the time window for each peak of interest. TEP = transcranial magnetic stimulation evoked potential; ROI = region of interest.*

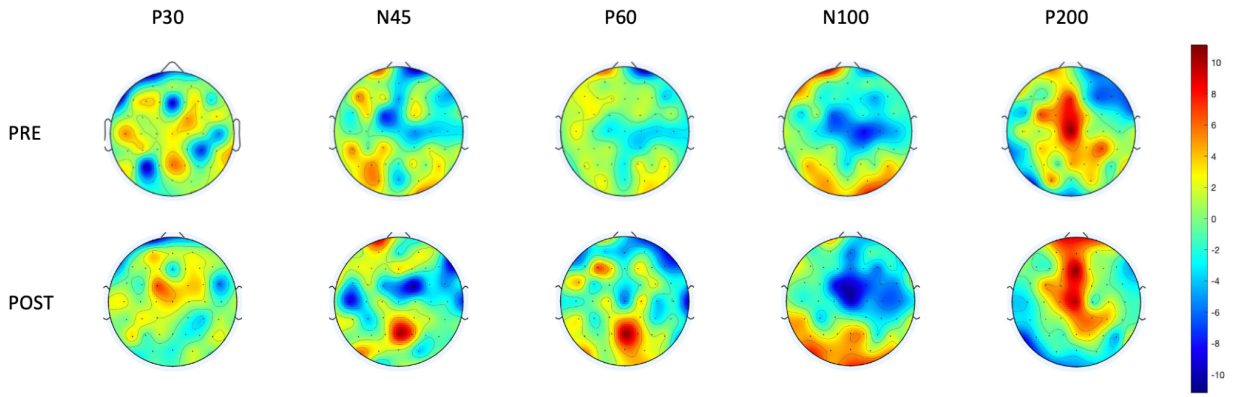

Figure S3: Active iTBS condition - Topographical plots of voltage (µV) scalp distribution for TEP components of interest, pre- and post-iTBS. *iTBS = intermittent theta burst stimulation; TEP = transcranial magnetic stimulation evoked potential.*

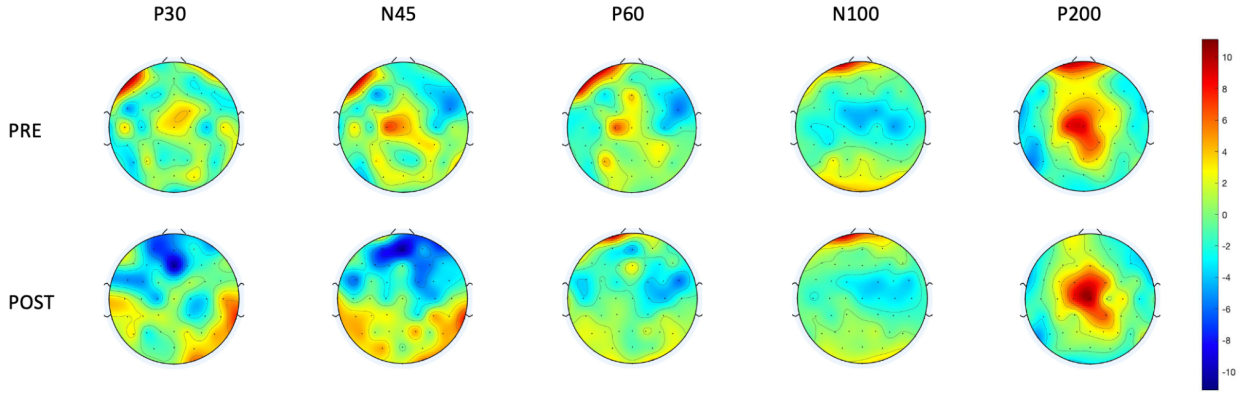

Figure S4: Sham iTBS condition - Topographical plots of voltage (µV) scalp distribution for TEP components of interest, pre- and post-sham. *TEP = transcranial magnetic stimulation evoked potential.*

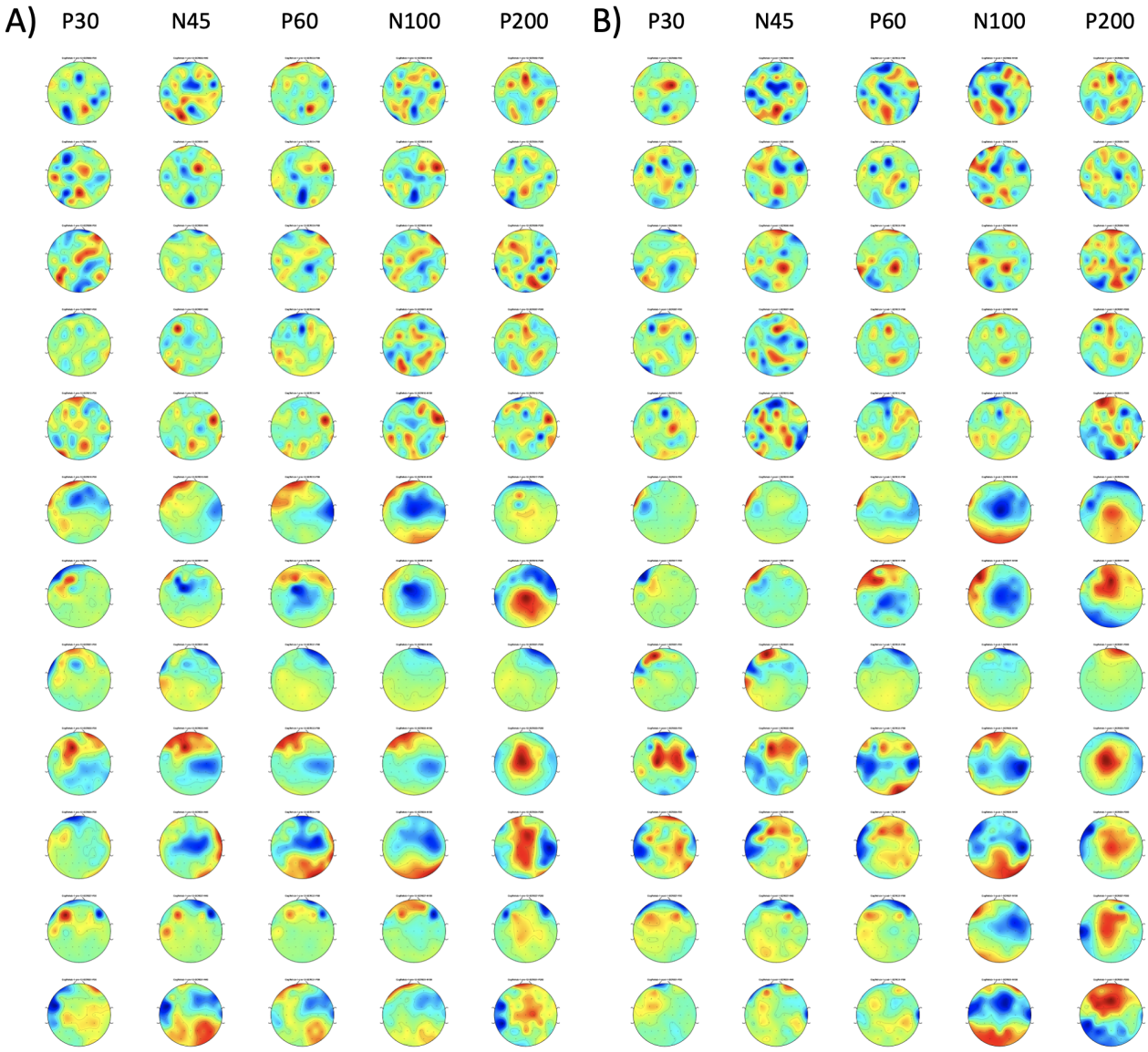

Figure S5. Active iTBS condition - Subject topographical plots of voltage (μV) scalp distribution for TEP components of interest*. A) PRE-iTBS, B) POST-iTBS. iTBS = intermittent theta burst stimulation; TEP = transcranial magnetic stimulation evoked potential.*

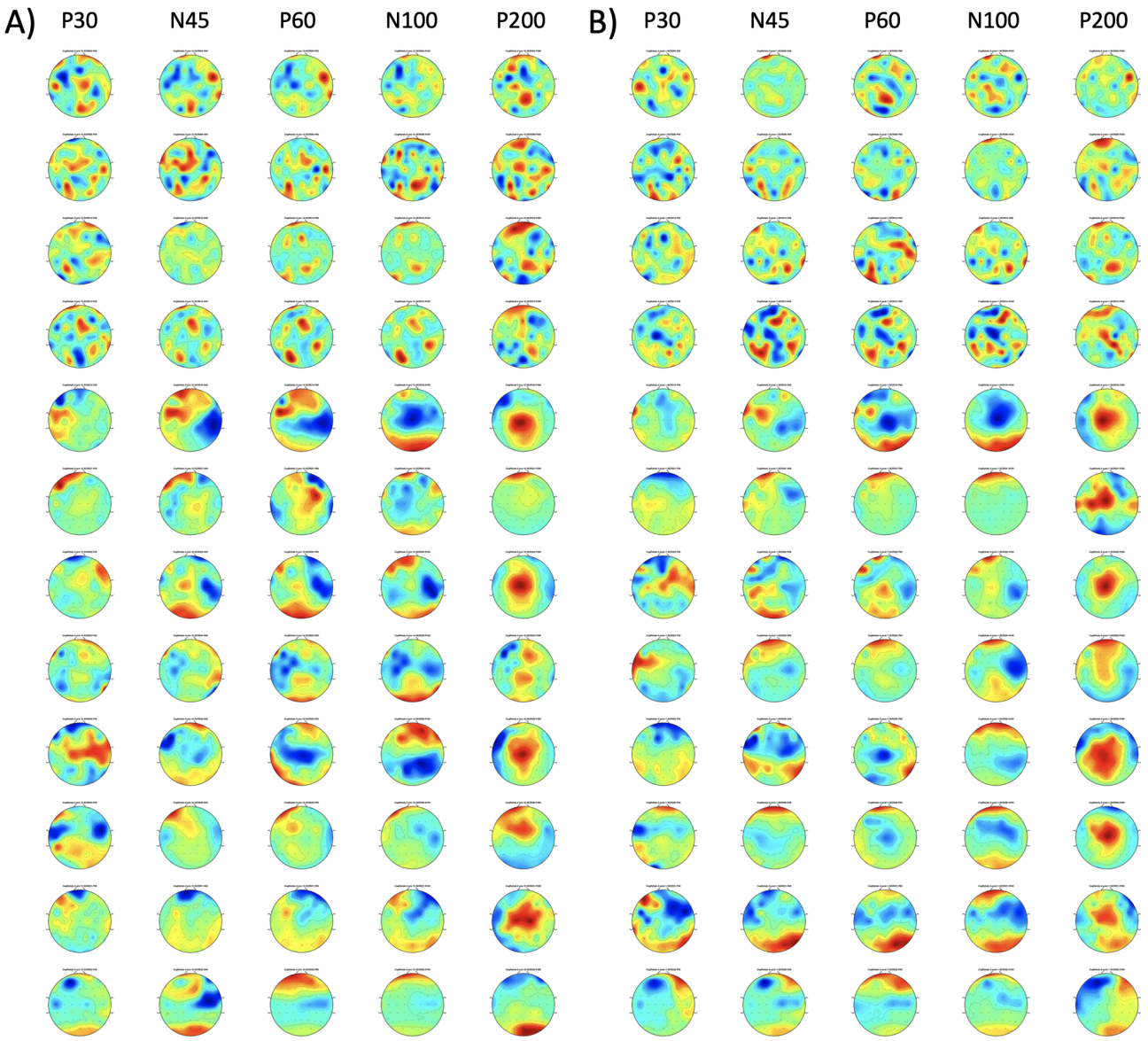

Figure S6. Sham iTBS condition - Subject topographical plots of voltage (μV) scalp distribution for TEP components of interest. *A) PRE-SHAM, B) POST-SHAM. TEP = transcranial magnetic stimulation evoked potential.*

Table S1. Type III Analysis of Variance Table with Satterthwaite's method – ANOVA Mixed Model for TEP components.

P30		Sum Sq	Mean Sq	NumDF	DenDF	F value	Pr(>F)
	age	12.75573	1.275573	10	2.977702	0.880	0.619
	sex	1.656627	1.656627	1	3.360706	1.143	0.355
	cap	0.082511	0.082511	1	2.403298	0.056	0.830
	condition	2.902143	2.902143	1	29.24372	2.002	0.167
	time	0.457396	0.457396	1	28.53087	0.315	0.578
	condition:time ‘**’	7.590361	7.590361	1	28.53087	5.238	0.029
N45		**Sum Sq**	**Mean Sq**	**NumDF**	**DenDF**	**F value**	**Pr(>F)**
	age	85.45694	8.545694	10	4.504407	2.133	0.223
	sex	11.47987	11.47987	1	7.579785	2.865	0.131
	cap	2.026996	2.026996	1	2.770419	0.505	0.532
	condition	1.667249	1.667249	1	30.66716	0.416	0.523
	time	1.332442	1.332442	1	29.40463	0.332	0.568
	condition:time	4.654544	4.654544	1	29.40463	1.161	0.289
P60		**Sum Sq**	**Mean Sq**	**NumDF**	**DenDF**	**F value**	**Pr(>F)**
	age	46.96936	4.696936	10	32	1.001	0.462
	sex	1.161453	1.161453	1	32	0.247	0.622
	cap	1.07035	1.07035	1	32	0.228	0.636
	condition	4.710432	4.710432	1	32	1.004	0.323
	time	2.735346	2.735346	1	32	0.583	0.450
	condition:time	0.015166	0.015166	1	32	0.003	0.955

N100		**Sum Sq**	**Mean Sq**	**NumDF**	**DenDF**	**F value**	**Pr(>F)**
	age	30.69346	3.069346	10	3.88255	0.883	0.605
	sex	2.227207	2.227207	1	4.510655	0.640	0.463
	cap	0.920411	0.920411	1	2.960497	0.264	0.642
	condition	3.926035	3.926035	1	29.95132	1.129	0.296
	time	0.658617	0.658617	1	29.23315	0.189	0.666
	condition:time	0.399207	0.399207	1	29.23315	0.114	0.737
P200		**Sum Sq**	**Mean Sq**	**NumDF**	**DenDF**	**F value**	**Pr(>F)**
	age	82.63825	8.263825	10	32	2.438	0.027
	sex	0.403061	0.403061	1	32	0.118	0.732
	cap	0.091287	0.091287	1	32	0.026	0.870
	condition	1.399711	1.399711	1	32	0.413	0.525
	time	0.930354	0.930354	1	32	0.274	0.603
	condition:time	2.163692	2.163692	1	32	0.638	0.430

*Note: TEP = transcranial magnetic stimulation evoked potential. **p < 0.05; *p < 0.15.*

Table S2. Tukey multiple comparisons of means (95% family-wise confidence level), evaluating time (pre-, post-).

Active iTBS condition									
TEP	**Df**	**Sum Sq**	**Mean Sq**	**F-value**	**Pr (>F)**	**diff**	**lwr**	**upr**	**p adj**
P30	1	5.89	5.887	2.054	0.166	0.991	-0.443	2.424	0.166
Sham condition									
TEP	**Df**	**Sum Sq**	**Mean Sq**	**F-value**	**Pr (>F)**	**diff**	**lwr**	**upr**	**p adj**
P30	1	2.16	2.161	1.154	0.294	-0.600	-1.759	0.558	0.294

*Note: TEP = transcranial magnetic stimulation evoked potential. **p < 0.05; *p < 0.15.*

Table S3. Total identified outliers and missing/incomplete data

Overall memory outlier(s) removed			Missing/incomplete memory data		
CR007			CR025 (working & visual episodic memory)		
Left DLPFC thickness outlier(s) removed					
-					
TEP amplitude outlier(s)					
Active iTBS			**Sham**		
PRE	P30	CR032	PRE	P30	CR027
	N45	-		N45	CR027
	P60	-		P60	CR027
	N100	-		N100	CR007
	P200	CR025		P200	-
POST	P30	-	POST	P30	-
	N45	CR018 CR030		N45	CR017 CR027
	P60	-		P60	-
	N100	CR018		N100	-
	P200	-		P200	CR027
TEP waveform outliers(s) per participant					
Active iTBS			**Sham**		
CR014			CR002, CR018		
Total TEP participant data removed (per condition)					
Active iTBS			**Sham**		
CR014, CR018, CR025, CR030, CR032			CR002, CR007, CR017, CR018, CR027		

Note: TEP data for 12 participants were included for each condition after outlier removal. One participant (CR007) and two memory domains (CR025) were not included in the final sample. TEP = transcranial magnetic stimulation evoked potential, iTBS = intermittent theta burst stimulation, DLPFC = dorsolateral prefrontal cortex.

Table S4: Active iTBS condition - Participant information for TEP component P30 (aims 1 & 2).

SUBJECT	PRE	POST	DIFF	OVERALL MEMORY	WORKING MEMORY	VISUAL EPISODIC	VERBAL EPISODIC	AGE	SEX	SFGDOR.L CT	MFG.L CT	DLPFC CT
CR002	1.253789	1.904412	0.650623	0.189082	0.597723	-0.05442	0.267443	38	male	2.9391	2.806	2.87255
CR004	-0.23563	5.325594	5.561224	-0.0549	0.335278	-0.26165	-0.03156	32	male	2.9486	2.9018	2.9252
CR006	0.073607	-0.51256	-0.58617	-0.1385	0.737252	-0.5208	-0.24968	34	male	2.9454	2.9131	2.92925
CR007	3.583967	1.690792	-1.89318	-	-	-	-	35	male	2.8147	2.8191	2.8169
CR012	0.580858	0.909595	0.328737	-0.11192	0.737252	-0.50808	-0.16879	43	male	2.9855	2.9282	2.95685
CR016	-2.26522	-0.79642	1.4688	0.10726	-0.2173	0.418385	-0.19043	21	male	2.9059	2.8892	2.89755
CR017	0.75811	3.749563	2.991453	-0.30299	-0.66055	0.140145	-0.83172	25	female	2.9514	2.9521	2.95175
CR021	-0.77256	0.071113	0.843676	0.610099	0.603261	0.417317	1.002503	34	male	2.8932	2.8185	2.85585
CR023	1.945321	0.915827	-1.02949	0.842966	0.597723	0.881438	1.011264	25	male	2.9635	2.8752	2.91935
CR024	-1.15417	0.5824	1.736573	0.153466	-0.48805	0.163058	0.775802	25	male	2.9319	2.9625	2.9472
CR027	2.532606	2.007147	-0.52546	0.356204	0.527958	0.163058	0.570741	37	male	2.7399	2.8172	2.77855
CR031	-0.0695	2.270333	2.339832	0.677076	0.737252	0.588951	0.793149	25	male	2.9754	2.9	2.9377

Note: TEP = transcranial magnetic stimulation evoked potential, DIFF = POST - PRE (amplitude, μV), SFGdor.L CT = left dorsolateral superior frontal gyrus cortical thickness (mm), MFG.L CT = left middle frontal gyrus cortical thickness (mm), DLPFC CT = dorsolateral prefrontal cortical thickness.

Table S5: Sham iTBS condition - Participant information for TEP component P30 (aims 1 & 2).

SUBJECT	PRE	POST	DIFF	OVERALL MEMORY	WORKING MEMORY	VISUAL EPISODIC	VERBAL EPISODIC	AGE	SEX	SFGDOR.L CT	MFG.L CT	DLPFC CT
CR004	0.887744	2.355202	1.467459	-0.0549	0.335278	-0.26165	-0.03156	32	male	2.9486	2.9018	2.9252
CR006	1.156615	-1.77675	-2.93336	-0.1385	0.737252	-0.5208	-0.24968	34	male	2.9454	2.9131	2.92925
CR012	0.777979	1.526436	0.748457	-0.11192	0.737252	-0.50808	-0.16879	43	male	2.9855	2.9282	2.95685
CR014	-0.8956	-2.19646	-1.30086	-0.61137	-1.97481	-0.08234	-0.30601	32	male	2.8648	2.8422	2.8535
CR016	-0.99539	-1.28569	-0.29031	0.10726	-0.2173	0.418385	-0.19043	21	male	2.9059	2.8892	2.89755
CR021	-0.28278	-1.82874	-1.54596	0.610099	0.603261	0.417317	1.002503	34	male	2.8932	2.8185	2.85585
CR023	-0.13037	-0.71965	-0.58928	0.842966	0.597723	0.881438	1.011264	25	male	2.9635	2.8752	2.91935
CR024	-1.23116	0.699741	1.930897	0.153466	-0.48805	0.163058	0.775802	25	male	2.9319	2.9625	2.9472
CR025	0.023036	-3.00678	-3.02982	0.208144	-	-	0.208144	26	female	2.9107	2.8056	2.85815
CR030	-1.2094	-0.89341	0.315989	-0.03527	-0.2173	-0.04221	0.160619	20	female	2.8359	2.7206	2.77825
CR031	-0.27975	-0.29324	-0.0135	0.677076	0.737252	0.588951	0.793149	25	male	2.9754	2.9	2.9377
CR032	-1.28697	-3.24768	-1.96071	-0.56884	-1.10308	-0.72201	0.271737	23	female	3.0214	2.9747	2.99805

Note: TEP = transcranial magnetic stimulation evoked potential, DIFF = POST - PRE (amplitude, μV), SFGdor.L CT = left dorsolateral superior frontal gyrus cortical thickness (mm), MFG.L CT = left middle frontal gyrus cortical thickness (mm), DLPFC CT = dorsolateral prefrontal cortical thickness.

Table S6: Participant information for aim 0 analyses (Linear Mixed Model ANOVA).

SUBJECT	CONDITION	VALUE	TIME	COMPONENT	AGE	SEX	CAP
CR002	Active	1.253789	1	P30	38	male	old
CR002	Active	1.904412	2	P30	38	male	old
CR004	Active	-0.23563	1	P30	32	male	old
CR004	Sham	2.355202	2	P30	32	male	old
CR004	Sham	0.887744	1	P30	32	male	old
CR004	Active	5.325594	2	P30	32	male	old
CR006	Active	0.073607	1	P30	34	male	old
CR006	Sham	-1.77675	2	P30	34	male	old
CR006	Sham	1.156615	1	P30	34	male	old
CR006	Active	-0.51256	2	P30	34	male	old
CR007	Active	3.583967	1	P30	35	male	old
CR007	Active	1.690792	2	P30	35	male	old
CR012	Active	0.580858	1	P30	43	male	old
CR012	Sham	0.777979	1	P30	43	male	old
CR012	Active	0.909595	2	P30	43	male	old
CR012	Sham	1.526436	2	P30	43	male	old
CR014	Sham	-0.8956	1	P30	32	male	old
CR014	Sham	-2.19646	2	P30	32	male	old
CR016	Active	-2.26522	1	P30	21	male	new
CR016	Sham	-1.28569	2	P30	21	male	new
CR016	Active	-0.79642	2	P30	21	male	new
CR016	Sham	-0.99539	1	P30	21	male	new
CR017	Active	0.75811	1	P30	25	female	new
CR017	Active	3.749563	2	P30	25	female	new
CR021	Active	-0.77256	1	P30	34	male	new
CR021	Sham	-0.28278	1	P30	34	male	new
CR021	Active	0.071113	2	P30	34	male	new
CR021	Sham	-1.82874	2	P30	34	male	new
CR023	Active	1.945321	1	P30	25	male	new
CR023	Active	0.915827	2	P30	25	male	new
CR023	Sham	-0.13037	1	P30	25	male	new
CR023	Sham	-0.71965	2	P30	25	male	new
CR024	Sham	-1.23116	1	P30	25	male	new
CR024	Active	-1.15417	1	P30	25	male	new
CR024	Sham	0.699741	2	P30	25	male	new
CR024	Active	0.5824	2	P30	25	male	new
CR025	Sham	0.023036	1	P30	26	female	new
CR025	Sham	-3.00678	2	P30	26	female	new
CR027	Active	2.532606	1	P30	37	male	new
CR027	Active	2.007147	2	P30	37	male	new
CR030	Sham	-0.89341	2	P30	20	female	new
CR030	Sham	-1.2094	1	P30	20	female	new
CR031	Active	2.270333	2	P30	25	male	new
CR031	Sham	-0.29324	2	P30	25	male	new

CR031	*Active*	*-0.0695*	*1*	*P30*	*25*	*male*	*new*
CR031	*Sham*	*-0.27975*	*1*	*P30*	*25*	*male*	*new*
CR032	*Sham*	*-1.28697*	*1*	*P30*	*23*	*female*	*new*
CR032	*Sham*	*-3.24768*	*2*	*P30*	*23*	*female*	*new*
CR002	*Active*	*-1.29555*	*1*	*N45*	*38*	*male*	*old*
CR002	*Active*	*-7.6658*	*2*	*N45*	*38*	*male*	*old*
CR004	*Active*	*-6.98687*	*1*	*N45*	*32*	*male*	*old*
CR004	*Sham*	*-5.86795*	*2*	*N45*	*32*	*male*	*old*
CR004	*Sham*	*-1.97257*	*1*	*N45*	*32*	*male*	*old*
CR004	*Active*	*1.928433*	*2*	*N45*	*32*	*male*	*old*
CR006	*Active*	*1.865252*	*1*	*N45*	*34*	*male*	*old*
CR006	*Sham*	*-0.3576*	*2*	*N45*	*34*	*male*	*old*
CR006	*Sham*	*1.375072*	*1*	*N45*	*34*	*male*	*old*
CR006	*Active*	*0.790635*	*2*	*N45*	*34*	*male*	*old*
CR007	*Active*	*-1.10959*	*1*	*N45*	*35*	*male*	*old*
CR007	*Active*	*-2.10401*	*2*	*N45*	*35*	*male*	*old*
CR012	*Active*	*-0.53247*	*1*	*N45*	*43*	*male*	*old*
CR012	*Sham*	*0.684849*	*1*	*N45*	*43*	*male*	*old*
CR012	*Active*	*-1.55419*	*2*	*N45*	*43*	*male*	*old*
CR012	*Sham*	*-0.11972*	*2*	*N45*	*43*	*male*	*old*
CR014	*Sham*	*-1.42616*	*1*	*N45*	*32*	*male*	*old*
CR014	*Sham*	*-3.50075*	*2*	*N45*	*32*	*male*	*old*
CR016	*Active*	*1.94123*	*1*	*N45*	*21*	*male*	*new*
CR016	*Sham*	*0.203942*	*2*	*N45*	*21*	*male*	*new*
CR016	*Active*	*1.456318*	*2*	*N45*	*21*	*male*	*new*
CR016	*Sham*	*1.988343*	*1*	*N45*	*21*	*male*	*new*
CR017	*Active*	*-3.27511*	*1*	*N45*	*25*	*female*	*new*
CR017	*Active*	*-2.2374*	*2*	*N45*	*25*	*female*	*new*
CR021	*Active*	*-2.2857*	*1*	*N45*	*34*	*male*	*new*
CR021	*Sham*	*0.936716*	*1*	*N45*	*34*	*male*	*new*
CR021	*Active*	*-0.50256*	*2*	*N45*	*34*	*male*	*new*
CR021	*Sham*	*1.105691*	*2*	*N45*	*34*	*male*	*new*
CR023	*Active*	*2.716659*	*1*	*N45*	*25*	*male*	*new*
CR023	*Active*	*1.182664*	*2*	*N45*	*25*	*male*	*new*
CR023	*Sham*	*0.065885*	*1*	*N45*	*25*	*male*	*new*
CR023	*Sham*	*-0.6452*	*2*	*N45*	*25*	*male*	*new*
CR024	*Sham*	*-2.18877*	*1*	*N45*	*25*	*male*	*new*
CR024	*Active*	*-0.88678*	*1*	*N45*	*25*	*male*	*new*
CR024	*Sham*	*2.381282*	*2*	*N45*	*25*	*male*	*new*
CR024	*Active*	*1.343564*	*2*	*N45*	*25*	*male*	*new*
CR025	*Sham*	*-1.41872*	*1*	*N45*	*26*	*female*	*new*
CR025	*Sham*	*-1.64638*	*2*	*N45*	*26*	*female*	*new*
CR027	*Active*	*0.446302*	*1*	*N45*	*37*	*male*	*new*
CR027	*Active*	*0.280991*	*2*	*N45*	*37*	*male*	*new*
CR030	*Sham*	*0.781962*	*2*	*N45*	*20*	*female*	*new*
CR030	*Sham*	*4.083647*	*1*	*N45*	*20*	*female*	*new*

CR031	*Active*	*0.395929*	*2*	*N45*	*25*	*male*	*new*
CR031	*Sham*	*-2.32627*	*2*	*N45*	*25*	*male*	*new*
CR031	*Active*	*-0.75773*	*1*	*N45*	*25*	*male*	*new*
CR031	*Sham*	*-3.47963*	*1*	*N45*	*25*	*male*	*new*
CR032	*Sham*	*0.702059*	*1*	*N45*	*23*	*female*	*new*
CR032	*Sham*	*-2.13053*	*2*	*N45*	*23*	*female*	*new*
CR002	*Active*	*-0.95814*	*1*	*P60*	*38*	*male*	*old*
CR002	*Active*	*-5.02345*	*2*	*P60*	*38*	*male*	*old*
CR004	*Active*	*-1.50994*	*1*	*P60*	*32*	*male*	*old*
CR004	*Sham*	*-3.14887*	*2*	*P60*	*32*	*male*	*old*
CR004	*Sham*	*-4.56693*	*1*	*P60*	*32*	*male*	*old*
CR004	*Active*	*1.584669*	*2*	*P60*	*32*	*male*	*old*
CR006	*Active*	*1.318683*	*1*	*P60*	*34*	*male*	*old*
CR006	*Sham*	*-1.00892*	*2*	*P60*	*34*	*male*	*old*
CR006	*Sham*	*-0.95441*	*1*	*P60*	*34*	*male*	*old*
CR006	*Active*	*0.114714*	*2*	*P60*	*34*	*male*	*old*
CR007	*Active*	*-0.70157*	*1*	*P60*	*35*	*male*	*old*
CR007	*Active*	*-4.23699*	*2*	*P60*	*35*	*male*	*old*
CR012	*Active*	*-1.78963*	*1*	*P60*	*43*	*male*	*old*
CR012	*Sham*	*-1.36923*	*1*	*P60*	*43*	*male*	*old*
CR012	*Active*	*-1.19639*	*2*	*P60*	*43*	*male*	*old*
CR012	*Sham*	*-0.33618*	*2*	*P60*	*43*	*male*	*old*
CR014	*Sham*	*-2.04727*	*1*	*P60*	*32*	*male*	*old*
CR014	*Sham*	*-5.63829*	*2*	*P60*	*32*	*male*	*old*
CR016	*Active*	*2.436603*	*1*	*P60*	*21*	*male*	*new*
CR016	*Sham*	*-0.97587*	*2*	*P60*	*21*	*male*	*new*
CR016	*Active*	*1.482173*	*2*	*P60*	*21*	*male*	*new*
CR016	*Sham*	*2.534988*	*1*	*P60*	*21*	*male*	*new*
CR017	*Active*	*-0.12082*	*1*	*P60*	*25*	*female*	*new*
CR017	*Active*	*2.960531*	*2*	*P60*	*25*	*female*	*new*
CR021	*Active*	*-2.42191*	*1*	*P60*	*34*	*male*	*new*
CR021	*Sham*	*2.797603*	*1*	*P60*	*34*	*male*	*new*
CR021	*Active*	*-1.80209*	*2*	*P60*	*34*	*male*	*new*
CR021	*Sham*	*3.822693*	*2*	*P60*	*34*	*male*	*new*
CR023	*Active*	*2.26329*	*1*	*P60*	*25*	*male*	*new*
CR023	*Active*	*0.54088*	*2*	*P60*	*25*	*male*	*new*
CR023	*Sham*	*-0.01834*	*1*	*P60*	*25*	*male*	*new*
CR023	*Sham*	*-0.56778*	*2*	*P60*	*25*	*male*	*new*
CR024	*Sham*	*-2.56179*	*1*	*P60*	*25*	*male*	*new*
CR024	*Active*	*-1.51261*	*1*	*P60*	*25*	*male*	*new*
CR024	*Sham*	*2.566887*	*2*	*P60*	*25*	*male*	*new*
CR024	*Active*	*1.944203*	*2*	*P60*	*25*	*male*	*new*
CR025	*Sham*	*-0.09503*	*1*	*P60*	*26*	*female*	*new*
CR025	*Sham*	*-0.35007*	*2*	*P60*	*26*	*female*	*new*
CR027	*Active*	*4.833801*	*1*	*P60*	*37*	*male*	*new*
CR027	*Active*	*1.082833*	*2*	*P60*	*37*	*male*	*new*

CR030	*Sham*	*-2.95374*	*2*	*P60*	*20*	*female*	*new*
CR030	*Sham*	*3.388501*	*1*	*P60*	*20*	*female*	*new*
CR031	*Active*	*0.656873*	*2*	*P60*	*25*	*male*	*new*
CR031	*Sham*	*-0.20614*	*2*	*P60*	*25*	*male*	*new*
CR031	*Active*	*1.572843*	*1*	*P60*	*25*	*male*	*new*
CR031	*Sham*	*-2.27922*	*1*	*P60*	*25*	*male*	*new*
CR032	*Sham*	*4.329783*	*1*	*P60*	*23*	*female*	*new*
CR032	*Sham*	*1.799089*	*2*	*P60*	*23*	*female*	*new*
CR002	*Active*	*0.683616*	*1*	*N100*	*38*	*male*	*old*
CR002	*Active*	*-3.94659*	*2*	*N100*	*38*	*male*	*old*
CR004	*Active*	*-3.51503*	*1*	*N100*	*32*	*male*	*old*
CR004	*Sham*	*-2.62033*	*2*	*N100*	*32*	*male*	*old*
CR004	*Sham*	*-3.29819*	*1*	*N100*	*32*	*male*	*old*
CR004	*Active*	*-3.29415*	*2*	*N100*	*32*	*male*	*old*
CR006	*Active*	*0.271445*	*1*	*N100*	*34*	*male*	*old*
CR006	*Sham*	*-0.75813*	*2*	*N100*	*34*	*male*	*old*
CR006	*Sham*	*-2.11073*	*1*	*N100*	*34*	*male*	*old*
CR006	*Active*	*-0.99009*	*2*	*N100*	*34*	*male*	*old*
CR007	*Active*	*-0.98068*	*1*	*N100*	*35*	*male*	*old*
CR007	*Active*	*-3.77421*	*2*	*N100*	*35*	*male*	*old*
CR012	*Active*	*-1.99458*	*1*	*N100*	*43*	*male*	*old*
CR012	*Sham*	*-1.30831*	*1*	*N100*	*43*	*male*	*old*
CR012	*Active*	*0.584526*	*2*	*N100*	*43*	*male*	*old*
CR012	*Sham*	*-1.59132*	*2*	*N100*	*43*	*male*	*old*
CR014	*Sham*	*-0.22913*	*1*	*N100*	*32*	*male*	*old*
CR014	*Sham*	*-3.91123*	*2*	*N100*	*32*	*male*	*old*
CR016	*Active*	*-4.99806*	*1*	*N100*	*21*	*male*	*new*
CR016	*Sham*	*-4.17737*	*2*	*N100*	*21*	*male*	*new*
CR016	*Active*	*-4.67496*	*2*	*N100*	*21*	*male*	*new*
CR016	*Sham*	*-2.78443*	*1*	*N100*	*21*	*male*	*new*
CR017	*Active*	*-3.86295*	*1*	*N100*	*25*	*female*	*new*
CR017	*Active*	*-2.04593*	*2*	*N100*	*25*	*female*	*new*
CR021	*Active*	*-5.12078*	*1*	*N100*	*34*	*male*	*new*
CR021	*Sham*	*-2.42095*	*1*	*N100*	*34*	*male*	*new*
CR021	*Active*	*-3.6137*	*2*	*N100*	*34*	*male*	*new*
CR021	*Sham*	*2.477339*	*2*	*N100*	*34*	*male*	*new*
CR023	*Active*	*2.966194*	*1*	*N100*	*25*	*male*	*new*
CR023	*Active*	*0.973177*	*2*	*N100*	*25*	*male*	*new*
CR023	*Sham*	*0.568354*	*1*	*N100*	*25*	*male*	*new*
CR023	*Sham*	*0.612403*	*2*	*N100*	*25*	*male*	*new*
CR024	*Sham*	*-4.85593*	*1*	*N100*	*25*	*male*	*new*
CR024	*Active*	*-4.60832*	*1*	*N100*	*25*	*male*	*new*
CR024	*Sham*	*-0.17598*	*2*	*N100*	*25*	*male*	*new*
CR024	*Active*	*-1.75461*	*2*	*N100*	*25*	*male*	*new*
CR025	*Sham*	*2.429674*	*1*	*N100*	*26*	*female*	*new*
CR025	*Sham*	*1.056767*	*2*	*N100*	*26*	*female*	*new*

CR027	*Active*	*2.981829*	*1*	*N100*	*37*	*male*	*new*
CR027	*Active*	*-0.69241*	*2*	*N100*	*37*	*male*	*new*
CR030	*Sham*	*-3.02858*	*2*	*N100*	*20*	*female*	*new*
CR030	*Sham*	*-0.74449*	*1*	*N100*	*20*	*female*	*new*
CR031	*Active*	*-1.6819*	*2*	*N100*	*25*	*male*	*new*
CR031	*Sham*	*0.307332*	*2*	*N100*	*25*	*male*	*new*
CR031	*Active*	*-1.73351*	*1*	*N100*	*25*	*male*	*new*
CR031	*Sham*	*-0.30585*	*1*	*N100*	*25*	*male*	*new*
CR032	*Sham*	*0.601333*	*1*	*N100*	*23*	*female*	*new*
CR032	*Sham*	*-3.27213*	*2*	*N100*	*23*	*female*	*new*
CR002	*Active*	*2.823553*	*1*	*P200*	*38*	*male*	*old*
CR002	*Active*	*-0.18131*	*2*	*P200*	*38*	*male*	*old*
CR004	*Active*	*5.656053*	*1*	*P200*	*32*	*male*	*old*
CR004	*Sham*	*1.797053*	*2*	*P200*	*32*	*male*	*old*
CR004	*Sham*	*-0.48315*	*1*	*P200*	*32*	*male*	*old*
CR004	*Active*	*1.927113*	*2*	*P200*	*32*	*male*	*old*
CR006	*Active*	*2.759764*	*1*	*P200*	*34*	*male*	*old*
CR006	*Sham*	*1.835711*	*2*	*P200*	*34*	*male*	*old*
CR006	*Sham*	*1.811313*	*1*	*P200*	*34*	*male*	*old*
CR006	*Active*	*2.228269*	*2*	*P200*	*34*	*male*	*old*
CR007	*Active*	*1.108451*	*1*	*P200*	*35*	*male*	*old*
CR007	*Active*	*2.165651*	*2*	*P200*	*35*	*male*	*old*
CR012	*Active*	*1.627222*	*1*	*P200*	*43*	*male*	*old*
CR012	*Sham*	*2.559337*	*1*	*P200*	*43*	*male*	*old*
CR012	*Active*	*0.464166*	*2*	*P200*	*43*	*male*	*old*
CR012	*Sham*	*-0.569*	*2*	*P200*	*43*	*male*	*old*
CR014	*Sham*	*0.618635*	*1*	*P200*	*32*	*male*	*old*
CR014	*Sham*	*3.808079*	*2*	*P200*	*32*	*male*	*old*
CR016	*Active*	*-1.49742*	*1*	*P200*	*21*	*male*	*new*
CR016	*Sham*	*1.524045*	*2*	*P200*	*21*	*male*	*new*
CR016	*Active*	*-1.40189*	*2*	*P200*	*21*	*male*	*new*
CR016	*Sham*	*-0.05426*	*1*	*P200*	*21*	*male*	*new*
CR017	*Active*	*-0.2757*	*1*	*P200*	*25*	*female*	*new*
CR017	*Active*	*3.771853*	*2*	*P200*	*25*	*female*	*new*
CR021	*Active*	*-2.38127*	*1*	*P200*	*34*	*male*	*new*
CR021	*Sham*	*4.013134*	*1*	*P200*	*34*	*male*	*new*
CR021	*Active*	*6.26385*	*2*	*P200*	*34*	*male*	*new*
CR021	*Sham*	*1.593917*	*2*	*P200*	*34*	*male*	*new*
CR023	*Active*	*3.842701*	*1*	*P200*	*25*	*male*	*new*
CR023	*Active*	*3.363909*	*2*	*P200*	*25*	*male*	*new*
CR023	*Sham*	*1.943133*	*1*	*P200*	*25*	*male*	*new*
CR023	*Sham*	*0.877751*	*2*	*P200*	*25*	*male*	*new*
CR024	*Sham*	*-0.38174*	*1*	*P200*	*25*	*male*	*new*
CR024	*Active*	*1.07139*	*1*	*P200*	*25*	*male*	*new*
CR024	*Sham*	*3.082351*	*2*	*P200*	*25*	*male*	*new*
CR024	*Active*	*1.980967*	*2*	*P200*	*25*	*male*	*new*

CR025	*Sham*	*3.864416*	*1*	*P200*	*26*	*female*	*new*
CR025	*Sham*	*1.845712*	*2*	*P200*	*26*	*female*	*new*
CR027	*Active*	*2.3471*	*1*	*P200*	*37*	*male*	*new*
CR027	*Active*	*3.320988*	*2*	*P200*	*37*	*male*	*new*
CR030	*Sham*	*3.807655*	*2*	*P200*	*20*	*female*	*new*
CR030	*Sham*	*5.451527*	*1*	*P200*	*20*	*female*	*new*
CR031	*Active*	*3.098721*	*2*	*P200*	*25*	*male*	*new*
CR031	*Sham*	*2.154241*	*2*	*P200*	*25*	*male*	*new*
CR031	*Active*	*1.483633*	*1*	*P200*	*25*	*male*	*new*
CR031	*Sham*	*1.967296*	*1*	*P200*	*25*	*male*	*new*
CR032	*Sham*	*-1.40396*	*1*	*P200*	*23*	*female*	*new*
CR032	*Sham*	*-3.60606*	*2*	*P200*	*23*	*female*	*new*