Developing optimal methods for theta burst prefrontal brain stimulation

Sung Wook Chung

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Monash Alfred Psychiatry Research Centre

Central Clinical School

Faculty of Medicine, Nursing and Health Sciences

Monash University

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ABSTRACT

More than a decade has passed since theta burst stimulation (TBS) has been adapted in humans. TBS is a modified form of repetitive transcranial magnetic stimulation (rTMS) which has the ability to change cortical activity in humans. The rapid induction of modulatory effects of TBS has attracted its use both in research and clinical trials, and the vast majority of the studies have been conducted in the motor cortex. Despite its benefits, wide adoption of this technique in the treatment of various psychiatric disorders has been limited due to the lack of understanding of its effects when it is applied in brain regions such as the prefrontal cortex which are most relevant to the treatment of psychiatric disorders. Furthermore, little is known about the effect of different stimulation parameters in this cortical area. The broad aim of this thesis was to develop optimal methods of TBS application and to understand the mechanisms underlying TBS-induced changes in the prefrontal cortex.

Five studies have been completed. The first study demonstrated the efficacy of TBS in changing corticospinal excitability in humans. Meta-analysis was performed to investigate the effects of two most commonly used TBS paradigms, intermittent and continuous TBS (iTBS and cTBS), in modulating motor evoked potentials (MEPs). Factors such as the number of pulses, frequency of stimulation and genetics contributed to the magnitude of the change.

Study two explored whether plastic changes following prefrontal application of TBS could be probed using concurrent TMS and electroencephalography (TMS-EEG). Single- and paired-pulse paradigms were used to measure cortical reactivity and cortical inhibition, respectively, via TMS-evoked potentials (TEPs) and TMS-evoked oscillations. Short-term plastic changes such the change in amplitude of N100 and TMS-evoked theta power were observed, which validated the utility of TMS-EEG in tracking TBS-induced changes, particularly following iTBS.

In study three, four and five, effects of different stimulation parameters of iTBS were investigated in the prefrontal cortex. These included intensity (study three), repeated application (study four) and frequency of iTBS (study five). Cortical reactivity was measured via TMS-EEG and working memory performance was used as a behavioural marker of neurophysiological changes.

In study three, prominent changes were observed in TMS-evoked activity, particularly in N100, and the magnitude of the changes were dependent on the intensity of stimulation, whereby intermediate intensity (75% individual's resting motor threshold (rMT)) resulted in the maximum increase rather than iTBS at 50% or 100% rMT.

In study four, both single and repeated iTBS with 15-min interval demonstrated a significant change in N100 compared to sham stimulation. However, repeated iTBS did show any significant difference in TEPs or working memory performance compared to a single block of

iTBS, which could potentially be explained by the homeostatic mechanism in healthy individuals.

Study five demonstrated the importance of the frequency of stimulation in determining the effect of iTBS in the prefrontal cortex. Two most commonly used methods of iTBS, bursts of 30 Hz and 50 Hz at 5 – 6 Hz, were compared with individualised frequency of stimulation developed via theta-gamma coupling during a memory task. Largest change in TMS-evoked activity, P60 in particular, was found following individualised iTBS, whereas conventional methods resulted in a large inter-individual variability. The neurophysiological changes showed close association to the behavioural correlate and mood changes, which demonstrated its potential use in both research and clinical trials.

This thesis describes the detailed investigation of TBS in order to optimise its use in the prefrontal cortex of healthy subjects. The findings demonstrate that TBS is able to exert plastic changes in the prefrontal cortex measured via TMS-EEG, and parameters of stimulation such as intensity and frequency of stimulation are important factors determining the magnitude of the neurophysiological changes. Moreover, TBS-induced changes assessed using TMS-EEG provide insight into the mechanisms of TBS in the prefrontal cortex. These findings have significant implications for the development of a more robust TBS protocol and our knowledge of the impact of different stimulation parameters in the prefrontal cortex which may facilitate a widespread use of TBS in clinical settings.

LIST OF PUBLICATIONS

PEER-REVIEWED PAPERS PUBLISHED/ACCEPTED DURING CANDIDATURE

1. **Chung SW**, Hoy KE, Fitzgerald PB. 2015a. Theta-burst stimulation: a new form of TMS treatment for depression? *Depression & Anxiety.* 32(3):182-92.

2. **Chung SW**, Rogasch NC, Hoy KE, Fitzgerald PB. 2015b. Measuring Brain Stimulation Induced Changes in Cortical Properties Using TMS-EEG. *Brain Stimulation.* 8(6):1010-20.

3. **Chung SW**, Hill AT, Rogasch NC, Hoy KE, Fitzgerald PB. 2016. Use of theta-burst stimulation in changing excitability of motor cortex: A systematic review and meta-analysis. *Neuroscience & Biobehavioural Reviews.* 63(4):43-64.

4. **Chung SW**, Lewis BP, Rogasch NC, Saeki T, Thomson RH, Hoy KE, Bailey NW, Fitzgerald PB. 2017. Demonstration of short-term plasticity in the dorsolateral prefrontal cortex with theta burst stimulation: A TMS-EEG study. *Clinical Neurophysiology.* 128(7):1117-26.

5. **Chung SW**, Rogasch NC, Hoy KE, Sullivan CM, Cash RFH, Fitzgerald PB. 2017. Impact of different intensities of intermittent theta burst stimulation on the cortical properties during TMS-EEG and working memory performance.

6. **Chung SW**, Rogasch NC, Hoy KE, Fitzgerald PB. 2017. The effect of single and repeated prefrontal intermittent theta burst stimulation on cortical reactivity and working memory.

PAPERS SUBMITTED DURING CANDIDATURE FOR PEER-REVIEW

7. **Chung SW**, Sullivan MC, Rogasch NC, Hoy KE, Neil W Baily, Cash RFH, Fitzgerald PB. 2017. The effects of individualised intermittent theta burst stimulation in the prefrontal cortex: a TMS-EEG study.

CONFERENCE PRESENTATIONS AND POSTERS DURING CANDIDATURE

1. **Chung SW**, Hill AT, Rogasch NC, Hoy KE, Fitzgerald PB. Use of theta-burst stimulation in changing excitability of motor cortex: a systematic review and meta-analysis. Students of Brain Research Symposium, Melbourne, Australia. Poster presentation (November, 2015)

2. **Chung, SW**, Rogasch NC, Hoy KE, Fitzgerald PB. Intensity-dependent effect of intermittent theta burst stimulation in prefrontal cortex: A TMS-EEG Study. 2nd Australasian Brain Stimulation Meeting, Melbourne, Australia. Oral Presentation (July, 2016)

3. **Chung, SW**, Lewis BP, Rogasch NC, Saeki T, Thomson R, Bailey NW, Hoy KE, Fitzgerald PB. Demonstration of short-term plasticity in the dorsolateral prefrontal cortex with theta burst stimulation: A TMS-EEG study. 6th International Conference of Transcranial Brain Stimulation, Göttingen, Germany. Poster Presentation (September, 2016)

4. **Chung, SW**, Lewis BP, Rogasch NC, Saeki T, Thomson R, Bailey NW, Hoy KE, Fitzgerald PB. Demonstration of short-term plasticity in the dorsolateral prefrontal cortex with theta burst stimulation: A TMS-EEG study. Students of Brain Research Symposium, Melbourne, Australia. Poster presentation (November, 2016)

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6. **Chung, SW**, Sullivan CM, Rogasch NC, Hoy KE, Cash RFH, Fitzgerald PB. The effects of individualised intermittent theta burst stimulation in the prefrontal cortex: a TMS-EEG study. 7th Australasian Cognitive Neuroscience Society Conference, Adelaide, Australia. Oral presentation (December, 2017)

DECLARATION

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes six (6) original papers published/accepted in peer reviewed journals and one (1) unpublished publications. The core theme of the thesis is developing optimal methods for theta burst prefrontal brain stimulation. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the Central Clinical School under the supervision of Professor Paul Fitzgerald.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of Chapters 3, 4, 7, 8, 9, 10 and 11, my contribution to the work involved the following:

Project design (in consultation with my supervisors and co-authors); review of appropriate literature; securing ethics approval; recruitment of participants; data collection; conducting data analysis; writing of papers. Supervisors and co-authors provided input into completed manuscript drafts.

Thesis Chapter	Publication Title	Status *(published, in press, accepted or returned for revision)*	Nature and % of student contribution	Co-author name(s) Nature and % of Co-author's contribution*	Co-author(s), Monash student Y/N*
3	Theta-burst stimulation: A new form of TMS treatment for depression?	Published	90%. Literature review, writing of manuscript	1) A/Prof Kate E. Hoy. Review of manuscript, supervisory input (5%). 2) Prof Paul B. Fitzgerald. Review of manuscript, supervisory input (5%).	No No
4	Measuring brain stimulation induced changes in cortical properties using TMS-EEG	Published	90%. Literature review, writing of manuscript	1) Dr Nigel C. Rogasch. Review of manuscript, supervisory input (4%). 2) A/Prof Kate E. Hoy. Review of manuscript, supervisory input (3%). 3) Prof Paul B. Fitzgerald. Review of manuscript, supervisory input (3%).	No No No
7	Use of theta-burst stimulation in changing excitability of motor cortex: A systematic review and meta-analysis	Published	85%. Meta-analysis, writing of manuscript	1) Aron T. Hill. Screening of included studies, review of manuscript (5%). 2) Dr Nigel C. Rogasch. Review of manuscript, supervisory input (4%). 3) A/Prof Kate E. Hoy. Review of manuscript, supervisory input (3%). 4) Prof Paul B. Fitzgerald. Review of manuscript, supervisory input (3%).	Yes No No No
8	Demonstration of short-term plasticity in the dorsolateral prefrontal cortex with theta burst stimulation: A TMS-EEG study	Published	70%. Data analysis, writing of manuscript	1) Lewis P. Benjamin. Participant recruitment, data collection (10%). 2) Dr Nigel C. Rogasch. Project design, review of manuscript, supervisory input (5%). 3) Dr Takashi Saeki. Data collection (5%). 4) Richard H. Thomson. Technical advice (2%). 5) Neil W. Bailey. Technical Advice (2%). 6) A/Prof Kate E. Hoy. Review of manuscript, supervisory input (3%). 7) Prof Paul B. Fitzgerald, Review of manuscript, supervisory input (3%).	No No No No No No No

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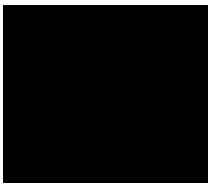
10	The effect of single and repeated prefrontal intermittent theta burst stimulation on cortical reactivity and working memory	Accepted	90%. Project design, participant recruitment, data collection, data analysis, writing of manuscript	1) Dr Nigel C. Rogasch. Review of manuscript, supervisory input (4%). 2) A/Prof Kate E. Hoy. Review of manuscript, supervisory input (3%). 3) Prof Paul B. Fitzgerald, Review of manuscript, supervisory input (3%).	No No No
11	The effects of individualised intermittent theta burst stimulation in the prefrontal cortex: a TMS-EEG study	Submitted	85%. Project design, method development, participant recruitment, data collection, data analysis, writing of manuscript	1) Caley M. Sullivan. Method development, technical advice, review of manuscript (5%). 2) Dr Nigel C. Rogasch. Review of manuscript, supervisory input (3%). 3) A/Prof Kate E. Hoy. Review of manuscript, supervisory input (2%). 4) Neil W. Bailey. Review of manuscript (1%). 5) Dr Robin F. H. Cash. Review of manuscript (1%). 6) Prof Paul B. Fitzgerald, Review of manuscript, supervisory input (3%).	No No No No No No

**If no co-authors, leave fields blank*

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student signature:  **Date: 8th November 2017**

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

Main Supervisor signature:  **Date: 8th November 2017**

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CHAPTER ONE

General introduction and overview

Introduction

The human brain has the capacity to change both structurally and functionally in response to environmental demands. This adaptation, often termed neuroplasticity, involves activity-dependent changes in strength or efficacy of pre-existing synaptic connections, and plays an important role in early development of neural circuits and encoding of new information (Citri and Malenka, 2008). Impairments in the mechanisms involved in neuroplastic processes can result in a wide variety of neuropsychiatric disorders (Pittenger, 2013). For these reasons, a large body of research has focused on elucidating the mechanisms underlying physiologically relevant synaptic plasticity both in animal and humans (Hara, 2015; Johansson, 2011; Kolb and Whishaw, 1998; Ohl and Scheich, 2005; Voss et al., 2013). In humans, brain plasticity can be explored relatively safely using non-invasive brain stimulation (NIBS) techniques (Bashir et al., 2014).

Over the last two decades, much progress has been made in the understanding of human brain function and dysfunction using NIBS. NIBS can be used as an investigative tool to explore behavioural correlates of neurophysiological changes following stimulation. For example, NIBS is used to understand the mechanisms underlying cognitive functions by inducing changes in the activity of a specific region of the brain which may result in altered behavioural task performance such as in working memory (Miniussi and Ruzzoli, 2013). In

addition, it can also act as a therapeutic tool in a number of neurological and psychiatric disorders characterised by brain network dysfunction (Rossini and Rossi, 2007).

The most commonly used forms of NIBS are transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). By stimulating the brain through the intact scalp, these techniques can generate temporary changes in the neural activity in the targeted region and in the distant interconnected network throughout the brain (Liew et al., 2014). In particular, TMS uses an electromagnetic induction to produce weak electric currents via rapid changes in magnetic field and triggers depolarisation of the neurons under the coil. When TMS is applied repetitively (repetitive TMS: rTMS), the excitability of stimulated cortical region can be altered, outlasting the duration of the stimulation (Maeda et al., 2000). This characteristic is particularly beneficial from a clinical perspective. Hence, rTMS is being extensively investigated for the treatment of psychiatric disorders and has been approved in the treatment of depression (George et al., 2013; Padberg and George, 2009), where prefrontal cortex is the main target for treatment. Recently, a modified form of rTMS known as theta-burst stimulation (TBS) has been investigated as a potential therapeutic tool (Duprat et al., 2016; Li et al., 2014) owing to its rapid induction of plastic changes compared to conventional rTMS (Huang et al., 2005). However, the vast majority of studies exploring the effects of TBS have been conducted in the motor cortex, and its effect is largely unexplored in the prefrontal cortex where the physiological effects of stimulation may not be the same. The investigation into physiological effects of brain stimulation in non-motor regions has recently become viable by combining TMS with electroencephalography (TMS-EEG) (Ilmoniemi and Kicic, 2010). With the help of this technique, it is possible to systematically explore the effect of TBS in the prefrontal cortex.

Establishing the optimal TBS parameters for prefrontal stimulation would facilitate the transition of TBS into clinical settings.

Thesis overview

This thesis consists of 12 chapters including seven manuscripts (four published, three in submission). In chapter 1, a brief introduction and overview of the thesis are provided.

Chapter 2 presents an overview of the background on TMS, TBS and TMS-EEG.

Chapter 3 is a published review on the use of TBS as a potential treatment for depression. In this review, the effectiveness of current treatment strategies for depression is discussed and the use of TMS in clinical settings is introduced. The effects of TBS both in motor and non-motor region, and the mechanisms involved in this technique are presented. Finally, the insights gained from recent studies of TBS in depression for the viability and safety of the method in clinical settings are discussed.

Chapter 4 contains a second published review on the use of TMS-EEG as a tool to measure neuromodulatory changes induced by different brain stimulation techniques. In this review, the four most commonly used neuromodulatory techniques are introduced. How cortical properties can be assessed using TMS-EEG and how these measures complement the

information gained from MEPs are then outlined. Finally, the existing studies that have used this technique to assess changes in cortical properties resulting from neuromodulatory paradigms both in motor and non-motor regions are reviewed.

Chapter 5 contains a brief introduction to working memory and its use as a behavioural marker.

Chapter 6 contains the summary of literature review, research objectives and aims of the study.

Chapter 7 contains a published systematic review and meta-analysis on the use of TBS in changing corticospinal excitability in humans. In this paper, the efficacy of two most commonly used TBS paradigms (iTBS and cTBS) in altering corticospinal excitability, short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) in the motor cortex are evaluated. The presence of publication bias is also examined. Finally, factors affecting the after-effects of TBS, such as stimulation parameters and genetics are discussed.

Chapter 8 contains the first published empirical paper which demonstrates TBS-induced plasticity in the left dorsolateral prefrontal cortex using TMS-EEG technique. In this paper, the effects of iTBS and cTBS are examined in the DLPFC using single- and paired-pulse paradigms. The change in cortical plastic is measured via TMS-evoked potentials, particularly in N100, and TMS-evoked oscillations. The utility of TMS-EEG in tracking TBS-

induced changes in DLPFC is discussed, together with a potential link between TMS-evoked N100 and cortical inhibition.

In Chapter 9, a second published paper presents the impact of different intensities of iTBS on cortical properties using TMS-EEG. In this paper, the importance of the intensity of prefrontal iTBS is demonstrated using three different intensities, 50%, 75% and 100% of individuals' resting motor threshold. The effect of iTBS on the working memory performance is also examined, and whether the intensity of iTBS has any effect on the behavioural outcome. Finally, potential clinical implications are discussed.

In Chapter 10, a third accepted manuscript, describes the effect of single and repeated application of left prefrontal iTBS. The change in cortical reactivity measured via TMS-EEG is compared to investigate whether a greater effect is achieved by a repeated stimulation. iTBS-induced change in the working memory task is also examined for the presence of any linear accumulative behavioural effect. Finally, the link between neurophysiological and behavioural changes are discussed.

Chapter 11 contains the final empirical paper, currently in submission, which compares individualised frequency of stimulation to two most commonly used iTBS methods (30 Hz and 50 Hz). In this study, the individualised frequency of stimulation is determined by theta-gamma coupling during a memory task. Neurophysiological changes are obtained via TMS-EEG and mood rating is compared between conditions. The working memory performance is

employed as a potential behavioural marker of neurophysiological changes following iTBS. The benefit of a more tailored stimulation is discussed.

Chapter 12 contains the summary of the experimental chapters and the implications of the results. In addition, limitations and future directions are included in this section. The thesis closes with a brief conclusion.

CHAPTER TWO

Overview of brain stimulation

Non-invasive brain stimulation (NIBS)

The past decade has seen remarkable progress in our understanding of human brain using NIBS techniques, particularly in elucidating the neural mechanisms underlying cortical reorganisation and establishing the link between synaptic plasticity and behaviour. Providing an effective means of modulating brain activity at local and distributed networks, NIBS allows the control of neural activity in a semi-controlled manner (Wagner et al., 2007). There is evidence suggesting that NIBS is capable of altering brain activity in a beneficial way both in healthy and neuropsychiatric populations, enhancing cognitive function and acting as a therapeutic agent for patients (Clark and Parasuraman, 2014; Fitzgerald et al., 2002a; Miniussi et al., 2008; Vicario and Nitsche, 2013). However, more recent studies have revealed large neurophysiological and behavioural variability in response to NIBS (Hamada et al., 2013; Hinder et al., 2014; Hordacre et al., 2017; Lopez-Alonso et al., 2014; Strube et al., 2015; Vallence et al., 2015), contradicting early robust findings. In addition, the mechanism of its effects on brain activity remains incompletely understood. The rapid increase in the interest and the demand of these techniques have surpassed our knowledge about NIBS, leaving a large gap in our understanding of basic mechanisms of action, and thus delaying the progress in more effective stimulation methods.

Transcranial magnetic stimulation

The first report of stimulating the human cerebral cortex through intact scalp was in 1980 (Merton and Morton, 1980) using transcranial electrical stimulation. However, the wide use of this technique was limited due to the pain elicited by the stimulation. In 1985, Barker and colleagues introduced an alternative method known as transcranial magnetic stimulation (TMS) (Barker et al., 1985). TMS relies on the principle of electromagnetic induction that was proposed by Michael Faraday in 1832 (Faraday, 1832). Using an insulated coil of wire placed over the scalp, a brief electric current (110 μs) is passed through the coil which induces a time-varying magnetic field of approximately 1 – 4 tesla in strength with a duration of approximately 1 ms (Wagner et al., 2007). Due to the low impedance property of the skull to magnetic fields, these pass through the skull and induce eddy currents in the brain. The capacity of this current to have an impact on the underlying nerve cells depends on the amplitude, direction and the duration of the current. It should be noted that the effect of TMS is achieved by the induced electric field, and not the direct effect of the applied magnetic field which acts only as a vehicle. By acting on the transmembrane potential, charges move across the neuronal membrane and when sufficient, these currents can depolarize cortical neurons and generate action potentials (Siebner and Rothwell, 2003).

The focal point of activation is in the area of the brain where the induced electrical field is at its maximum (Thielscher and Kammer, 2004) which depends on the shape and design of the coil. Modelling including the conductive properties of tissue in the head has provided mapping of the induced electric field distributions generated by different types of coils that are commercially available (Deng et al., 2013; Epstein and Davey, 2002; Salinas et al., 2007),

and has shown that the ability to stimulate deeper brain regions can be obtained at the expense of wider electric field distribution (Deng et al., 2013). In general, figure-of-eight coils provide higher focality than circular coils which may activate neurons within 5 cm^2 (Deng et al., 2013). Due to higher impedance of grey matter compared to white matter and the exponential decay of the magnetic field over distance, electrical currents are weaker in subcortical structures of the brain, and therefore they are not activated by TMS (Klomjai et al., 2015).

TMS can activate different types of neural elements which can generate a mixture of both excitatory and inhibitory effects both locally and in distant but interconnected regions of the cortex (Siebner and Rothwell, 2003). TMS was originally developed as a diagnostic tool to study brain function, particularly in motor pathways (Keck et al., 1998). TMS preferentially activates horizontally aligned neurons that are parallel to the coil and the brain surface, which are believed to be cortical interneurons perpendicular to the central sulcus (Di Lazzaro et al., 1998). When applied to the motor cortex, TMS evokes descending volleys in the pyramidal tract which were observed via epidural recording from the spinal cord (Nakamura et al., 1996). The early volley is called a direct wave (D-wave) and subsequent volleys are called indirect waves (I-wave). The D-wave results from direct stimulation of pyramidal tract axons, while I-waves are caused by trans-synaptic activation of the same pyramidal tract neurons (Kernell and Chien-Ping, 1967). Depending on the orientation of the coil, the direction of the current and the intensity of the stimulation, TMS recruits different descending corticospinal waves, suggesting different populations of cortical neurons are activated (Di Lazzaro et al., 2001). The activation of motor neurons in response to corticospinal waves elicited by TMS can result in motor evoked potentials (MEPs) obtained from a relaxed hand muscle of the contralateral site (Rossini et al., 2015), and measuring the

amplitude and the latency of the evoked responses can be used to assess the excitability and transduction time of the corticospinal system. Such measures can act an index of corticospinal pathway dysfunction in patients with multiple sclerosis (Jones et al., 1991; Jorgensen et al., 2005), spinal cord injury (Ellaway et al., 2007; Raffaele, 2015) and stroke (Boniface, 2001; Cortes et al., 2012). Beyond the motor system, TMS is also used to investigate cognitive functions, such as attention (Rushworth and Taylor, 2006; Zaman, 2016), learning (Baldassarre et al., 2016; Walsh et al., 1998) and memory (Gagnon et al., 2011; Kirschen et al., 2006; Osaka et al., 2007). For example, a single-TMS pulse can temporarily disrupt the information processing of underlying cortex. Such transient 'virtual lesion' of a specific area of the cortex provides insight to brain – behaviour relationships in a non-invasive way (Pascual-Leone et al., 1999). TMS, therefore, has become widely adopted in the field of neuroscience.

When TMS was first introduced in the 1980s, TMS machines were only able to trigger 1 stimulus every ~4 s (~0.25 Hz) (Suppa et al., 2016). Advances in technology allowed for repetitive application of TMS at a higher frequency and conventional rTMS paradigms typically range from <1 Hz to 20 Hz (Caparelli et al., 2012; Filipovic et al., 2010; Li et al., 2017). Depending on the length, intensity or frequency of stimulation, rTMS has been shown to transiently alter cortical excitability beyond the stimulation duration of up to approximately 60 mins (Iyer et al., 2003; Klomjai et al., 2015). The underlying mechanism of rTMS has been explained through animal studies of activity-dependent synaptic plasticity where repetitive electrical stimulation led to NMDA-receptor dependent long-term potentiation and depression (LTP/LTD; increase/decrease in synaptic strength) (Bliss and Lomo, 1973; Dudek and Bear, 1993). This unique property has led to a wide variety of applications of TMS in both research and potential new therapeutic areas (Fitzgerald et al.,

2002a). In-depth investigation of neuroplasticity has become feasible in humans using TMS whereby neuroimaging techniques such as functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) are measured before and after plasticity-inducing protocols, and the change in neural activity is quantified by assessing changes in the outcome measure. Such combination of rTMS with brain imaging techniques allows for the investigation of mechanisms underlying plasticity (Hallett, 1996a, b; Russmann et al., 2009) and provides additional information on the functional correlates to the plastic changes (Bestmann et al., 2003; Esser et al., 2006; Ferreri and Rossini, 2013; Roberts et al., 2010). Furthermore, behavioural changes can also be assessed following rTMS and these changes can be linked to the changes in neurophysiology (Cowey and Walsh, 2001; Pascual-Leone et al., 1999; Walsh and Cowey, 2000).

In addition to experimental and diagnostic use, rTMS is utilised in clinical trials. From a therapeutic perspective, the long-lasting influences of rTMS on the brain is appealing because disorganised neural circuity is often observed in neurological and psychiatric disorders, which can lead to secondary dysfunction in synaptic strength (Kobayashi and Pascual-Leone, 2003; Machado et al., 2013; Paes et al., 2011). Over the last 15 years, a large number of studies have been conducted using rTMS in the treatment of disorders such as major depressive disorder and schizophrenia (George et al., 2010; Machado et al., 2013) where prefrontal cortex is the main target area. Early studies of the antidepressant efficacy of rTMS showed clear therapeutic benefits (Fitzgerald et al., 2006; Fitzgerald et al., 2003), and a series of meta-analyses corroborates the outcome of these studies (Gaynes et al., 2014; Leggett et al., 2015; Schutter, 2009). The efficacy of rTMS treatment has also been supported by two large multisite studies, both of which demonstrated efficacy greater than

placebo. However, the overall response rates in these trials were modest (George et al., 2010; O'Reardon et al., 2007b).

Despite a large number of studies conducted with TMS in recent years, significant uncertainties remain about its mechanism of action. Although TMS pulses can directly excite neurons, different neuronal populations are thought to undergo depolarisation depending on the stimulation intensity (Siebner et al., 2009). Stimulation at lower intensities is believed to preferentially activate interneurons with indirect effects on projecting pyramidal neurons, whereas at higher intensities, direct depolarisation of these neurons is thought to occur (Reis et al., 2008).

In addition, varying frequency of stimulation pulses can lead to different after-effects. For example, high-frequency rTMS (5 – 20 Hz) tends to increase cortical excitability (Pascual-Leone et al., 1994) while low-frequency stimulation (~1 Hz) generally produces a reduction in cortical excitability (Chen et al., 1997). However, although these changes in cortical excitability can be observed at a group level, they are not always seen within individuals and instead, different rTMS frequencies can result in divergent modulatory effects on cortical excitability (Maeda et al., 2000). Such inter-individual variability may be a significant factor in limiting response to the therapeutic use of rTMS.

Theta burst stimulation

In response to some of these limitations, researchers have investigated more effective ways of modifying brain activity using TMS methods. Some of these approaches have attempted to replicate forms of stimulation that are believed to more closely mimic the way neurons

fire in animal models (Capocchi et al., 1992; Larson et al., 1986; Staubli and Lynch, 1987), known as theta burst stimulation (TBS). TBS adopts two characteristics of hippocampal physiology, one of which is the complex-spike discharges of the pyramidal neurons (Douglas and Goddard, 1975) and the other is the hippocampal excitability that is phase-locked to the theta rhythm (~6 Hz) (Rudell et al., 1980). The effect of high-frequency stimulation pattern mimicking the complex-discharges (a burst of 8 pulses at 400 Hz) alone induced an LTP in rats (Douglas, 1977; Douglas and Goddard, 1975), however with limited efficacy. When combined within a theta rhythm, however, these high-frequency bursts resulted in a robust and reliable LTP in the CA1 region of hippocampal slices (Larson et al., 1986). In animal studies, a four-pulse burst at 100 Hz was used to mimic the high-frequency discharges repeated every 5 Hz. The repetition frequency was found to be an important factor as frequencies lower or higher than 5 Hz resulted in less effective induction of LTP (Larson and Lynch, 1986). One of the possible mechanisms behind the frequency-dependent modulation is the multi-step induction mechanism (Larson and Munkacsy, 2015). A single burst of TBS is not able to induce LTP on its own due to the activation of both excitatory and inhibitory circuits, leading to no net effect. However, the first burst primes the subsequent burst that arrives 200 ms later and induces LTP. A feed-forward postsynaptic $GABA_B$-mediated inhibition is activated following a burst that blocks excitatory postsynaptic potentials (EPSPs) evoked by the current burst and the subsequent burst within 100 – 150 ms. This feed-forward inhibition also becomes suppressed after its own activation via $GABA_B$ autoreceptor-mediated disinhibition (Davies et al., 1990), termed disinhibition. The second burst at 200 ms is thought to evoke maximal postsynaptic depolarisation in the pyramidal neuron, as NMDA receptor activation at excitatory synapses is enhanced during this period of disinhibition (Davies and Collingridge, 1996).

In 2005, Huang and colleagues (Huang et al., 2005) adopted this technique in humans, using a slightly different pattern – pulses were applied in bursts of three at high frequency (50 Hz) with an inter-burst interval at low frequency (5 Hz) for a total number of 600 pulses. Two types of TBS have been developed which are now widely used. Intermittent TBS (iTBS) involves applying TBS in 2 s trains every 10 s and has been shown to have an LTP-like plastic effect up to about 15 mins. An opposite outcome (LTD-like effect) was obtained following continuous TBS (cTBS), which involves either 20 or 40 s of TBS without any interruption and the after-effect lasted up to 20 or 60 mins respectively (Huang et al., 2005). Since its first adaptation in humans, a large number of studies have used this technique and it is now generally accepted that iTBS increases excitability up to about 30 mins while cTBS decreases up to about 60 mins (Wischnewski and Schutter, 2015). However, more recent studies have shown substantial inter-subject variability (Hamada et al., 2013; Hinder et al., 2014; Lopez-Alonso et al., 2014). In order to enhance the efficacy of TBS in the motor cortex, several studies have modified the parameter of stimulation such as intensity (McAllister et al., 2009), number of pulses (Gamboa et al., 2011; Goldsworthy et al., 2012a) and frequency (Goldsworthy et al., 2012b; Wu et al., 2012a), however, with inconsistent results. These studies suggest that parameters of stimulation can impact the outcome of stimulation to a certain extent. One major difference between these TBS approaches and standard rTMS is in the duration of administration. A typical rTMS protocol takes between 20 and 45 min whereas these TBS paradigms can achieve similar results within 1 to 3 min (Huang et al., 2005). TBS is also well-tolerated and does not appear to be associated with a significant rate of adverse events in healthy or patient populations (Chistyakov et al., 2010; Hong et al., 2015; Oberman et al., 2011; Wu et al., 2012b).

Despite the emerging evidence for the potential value of TBS, its use has not yet substantially spread into clinical applications. One of the major reasons for this delay is that the vast majority of studies exploring the effects of TBS have been conducted in the motor cortex. However, the treatment of disorders such as depression involves stimulation of the prefrontal cortex where the physiological effects of stimulation may not be the same. It is, therefore, important to systematically explore the effects of TBS applied to non-motor brain region to try and better establish the basis for clinical applications of this technique. In the next section, we review the clinical prospects of TMS and TBS in detail.

CHAPTER THREE

TMS, TBS and depression

Chung SW, Hoy KE, Fitzgerald PB. 2015a. Theta-burst stimulation: a new form of TMS treatment for depression? *Depression & Anxiety.* 32(3):182-92.

Preamble to review paper

The following published paper provides a review of theta burst stimulation as a potential treatment for depression. This review provides an overview of TMS and TBS, and the neurobiological mechanisms including long-term potentiation and depression (LTP/LTD) – like processes as well as the involvement of GABAergic inhibitory transmission. In addition, the use of TBS in treating major depressive disorder and its safety are reviewed.

Theoretical Review

THETA-BURST STIMULATION: A NEW FORM OF TMS TREATMENT FOR DEPRESSION?

Sung Wook Chung, B.Sc. (Hons.), Kate E. Hoy, B.B.N.Sc. (Hons.), D.Psych. (Clin. Neuro.), and Paul B. Fitzgerald, MBBS, Ph.D.*

Major depressive disorder (MDD) is a common debilitating condition where only one third of patients achieve remission after the first antidepressant treatment. Inadequate efficacy and adverse effects of current treatment strategies call for more effective and tolerable treatment options. Transcranial magnetic stimulation (TMS) is a noninvasive approach to manipulate brain activity and alter cortical excitability. There has been more than 15 years of research on the use of repetitive form of TMS (rTMS) for the treatment of patients with depression, which has shown it to be an effective antidepressant treatment. Even though rTMS treatment has shown efficacy in treating depression, there is a high degree of interindividual variability in response. A newer form of rTMS protocol, known as theta-burst stimulation (TBS), has been shown to produce similar if not greater effects on brain activity than standard rTMS. TBS protocols have a major advantage over standard rTMS approaches in their reduced administration duration. Conventional rTMS procedures last between 20 and 45 min, as compared to TBS paradigms that require 1 to 3 min of stimulation. Recently, a small number of studies have suggested that TBS has similar or better efficacy in treating depression compared to rTMS. Optimization, identification of response predictors, and clarification of neurobiological mechanisms of TBS is required if it is to be further developed as a less time intensive, safe, and effective treatment for MDD. Depression and Anxiety 32:182–192, 2015.

Key words: *transcranial magnetic stimulation; theta-burst stimulation; depression; dorsolateral prefrontal cortex; electroencephalography; brain stimulation*

Monash Alfred Psychiatry Research Centre, Central Clinical School, The Alfred and Monash University, Melbourne, Australia

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*Correspondence to: Paul B. Fitzgerald, Monash Alfred Psychiatry Research Centre, Central Clinical School, The Alfred and Monash University, Level 4, 607 Saint Kilda Road, Melbourne, Victoria 3004, Australia. E-mail: paul.fitzgerald@monash.edu
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DEPRESSION

Major depressive disorder (MDD) is one of the most common mental disabilities worldwide, with global point prevalence of 4.7%.[1] The World Health Organization predicts MDD to be the leading cause of disease burden by 2030.[2] Even with effective treatments available, only one third of MDD patients achieve remission after the first antidepressant treatment,[3] with failure to respond to two consecutive antidepressant trials leading to an even greater reduction in remission rates.[4,5] An analysis study of antidepressant response reported that as many as 34% of the depressed patients were treatment-resistant, whereas another 15% only responded partially, following standard doses of antidepressants for 6 weeks or more.[6] In addition, in a recent study, the recurrence rate of MDD despite specialized mental care 5 years after recovery was 60%, and up to 85% over 15 years.[7] These findings question the effectiveness of current treatment strategies. Apart from inadequate efficacy, side effects

can occur frequently with antidepressant medication and this can be a significant factor for discontinuation.[8] There is clearly a need for more effective and tolerable alternative treatment options.

ALTERNATIVE TREATMENT

One of the main alternatives for treatment-resistant depression (TRD) is electroconvulsive therapy (ECT), and even though the side-effect profile has improved over time, it is still associated with cognitive side-effects.[9] Adverse side effects (e.g., memory impairment), requirement to induce a seizure under general anesthesia and the stigma associated with ECT have led patients to seek a more noninvasive procedure with fewer side effects. One such alternative is "transcranial magnetic stimulation" (TMS).[10]

TMS

TMS is a widely used technique in the neurosciences and involves stimulating the brain through the intact scalp.[11] TMS produces a magnetic field that passes freely into the brain and induces electrical activity in underlying neurons, which results in their depolarization.[12] A single TMS pulse can produce the acute effect of neural circuit activation that is generally short-lived (up to hundreds of milliseconds).[13] By applying stimulation repetitively, however, TMS has been shown to alter the excitability of the stimulated area in the brain,[14] outlasting the period of the stimulation. This characteristic of repetitive TMS (rTMS) is particularly beneficial from a therapeutic perspective.[15] Depending on the frequency of stimulation, the effect on cortical excitability can generally be either excitatory or inhibitory.[16] Low-frequency rTMS (1 Hz) has been shown to reduce cortical excitability when applied for 15 min,[17] whereas high-frequency rTMS (5–20 Hz) has been observed to increase excitability.[18] However, there is no consistent evidence that low-frequency rTMS produces inhibitory effects, and even though most studies of high-frequency rTMS showed increased excitability, varying results were reported.[19] rTMS appears to mimic the effects of long-term depression (LTD) and long-term potentiation (LTP),[20] and it may exert its therapeutic effects in depression via modifying plasticity.

rTMS IN DEPRESSION

Dysfunction of neural circuits is associated with the pathophysiology of many psychiatric disorders,[21] and the modulatory effects of rTMS in the stimulated area have allowed for treatment of mood disorders, particularly showing significant efficacy in depressed patients.[9] More than 15 years of research has been conducted on the use of rTMS for the treatment of patients with depression,[15] with a large number of rTMS treatment trials in MDD targeted to dorsolateral prefrontal cortex (DLPFC).[22] An early depression study using positron emission tomography (PET) showed reduction of glucose metabolism in prefrontal cortex (PFC) areas, including the DLPFC,[23] followed by a series of PET studies that demonstrated a correlation between the effects of antidepressant treatment and normalization of hypoactivity in the PFC.[24,25] Based in part on this research, rTMS targeting of DLPFC has become the conventional stimulation approach in depression treatment. However, a recent review explored alternative stimulation sites to improve rTMS efficacy, suggesting a range of other options such as dorsomedial PFC, frontopolar cortex, ventromedial PFC, and ventrolateral prefrontal cortex.[26]

In regard to targeting the DLPFC, the presence of interhemispheric asymmetry in prefrontal regions in clinically depressed patients has allowed for several therapeutic options.[27] There are two commonly used rTMS protocols in treating depression – high-frequency rTMS (5–20 Hz) targeting left DLPFC[28] and low-frequency rTMS (~1 Hz) over the right DLPFC.[29] The majority of depression studies have been conducted using high-frequency rTMS (at or above motor threshold) to the left DLPFC since its initial demonstration of antidepressant efficacy in an open study,[30] and subsequent randomized sham-controlled trials[31–34] and meta-analyses[35–37] support its effectiveness. On the other hand, there are now a growing number of studies suggesting that low-frequency rTMS is as effective as high-frequency rTMS in the treatment of depression.[38–43] Different parameters commonly used in treating depression are summarized in Table 1.

Even though many studies support the antidepressant effect of rTMS, varying outcomes have been reported among early studies, and some have shown no beneficial effects.[44–46] Early rTMS protocols have shown less antidepressant effect compared to more recent protocols,[47] which may explain such variability. Different frequencies ranging from 5 Hz to 20 Hz have been investigated,[30,48,49] with 10 Hz being most frequently used.[50,51] The largest multisite randomized controlled trial (301 medication-free patients) to date showed significant antidepressant results compared to sham using 10 Hz,[52] followed by a more recent sham-controlled randomized trial involving 190 intention-to-treat patients that reported clinically meaningful antidepressant effects compared to sham with 10 Hz rTMS.[33]

A recent meta-analysis on the clinical relevance of rTMS concluded unfavorably toward its antidepressant effect,[53] but it did not examine the treatment duration and cumulative dose as factors affecting the outcome. It is critical to note that fairly clear dose–response relationship has emerged in depression treatment with rTMS in the recent years,[54,55] and rTMS clinical trial reports reveal reasonably consistent efficacy signals.[33,55,56]

Recently, low-field magnetic stimulation inducing low, pulsed electric field (≤1 V/m, 1 kHz) has demonstrated rapidly acting antidepressant responses,[57] supporting the previous studies of antidepressant properties with low magnetic field.[58–60] The field strength

TABLE 1. Commonly used rTMS and TBS parameters in treating depression

Parameters	rTMS		TBS	
	Low-frequency rTMS	High-frequency rTMS	cTBS	iTBS
Intensity (motor threshold)	110% rMT	120% rMT	80% aMT/rMT	80% aMT/rMT
Frequency of stimulation	1 Hz	10 Hz	50 Hz	50 Hz
Interstimulus interval (ISI)	1 s	100 ms	20 ms	20 ms
Train duration	20 min	4 s	20 or 40 s	2 s
Intertrain interval (ITI)	–	25 s	200 ms	200 ms
Interblock interval (IBI)	–	–	–	10 s
Number of trains	-	75 trains	-	10 trains each block
Total number of stimulus[a]	1,200	3,000	300 or 600	600
Administration site	Right DLPFC	Left DLPFC	Right DLPFC	Left DLPFC

[a]Total number of stimulus given per day may vary.
aMT/rMT, active/resting motor threshold; DFLPC, dorsolateral prefrontal cortex; cTBS/iTBS, continuous/intermittent theta-burst stimulation; rTMS, repetitive transcranial magnetic stimulation.

was significantly lower than rTMS for depression treatment (100 V/m, 10 Hz), and therefore, it is not clear whether high field strength is required to obtain the therapeutic effects of rTMS in depression treatment.

The differences in the possible methods of rTMS treatment delivery and the techniques involved can result in varying outcome, and a mixed combination of different variables used in rTMS parameters across studies (such as stimulus frequency, intensity, and number of stimuli) may limit systemic comparisons. Additionally, interpretation of the results in clinical trials may be affected by interindividual variability of response to rTMS,[61] and therefore, standardizing rTMS parameters and developing a better understanding of different rTMS applications would benefit future research and also provide more efficacious clinical outcome. There is also potential value in exploring rTMS-related stimulation options that may produce greater brain effects.

THETA-BURST STIMULATION (TBS)

In search for more effective ways of modifying brain activity, researchers have been investigating novel ways of applying rTMS. Several animal model studies have demonstrated effectiveness in inducing synaptic plasticity using bursts of high-frequency theta stimulations.[62–64] Mimicking LTP and LTD inducing paradigms in such animal models laid the basis for the development of patterned rTMS protocols known as TBS.[65]

TBS involves pulses being applied in bursts of three at high frequency (50 Hz) with an interburst interval of 200 ms (5 Hz, which is in the range of theta frequency). Based on animal experiments that showed powerful effects on synaptic plasticity using repeated short bursts of high-frequency stimulation at 50–100 Hz given three to five times per second (theta range),[66,67] a pilot study investigated the effect of a single short burst of 50 Hz rTMS at low intensity in human motor cortex, and reported TBS could safely be applied to human cortex to study long-term potentiation.[68] TBS requires less stimulation time and lower intensity (typically 80% of the active motor threshold (aMT)) to produce longer lasting effects in the human cerebral cortex compared to other known rTMS protocols.[65] There are two different patterns of TBS that are commonly used, continuous (cTBS) and intermittent (iTBS), which have opposite effects (Fig. 1). In cTBS, either 300 pulses (20 s) or 600 pulses (40 s) of TBS are delivered without any interruption. This paradigm reduces cortical excitability beyond its stimulation duration by approximately 20 min for 300 pulses of cTBS, and up to 1 hr for 600 pulses of cTBS. In iTBS, 2 s of TBS trains (30 pulses) are repeated every 10 s for 190 s, with a total number of 600 pulses. iTBS produces facilitatory effects on motor cortex excitability that outlast the stimulation time for at least 15 min.[65]

Similar protocols to above-mentioned TBS paradigms have been used in animal models to induce facilitation[62,69] or to produce suppression,[70] but it is unclear how the parameters were developed for human cortex. In an earlier study of rat hippocampus, variable amounts of LTP were observed depending on how many trains of TBS were delivered.[71] A recent study in human has demonstrated the importance of break during 5 Hz rTMS for facilitation, as the after-effects reversed into inhibition when 5 Hz was applied continuously[72], which may explain the rationale behind the development of different TBS protocols.

It is believed that these after-effects of TBS originate from the cortex since spinal H-reflexes are unaffected by the intervention.[65] The cortical origin of the effects of TBS is also suggested by direct recordings of corticospinal activity. TMS can produce multiple descending corticospinal volleys containing a direct (D) wave followed by several indirect (I) waves, I1, I2, and I3, which can be recorded using electrodes inserted into the epidural space over the spinal cord.[73] The D-wave is thought to be caused by direct activation of corticospinal axons, and the I-waves by transsynaptic activation of the excited neurons.[74] TBS effects on cortical circuits showed

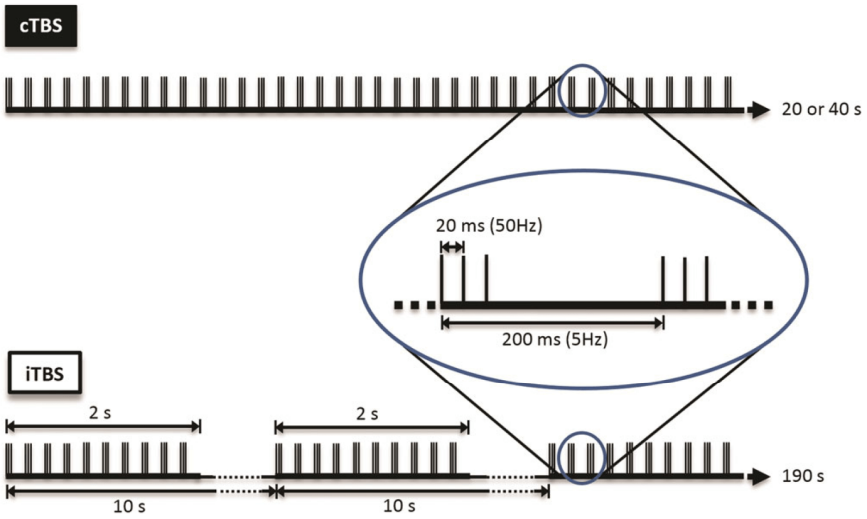

Figure 1. Different TBS protocols. TBS pattern consists of three bursts of pulses given at 50 Hz every 200 ms. When stimulated continuously (cTBS) for either 20 or 40 s, it induces LTD-like effect. However, when stimulated intermittently (iTBS) at 2 s every 10 s for 190 s, it induces LTP-like effect.

preferential decrease in the amplitude of I1 wave using cTBS,[75] whereas increase in the amplitude of later I-waves, but not the I1 wave, was observed with iTBS.[76] Such selective stimulation accommodates sophisticated investigation of facilitatory and inhibitory cortical interactions in humans. Furthermore, a recent study suggested that the after-effects of TBS protocols may be influenced by the recruitment of early and late I-waves, and optimizing the conditions for late I-wave recruitment would be necessary to improve TBS effects.[77]

MECHANISMS – ANIMAL MODELS

The neural mechanisms involved in the effects of TBS are inadequately understood in humans, though animal model studies aid in our understanding of this technique. A rat model study with cortical TBS stimulation demonstrated acute and long-term effects on the expression of glutamic acid isoforms in cortical inhibitory interneurons that are important for γ-aminobutyric acid (GABA) synthesis in neurotransmission.[78] Both cTBS and iTBS promoted GABAergic neurotransmission at the cellular level in the targeted rat cortex, whereas these parameters caused different effects on the cortical expression of calcium-binding proteins such as calbidin D-28k (CB) and parvalbumin (PV).[79] The latter study suggested that the iTBS may target the inhibition of pyramidal cell output by decreasing interneuronal PV expression, and cTBS influences the inhibitory activity of interneurons expressing CB that regulate the synaptic inputs to pyramidal cells. However, even though different inhibitory modulation was observed within the targeted cortex for different TBS patterns in the rat model, it may not necessarily translate into human studies of TBS.[79]

MECHANISMS – HUMAN MODELS

Partially supporting these animal findings, a magnetic resonance spectroscopy study in humans revealed TBS modulation of GABA.[80] Increased GABA concentration was seen in primary motor cortex (M1) after cTBS stimulation with no significant changes in glutamate/glutamine levels. Furthermore, the involvement of the GABA receptor as a mediator for neuronal modulation was proposed.[81] The GABAergic inhibitory transmission between hippocampal interneurons and pyramidal neurons can be enhanced by activating the *N*-methyl-D-aspartate receptor (NMDA-R),[82] and the effects of cTBS-induced suppression and iTBS-induced facilitation were blocked by memantine, an NMDA-R antagonist, suggesting the after-effects might be mediated by LTD/LTP-like synaptic plasticity.[83] Additionally, TBS effects can also be modulated by dopamine as blocking D2 receptors impaired the effects of both cTBS and iTBS.[84] The activation of the D2 receptor suppresses NMDA-R activation,[85] as well as GABAergic inhibition,[86] indicating the existence of complexity involved in TBS-induced plasticity. Therefore, more studies are needed to enhance our understanding of its mechanism in humans.

MOTOR VERSUS NONMOTOR

The effects of TBS were first elucidated when it was applied to the motor cortex, and the majority of studies exploring the after-effects of TBS have studied this site.[65,83,87,88] This is, in part, because the modulatory effects on the motor cortical excitability can be assessed relatively directly[89] compared to nonmotor regions.

M1 excitability can be evaluated by measuring parameters such as motor-evoked potentials (MEPs), short-interval intracortical inhibition (SICI), and intracortical facilitation (ICF) using single-pulse (sp) TMS and paired-pulse (pp) TMS.[90] When applied over M1 in healthy individuals, cTBS showed reduction in MEPs and SICI, whereas iTBS had the opposite effect.[65] However, several studies did not find significant changes in SICI following both, or either one of TBS protocols.[91–94] One reason could be that the TBS effects on SICI are highly intensity dependent.[94] Different findings were observed in modulating ICF with TBS, where ICF remained unchanged with cTBS,[87,95] or showed decrease in ICF.[65,96] There was no effect in modulation of ICF with iTBS.[65,87] These varied results may be due to the opposite current direction used in two studies as responses in these paradigms are dependent on stimulation parameters.

Several attempts have been made to optimize the effects of TBS in motor cortex with modulation of variables such as frequency,[97–99] stimulation duration,[100] and a paired application,[101] but there is no consensus as to the optimal methods of applying TBS as yet. It is also unclear whether the optimized TBS parameters for motor cortex stimulation would result in similar effects in PFC, where only limited optimization effort has been made.

TBS influences on the modulation of corticocortical and intracortical circuits have been demonstrated in other brain regions with respect to M1. Remote suppression of M1 excitability can be caused by cTBS on premotor cortex,[102] and when cTBS was applied to the primary somatosensory cortex, an increase in MEPs was seen with no change in SICI or ICF on M1 circuitry.[96] In addition, the evidence of cerebellar efferent modulation to the motor cortex was observed when the induction of cTBS over lateral cerebellum caused a reduction in SICI within the contralateral M1.[103]

However, evaluation of TBS effects in other brain regions, such as parietal cortex and PFC, requires different approaches. The availability of neuroimaging techniques, such as PET, electroencephalography, functional MRI, and functional near-infrared spectroscopy, allows researchers to investigate the effects of TBS in nonmotor regions.[104–107] One recent study demonstrated hemodynamic change in prefrontal regions upon TBS stimulation, but this was an indirect measurement of prefrontal cortical activity.[108]

TBS stimulation over different brain regions has also been employed with therapeutic intent, such as in visual neglect,[109] tinnitus,[110,111] pain,[112] and depression.[113–115] However, despite the effectiveness of TBS in motor cortical modulation, its use has not yet substantially spread into clinical applications. This is likely due to this lack of investigation of the effects of TBS on more clinically relevant brain regions. In particular, the physiological effects of TBS in PFC, where abnormalities are prevalent for major depression[116] and schizophrenia[117], are not likely to be the same as in the motor cortex and require investigation.

STUDIES OF TBS IN DEPRESSION

TBS has been shown to be effective in modulating motor cortex physiology and behavior in healthy populations,[83,95] and has clear potential as a therapeutic tool in MDD.[114] As discussed above, an imbalance between left and right DLPFC activity has been proposed in MDD,[118] and different TBS paradigms could be applied to counter this interhemispheric asymmetry; iTBS to the left and cTBS to the right DLPFC. However, currently there are only a few studies investigating the antidepressant efficacy of TBS (summarized in Table 2).

Preliminary studies of antidepressant efficacy of TBS suggested its potential therapeutic applications in patients with major depression.[113,119] In one of the first studies, clinical improvement was observed after 2 weeks of treatment with, twice daily, iTBS (1,200 pulses/day) to the left DLPFC, as well as patients who received cTBS (1,200, 1,800, or 3,600 pulses/day) to the right DLPFC.[119] Different stimulation doses were used in four groups in the trial; three of the groups received cTBS after an initial comparison between iTBS and cTBS suggested greater efficacy with the latter. Antidepressant efficacy was lower for iTBS (28.6% improvement rate) than cTBS (50.0% improvement rate). Without significant adverse effects, dose-dependent efficacy was reported with more pulses of cTBS, suggesting that the extended number of TBS pulses may improve clinical outcome.

Similar TBS parameters (refer to Table 2) were used for a case series conducted by Holzer and Padberg (2010), which suggested antidepressant efficacy of iTBS. Significant reductions in Hamilton Rating Scale for Depression (HDRS, 43%) and Beck Depression Inventory (BDI, 49%) were seen after a 3-week course of treatment.[113] Longer treatment duration in this study may have resulted in better outcome as the treatment response to rTMS became clinically meaningful after 4 to 6 weeks of active treatment.[120] Even though there clearly was an antidepressant outcome in all groups, both studies were open with no sham control groups, and placebo effect needs to be considered.

A different approach has combined left-sided iTBS and right-sided cTBS successively. This randomized controlled pilot study investigated the efficacy of bilateral TBS to the DLPFC in 32 patients with MDD and found that antidepressant efficacy was significantly higher with bilateral TBS than sham TBS.[115] Treatment responses quantified by the Montgomery–Åsberg Depression Rating Scale (MADRS) showed nine responders (56%) and seven patients (44%) with remission in an active group, compared to sham group that had four responders (24%) and three patients (19%) with remission.

TABLE 2. TBS treatment trials in depression

Study	Subjects	TBS parameters	Significant difference (active vs. sham)	Results
Chistyakov *et al.*, 2010	33 medication-resistant MDD patients	10 sessions over 2 weeks, 50 Hz interstimulus interval repeated every 5 Hz. Group 1: 90% aMT, iTBS to left DLPFC, 600 stimuli repeated twice daily (1,200 stimuli) Group 2: 90% aMT, cTBS to right DLPFC, 600 stimuli repeated twice daily (1,200 stimuli) Group 3: 100% aMT, cTBS to right DLPFC, 900 stimuli repeated twice daily (1,800 stimuli) Group 4: 100% aMT, cTBS to right DLPFC, two consecutive trains of 900 stimuli each separated by a 30-min interval and repeated twice daily (3,600 stimuli)	n/a	18 of 32 (56.3%) patients reported improvement in depressive symptoms (50% decline on the HDRS). CTBS showed more effectiveness than iTBS. Dose-dependent improvement seen with cTBS (Group 2, 3, and 4). Improvement was seen in the following: Group 1: 2 of 7 (28.6%) Group 2: 3 of 6 (50.0%) Group 3: 3 of 5 (60.0%) Group 4: 10 of 14 (71.4%)
Holzer and Padberg., 2010	Seven medication-resistant MDD patients	Three-week course, 50 Hz interstimulus interval repeated every 5 Hz. 80% rMT, iTBS to left DLPFC, 600 stimuli repeated twice (10-min interval) daily (1,200 stimuli)	n/a	43 and 49% decline on HDRS and BDI, respectively. 70% (five of seven) response rate and 42% (three of seven) remission rate.
Li *et al.*, 2014	60 patients with TRD	10 sessions over 2 weeks, 50 Hz interstimulus interval repeated every 5 Hz at 80% aMT. Group 1: cTBS to right DLPFC, 1,800 stimuli daily Group 2: iTBS to left DLPFC, 1,800 stimuli daily Group 3: Combination of cTBS to right DLFPC (1,800 stimuli) and iTBS to left DLPFC (1,800 stimuli) successively (3,600 stimuli per day) Group 4: Sham TBS (either iTBS or cTBS) with 90° coil set	Yes	Significant decrease in HDRS scores in active TBS groups (especially with paradigms involving iTBS to the left DLPFC) compared to sham group. Group 1: 3 of 15 responders (−22.5% decrease in HDRS) Group 2: 6 of 15 responders(−42.3% decrease in HDRS) Group 3: 10 of 15 responders (−52.5% decrease in HDRS) Group 4: 2 of 15 responders (−17.4% decrease in HDRS)
Plewnia *et al.*, 2014	32 patients with MDD	30 sessions over 6 weeks, 50Hz interstimulus interval repeated every 5 Hz. 80% rMT, combination of 600 stimuli of iTBS to left DLPFC and 600 stimuli of cTBS to right DLPFC successively (1,200 stimuli per day) Sham with 45° coil set	Yes	Significantly superior effect in the active group (9 of 16 [56%] response, 7 of 16 [44%] remission) compared to sham group (4 of 16 [25%] response, 3 of 16 [19%] remission) quantified by MADRS scores.

aMT/rMT, active/resting motor threshold; BDI, Beck Depression Inventory; cTBS/iTBS, continuous/intermittent theta-burst stimulation; DLPFC, dorsolateral prefrontal cortex; HDRS, Hamilton Rating Scale for Depression; MDD, major depressive disorder; n/a, not applicable; TRD, treatment-resistant depression.

A more recent study compared antidepressant efficacy of different TBS paradigms in 60 patients with TRD. Fifteen patients were assigned to each group; right-sided cTBS (1,800 stimuli), left-sided iTBS (1,800 stimuli), bilateral TBS (3,600 stimuli), and a sham.[114] This randomized sham-controlled 2-week trial demonstrated a greater response rate (66.7%) in a group with bilateral stimulation (successive stimulation in a randomly assigned order), and iTBS on the left DLPFC (40%) compared to cTBS (20%) and sham group (13.3%).

Moreover, TBS treatment outcomes were associated with different refractoriness levels. Treatment resistance (i.e., antidepressant treatment failures), severity of symptoms, and duration of presenting episode were measured prior to randomization in terms of refractoriness scores, and categorized into three levels – low, moderate, and high refractoriness. Patients with lower refractoriness scores were also responsive to sham stimulation, but the sham responses gradually decreased as the treatment refractoriness level increased. Bilateral stimulation and iTBS were statistically more effective in patients with moderate to high refractoriness level, and cTBS showed antidepressant efficacy in treatment of patients with moderate refractoriness. The best response was seen in moderate refractoriness group, and it was suggested that patients in this group may have an underlying brain dysfunction that is more treatable by TBS.[114] This indicates that lower refractoriness scores are predictors for better TBS responses.

Twelve-week followup of the TBS data revealed 57.9% response rate in total,[114] which is similar to the response rate of acute-phase treatment with rTMS (58%) measured by the Clinical Global Impression – Severity (CGI-S).[56] It is worth noting that the change in mean HDRS of bilateral TBS treatment was 52.5% after 2 weeks,[114] a rate higher than most rTMS trials.[22]

TBS has shown a promising future in depression treatment. However, it is important to note that larger randomized controlled trials are required before the jury is out, since the studies that have been published so far are preliminary, mostly open, uncontrolled, and underpowered.

These studies of TBS have used mostly similar parameters, with some variation in stimulation intensity. The main difference can be seen in the stimulation duration (Table 2). Similar to recent rTMS trials, there appears to be a likelihood of dose dependence of antidepressant efficacy. However, this requires further investigation as simply prolonging the stimulation duration has resulted in reversed effects with motor cortex TBS.[100] Repeated stimulation at an interval of 10 to 15 min may produce increased antidepressant efficacy as a paired application of cTBS at 10-min intervals prolonged neuroplastic changes in M1 excitability,[101] and repeated trains of right parietal cTBS (up to four trains with 15-min interval) induced long-lasting improvement of visual neglect.[109] The latter study used a modified TBS paradigm with 30 Hz interstimulus interval and repeated every 6 Hz that was found to induce a superior neuroplastic response within M1 than standard cTBS paradigm.[99]

SAFETY OF TBS

TMS is generally well-tolerated with a few mild side effects such as headache and neck pain. However, it poses a risk of seizure, and extensive safety guidelines for TMS have been established.[121] Theoretically, TBS has the potential of having a higher risk of seizure induction than rTMS due to its high-frequency bursts (50Hz), but it can also be viewed as a safer protocol as it uses less pulses in a shorter duration and at lower intensity. Due to lack of safety studies of TBS, current TMS safety guidelines do not include recommended procedures for minimizing adverse effects of TBS.[121] However, the application of TBS in research and clinical fields has increased since its introduction, and its safety has been investigated.[122] A recent meta-analysis reported that seizure has only occurred once with TBS to date, and it accounts for the crude risk of seizure per session of 0.02%. The overall crude risk of mild adverse events was estimated to be 1.1%, and these findings were comparable with high-frequency rTMS protocols. It should be noted that the seizure occurred at an intensity of 100% resting motor threshold (rMT) on M1,[123] while most studies followed original TBS paradigm at 80% aMT.[65] In addition, TBS safety study in children less than 18 years of age showed no serious adverse events.[124]

Safety of TBS was assessed in the studies of antidepressant efficacy, and it was found to be safe with no seizure occurrence.[114,115,119] Common side effects included headache and dizziness in a few patients in both active and sham group. Notably, dizziness was more prevalent in active group, especially with bilateral stimulation.[114] The author also reported a correlation between sequence of stimulation and dizziness ratio. It was found that most patients with dizziness received cTBS first followed by iTBS (four of seven), whereas only a small number of patients suffered from dizziness with the opposite sequence (one of eight). Increased intensity from 80 to 100% aMT and the number of stimuli from 1,200 to 3,600 each day did not cause any significant adverse effects,[119] which would allow for wider range of stimulation parameters to devise optimal efficacy. Despite the safe and efficacious application of TBS, a careful examination is required prior to and during the TBS stimulation.

CONCLUSIONS AND FUTURE DIRECTIONS

Studies of the modulation of plasticity in human motor cortices with TBS suggest that it is one of the most powerful tools for therapeutic noninvasive brain stimulation. Current research efforts are in progress to improve clinical efficacy of depression treatment, however, widespread clinical use of TBS is yet to emerge. TBS protocols have a major advantage over standard rTMS approaches in its administration duration. This, together with the fact that TBS uses a lower stimulation intensity of 80% instead of 120% used in rTMS, may allow for more comfortable treatment conditions in a therapeutic setting. However, the variety of parameters such as frequency, duration, total number of pulses, or total number of treatment sessions needs further investigation in order to optimize TBS efficacy.[88] It would also be worth looking at the effects of lower intensity TBS in depression. Long-lasting alterations in cortical excitability are

desirable for clinical applications, and therefore, a wider range of stimulation parameters deserve a closer look.

It must be noted that TBS protocols use very high-frequency stimulation, which may pose a higher risk of adverse events such as seizure.[122] Because TMS is known to carry a risk of seizures, safety guidelines for use of TMS have been established.[121] The lack of safety studies for TBS stresses the necessity to explore its equivalent guidelines. At this time, given the limited safety data, TBS protocols for depression or other psychiatric disorders should only be delivered in the context of a research study with special informed consent procedures. Currently, there is no FDA-cleared device for the delivery of TBS to patients for clinical care.

It is critical to develop more effective stimulation paradigms before larger studies can be conducted. In order to develop better forms of TBS, a further research is required to better understand the neurophysiological and clinical features of depressed patients who respond to TBS. The identification of reliable predictors for better TBS responses is another important future research area. Elucidation on the neurobiological mechanisms of the effect of TBS treatment in depression will contribute to identifying optimal forms of TBS, which can lead to personalized medicine with better clinical results. Finally, large treatment studies are required to better understand the mechanisms of treatment response, and these approaches will help establish TBS as a safe and effective treatment option for patients with MDD.

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REFERENCES

1. Ferrari AJ, Somerville AJ, Baxter AJ, et al. Global variation in the prevalence and incidence of major depressive disorder: a systematic review of the epidemiological literature. Psychol Med 2013;43:471–481.
2. World Health Organization. The Global Burden of Disease: 2004 Update. Geneva: World Health Organization; 2008: 146.
3. Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006;163:28–40.
4. Sinyor M, Schaffer A, Levitt A. The sequenced treatment alternatives to relieve depression (STAR*D) trial: a review. Can J Psychiatry 2010;55:126–135.
5. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006;163:1905–1917.
6. Fava M, Davidson KG. Definition and epidemiology of treatment-resistant depression. Psychiatr Clin North Am 1996;19:179–200.
7. Hardeveld F, Spijker J, De Graaf R, et al. Prevalence and predictors of recurrence of major depressive disorder in the adult population. Acta Psychiatr Scand 2010;122:184–191.
8. Demyttenaere K, Enzlin P, Dewe W, et al. Compliance with antidepressants in a primary care setting, 1: Beyond lack of efficacy and adverse events. J Clin Psychiatry 2001;62(Suppl 22):30–33.
9. Holtzheimer PE, Mayberg HS. Neuromodulation for treatment-resistant depression. F1000 Med Rep 2012;4:22.
10. Cristancho MA, Helmer A, Connolly R, et al. Transcranial magnetic stimulation maintenance as a substitute for maintenance electroconvulsive therapy: a case series. J ECT 2013;29:106–108.
11. Verdon CM, Saba G, Januel D. [Transcranial magnetic stimulation in cognition and neuropsychology]. Encephale 2004;30:363–368.
12. Kobayashi M, Pascual-Leone A. Transcranial magnetic stimulation in neurology. Lancet Neurol 2003;2:145–156.
13. Allen EA, Pasley BN, Duong T, Freeman RD. Transcranial magnetic stimulation elicits coupled neural and hemodynamic consequences. Science 2007;317:1918–1921.
14. Maeda F, Keenan JP, Tormos JM, et al. Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation. Clin Neurophysiol 2000;111:800–805.
15. Fitzgerald PB, Daskalakis ZJ. The effects of repetitive transcranial magnetic stimulation in the treatment of depression. Expert Rev Med Devices 2011;8:85–95.
16. Pascual-Leone A, Tormos JM, Keenan J, et al. Study and modulation of human cortical excitability with transcranial magnetic stimulation. J Clin Neurophysiol 1998;15:333–343.
17. Chen R, Classen J, Gerloff C, et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology 1997;48:1398–1403.
18. Pascual-Leone A, Grafman J, Hallett M. Modulation of cortical motor output maps during development of implicit and explicit knowledge. Science 1994;263:1287–1289.
19. Fitzgerald PB, Fountain S, Daskalakis ZJ. A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. Clin Neurophysiol 2006;117:2584–2596.
20. Paulus W. Toward establishing a therapeutic window for rTMS by theta burst stimulation. Neuron 2005;45:181–183.
21. Price JL, Drevets WC. Neural circuits underlying the pathophysiology of mood disorders. Trends Cogn Sci 2012;16:61–71.
22. Daskalakis ZJ, Levinson AJ, Fitzgerald PB. Repetitive transcranial magnetic stimulation for major depressive disorder: a review. Can J Psychiatry 2008;53:555–566.
23. Baxter LR Jr., Schwartz JM, Phelps ME, et al. Reduction of prefrontal cortex glucose metabolism common to three types of depression. Arch Gen Psychiatry 1989;46:243–250.
24. Mayberg HS, Liotti M, Brannan SK, et al. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. Am J Psychiatry 1999;156:675–682.
25. Drevets WC, Bogers W, Raichle ME. Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism. Eur Neuropsychopharmacol 2002;12:527–544.
26. Downar J, Daskalakis ZJ. New targets for rTMS in depression: a review of convergent evidence. Brain Stimul 2013;6:231–240.
27. Lefaucheur JP, Lucas B, Andraud F, et al. Inter-hemispheric asymmetry of motor corticospinal excitability in major depression studied by transcranial magnetic stimulation. J Psychiatr Res 2008;42:389–398.
28. George MS, Nahas Z, Molloy M, et al. A controlled trial of daily left prefrontal cortex TMS for treating depression. Biol Psychiatry 2000;48:962–970.

29. Klein E, Kreinin I, Chistyakov A, et al. Therapeutic efficacy of right prefrontal slow repetitive transcranial magnetic stimulation in major depression: a double-blind controlled study. Arch Gen Psychiatry 1999;56:315–320.
30. George MS, Wassermann EM, Williams WA, et al. Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. Neuroreport 1995;6:1853–1856.
31. George MS, Wassermann EM, Kimbrell TA, et al. Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: a placebo-controlled crossover trial. Am J Psychiatry 1997;154:1752–1756.
32. Fitzgerald PB, Brown TL, Marston NA, et al. Transcranial magnetic stimulation in the treatment of depression: a double-blind, placebo-controlled trial. Arch Gen Psychiatry 2003;60:1002–1008.
33. George MS, Lisanby SH, Avery D, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry 2010;67:507–516.
34. Avery DH, Holtzheimer PE, 3rd, Fawaz W, et al. A controlled study of repetitive transcranial magnetic stimulation in medication-resistant major depression. Biol Psychiatry 2006;59:187–194.
35. Schutter DJ. Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in double-blind sham-controlled designs: a meta-analysis. Psychol Med 2009;39:65–75.
36. Slotema CW, Blom JD, Hoek HW, Sommer IE. Should we expand the toolbox of psychiatric treatment methods to include Repetitive Transcranial Magnetic Stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders. J Clin Psychiatry 2010;71:873–884.
37. Berlim MT, van den Eynde F, Tovar-Perdomo S, Daskalakis ZJ. Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. Psychol Med 2014;44:225–239.
38. Berlim MT, van den Eynde F, Jeff Daskalakis Z. Clinically meaningful efficacy and acceptability of low-frequency repetitive transcranial magnetic stimulation (rTMS) for treating primary major depression: a meta-analysis of randomized, double-blind and sham-controlled trials. Neuropsychopharmacology 2013;38:543–551.
39. Eche J, Mondino M, Haesebaert F, et al. Low- vs high-frequency repetitive transcranial magnetic stimulation as an add-on treatment for refractory depression. Front Psychiatry 2012;3:13.
40. Fitzgerald PB, Hoy K, Daskalakis ZJ, Kulkarni J. A randomized trial of the anti-depressant effects of low- and high-frequency transcranial magnetic stimulation in treatment-resistant depression. Depress Anxiety 2009;26:229–234.
41. Isenberg K, Downs D, Pierce K, et al. Low frequency rTMS stimulation of the right frontal cortex is as effective as high frequency rTMS stimulation of the left frontal cortex for antidepressant-free, treatment-resistant depressed patients. Ann Clin Psychiatry 2005;17:153–159.
42. Rossini D, Lucca A, Magri L, et al. A symptom-specific analysis of the effect of high-frequency left or low-frequency right transcranial magnetic stimulation over the dorsolateral prefrontal cortex in major depression. Neuropsychobiology 2010;62:91–97.
43. Stern WM, Tormos JM, Press DZ, et al. Antidepressant effects of high and low frequency repetitive transcranial magnetic stimulation to the dorsolateral prefrontal cortex: a double-blind, randomized, placebo-controlled trial. J Neuropsychiatry Clin Neurosci 2007;19:179–186.
44. Herwig U, Fallgatter AJ, Hoppner J, et al. Antidepressant effects of augmentative transcranial magnetic stimulation: randomised multicentre trial. Br J Psychiatry 2007;191:441–448.
45. Loo CK, Mitchell PB, Croker VM, et al. Double-blind controlled investigation of bilateral prefrontal transcranial magnetic stimulation for the treatment of resistant major depression. Psychol Med 2003;33:33–40.
46. Hausmann A, Kemmler G, Walpoth M, et al. No benefit derived from repetitive transcranial magnetic stimulation in depression: a prospective, single centre, randomised, double blind, sham controlled "add on" trial. J Neurol Neurosurg Psychiatry 2004;75:320–322.
47. Gross M, Nakamura L, Pascual-Leone A, Fregni F. Has repetitive transcranial magnetic stimulation (rTMS) treatment for depression improved? A systematic review and meta-analysis comparing the recent vs. the earlier rTMS studies. Acta Psychiatr Scand 2007;116:165–173.
48. Pascual-Leone A, Rubio B, Pallardo F, Catala MD. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. Lancet 1996;348:233–237.
49. Fitzgerald PB, Huntsman S, Gunewardene R, et al. A randomized trial of low-frequency right-prefrontal-cortex transcranial magnetic stimulation as augmentation in treatment-resistant major depression. Int J Neuropsychopharmacol 2006;9:655–666.
50. Padberg F, Zwanzger P, Thoma H, et al. Repetitive transcranial magnetic stimulation (rTMS) in pharmacotherapy-refractory major depression: comparative study of fast, slow and sham rTMS. Psychiatry Res 1999;88:163–171.
51. Rossini D, Lucca A, Zanardi R, et al. Transcranial magnetic stimulation in treatment-resistant depressed patients: a double-blind, placebo-controlled trial. Psychiatry Res 2005;137:1–10.
52. O'Reardon JP, Solvason HB, Janicak PG, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry 2007;62:1208–1216.
53. Lepping P, Schonfeldt-Lecuona C, Sambhi RS, et al. A systematic review of the clinical relevance of repetitive transcranial magnetic stimulation. Acta Psychiatr Scand 2014;130:326–341.
54. Holtzheimer PE, 3rd, McDonald WM, Mufti M, et al. Accelerated repetitive transcranial magnetic stimulation for treatment-resistant depression. Depress Anxiety 2010;27:960–963.
55. Hadley D, Anderson BS, Borckardt JJ, et al. Safety, tolerability, and effectiveness of high doses of adjunctive daily left prefrontal repetitive transcranial magnetic stimulation for treatment-resistant depression in a clinical setting. J ECT 2011;27:18–25.
56. Carpenter LL, Janicak PG, Aaronson ST, et al. Transcranial magnetic stimulation (TMS) for major depression: a multisite, naturalistic, observational study of acute treatment outcomes in clinical practice. Depress Anxiety 2012;29:587–596.
57. Rohan ML, Yamamoto RT, Ravichandran CT, et al. Rapid mood-elevating effects of low field magnetic stimulation in depression. Biol Psychiatry 2014;76:186–193.
58. Carlezon WA, Jr., Rohan ML, Mague SD, et al. Antidepressant-like effects of cranial stimulation within a low-energy magnetic field in rats. Biol Psychiatry 2005;57:571–576.
59. Rohan M, Parow A, Stoll AL, et al. Low-field magnetic stimulation in bipolar depression using an MRI-based stimulator. Am J Psychiatry 2004;161:93–98.
60. Martiny K, Lunde M, Bech P. Transcranial low voltage pulsed electromagnetic fields in patients with treatment-resistant depression. Biol Psychiatry 2010;68:163–169.

61. Maeda F, Keenan JP, Tormos JM, et al. Interindividual variability of the modulatory effects of repetitive transcranial magnetic stimulation on cortical excitability. Exp Brain Res 2000;133:425–430.
62. Capocchi G, Zampolini M, Larson J. Theta burst stimulation is optimal for induction of LTP at both apical and basal dendritic synapses on hippocampal CA1 neurons. Brain Res 1992;591:332–336.
63. Larson J, Wong D, Lynch G. Patterned stimulation at the theta frequency is optimal for the induction of hippocampal long-term potentiation. Brain Res 1986;368:347–350.
64. Staubli U, Lynch G. Stable hippocampal long-term potentiation elicited by 'theta' pattern stimulation. Brain Res 1987;435:227–234.
65. Huang YZ, Edwards MJ, Rounis E, et al. Theta burst stimulation of the human motor cortex. Neuron 2005;45:201–206.
66. Hess G, Aizenman CD, Donoghue JP. Conditions for the induction of long-term potentiation in layer II/III horizontal connections of the rat motor cortex. J Neurophysiol 1996;75:1765–1778.
67. Urban J, Kossut M, Hess G. Long-term depression and long-term potentiation in horizontal connections of the barrel cortex. Eur J Neurosci 2002;16:1772–1776.
68. Huang YZ, Rothwell JC. The effect of short-duration bursts of high-frequency, low-intensity transcranial magnetic stimulation on the human motor cortex. Clin Neurophysiol 2004;115:1069–1075.
69. Heynen AJ, Bear MF. Long-term potentiation of thalamocortical transmission in the adult visual cortex in vivo. J Neurosci 2001;21:9801–9813.
70. Takita M, Izaki Y, Jay TM, et al. Induction of stable long-term depression in vivo in the hippocampal-prefrontal cortex pathway. Eur J Neurosci 1999;11:4145–4148.
71. Abraham WC, Huggett A. Induction and reversal of long-term potentiation by repeated high-frequency stimulation in rat hippocampal slices. Hippocampus 1997;7:137–145.
72. Rothkegel H, Sommer M, Paulus W. Breaks during 5Hz rTMS are essential for facilitatory after effects. Clin Neurophysiol 2010;121:426–430.
73. di Lazzaro V, Ziemann U. The contribution of transcranial magnetic stimulation in the functional evaluation of microcircuits in human motor cortex. Front Neural Circuits 2013;7:18.
74. Patton HD, Amassian VE. Single and multiple-unit analysis of cortical stage of pyramidal tract activation. J Neurophysiol 1954;17:345–363.
75. di Lazzaro V, Pilato F, Saturno E, et al. Theta-burst repetitive transcranial magnetic stimulation suppresses specific excitatory circuits in the human motor cortex. J Physiol 2005;565:945–950.
76. di Lazzaro V, Pilato F, Dileone M, et al. The physiological basis of the effects of intermittent theta burst stimulation of the human motor cortex. J Physiol 2008;586:3871–3879.
77. Hamada M, Murase N, Hasan A, et al. The role of interneuron networks in driving human motor cortical plasticity. Cereb Cortex 2013;23:1593–1605.
78. Trippe J, Mix A, Aydin-Abidin S, et al. Theta burst and conventional low-frequency rTMS differentially affect GABAergic neurotransmission in the rat cortex. Exp Brain Res 2009;199:411–421.
79. Benali A, Trippe J, Weiler E, et al. Theta-burst transcranial magnetic stimulation alters cortical inhibition. J Neurosci 2011;31:1193–1203.
80. Stagg CJ, Wylezinska M, Matthews PM, et al. Neurochemical effects of theta burst stimulation as assessed by magnetic resonance spectroscopy. J Neurophysiol 2009;101:2872–2877.
81. Thickbroom GW. Transcranial magnetic stimulation and synaptic plasticity: experimental framework and human models. Exp Brain Res 2007;180:583–593.
82. Xue JG, Masuoka T, Gong XD, et al. NMDA receptor activation enhances inhibitory GABAergic transmission onto hippocampal pyramidal neurons via presynaptic and postsynaptic mechanisms. J Neurophysiol 2011;105:2897–2906.
83. Huang YZ, Chen RS, Rothwell JC, Wen HY. The after-effect of human theta burst stimulation is NMDA receptor dependent. Clin Neurophysiol 2007;118:1028–1032.
84. Monte-Silva K, Ruge D, Teo JT, et al. D2 receptor block abolishes theta burst stimulation-induced neuroplasticity in the human motor cortex. Neuropsychopharmacology 2011;36:2097–2102.
85. Seamans JK, Yang CR. The principal features and mechanisms of dopamine modulation in the prefrontal cortex. Prog Neurobiol 2004;74:1–58.
86. Seamans JK, Gorelova N, Durstewitz D, Yang CR. Bidirectional dopamine modulation of GABAergic inhibition in prefrontal cortical pyramidal neurons. J Neurosci 2001;21:3628–3638.
87. Suppa A, Ortu E, Zafar N, et al. Theta burst stimulation induces after-effects on contralateral primary motor cortex excitability in humans. J Physiol 2008;586:4489–4500.
88. Gamboa OL, Antal A, Laczo B, et al. Impact of repetitive theta burst stimulation on motor cortex excitability. Brain Stimul 2011;4:145–151.
89. Cardenas-Morales L, Nowak DA, Kammer T, et al. Mechanisms and applications of theta-burst rTMS on the human motor cortex. Brain Topogr 2010;22:294–306.
90. Bunse T, Wobrock T, Strube W, et al. Motor cortical excitability assessed by transcranial magnetic stimulation in psychiatric disorders: a systematic review. Brain Stimul 2014;7:158–169.
91. di Lazzaro V, Dileone M, Pilato F, et al. Modulation of motor cortex neuronal networks by rTMS: comparison of local and remote effects of six different protocols of stimulation. J Neurophysiol 2011;105:2150–2156.
92. Hasan A, Hamada M, Nitsche MA, et al. Direct-current-dependent shift of theta-burst-induced plasticity in the human motor cortex. Exp Brain Res 2012;217:15–23.
93. Doeltgen SH, Ridding MC. Modulation of cortical motor networks following primed theta burst transcranial magnetic stimulation. Exp Brain Res 2011;215:199–206.
94. McAllister SM, Rothwell JC, Ridding MC. Selective modulation of intracortical inhibition by low-intensity theta burst stimulation. Clin Neurophysiol 2009;120:820–826.
95. Talelli P, Cheeran BJ, Teo JT, Rothwell JC. Pattern-specific role of the current orientation used to deliver theta burst stimulation. Clin Neurophysiol 2007;118:1815–1823.
96. Jacobs MF, Tsang P, Lee KG, et al. 30 Hz theta-burst stimulation over primary somatosensory cortex modulates corticospinal output to the hand. Brain Stimul 2014;7:269–274.
97. Brownjohn PW, Reynolds JN, Matheson N, et al. The effects of individualized theta burst stimulation on the excitability of the human motor system. Brain Stimul 2014;7:260–268.
98. Wu SW, Shahana N, Huddleston DA, Gilbert DL. Effects of 30Hz theta burst transcranial magnetic stimulation on the primary motor cortex. J Neurosci Methods 2012;208:161–164.
99. Goldsworthy MR, Pitcher JB, Ridding MC. A comparison of two different continuous theta burst stimulation paradigms applied to the human primary motor cortex. Clin Neurophysiol 2012;123:2256–2263.
100. Gamboa OL, Antal A, Moliadze V, Paulus W. Simply longer is not better: reversal of theta burst after-effect with prolonged stimulation. Exp Brain Res 2010;204:181–187.

101. Goldsworthy MR, Pitcher JB, Ridding MC. The application of spaced theta burst protocols induces long-lasting neuroplastic changes in the human motor cortex. Eur J Neurosci 2012;35:125–134.
102. Huang YZ, Rothwell JC, Lu CS, et al. The effect of continuous theta burst stimulation over premotor cortex on circuits in primary motor cortex and spinal cord. Clin Neurophysiol 2009;120:796–801.
103. Koch G, Mori F, Marconi B, et al. Changes in intracortical circuits of the human motor cortex following theta burst stimulation of the lateral cerebellum. Clin Neurophysiol 2008;119:2559–2569.
104. Grossheinrich N, Rau A, Pogarell O, et al. Theta burst stimulation of the prefrontal cortex: safety and impact on cognition, mood, and resting electroencephalogram. Biol Psychiatry 2009;65:778–784.
105. Hubl D, Nyffeler T, Wurtz P, et al. Time course of blood oxygenation level-dependent signal response after theta burst transcranial magnetic stimulation of the frontal eye field. Neuroscience 2008;151:921–928.
106. Ko JH, Monchi O, Ptito A, et al. Theta burst stimulation-induced inhibition of dorsolateral prefrontal cortex reveals hemispheric asymmetry in striatal dopamine release during a set-shifting task: a TMS-[(11)C]raclopride PET study. Eur J Neurosci 2008;28:2147–2155.
107. Mochizuki H, Furubayashi T, Hanajima R, et al. Hemoglobin concentration changes in the contralateral hemisphere during and after theta burst stimulation of the human sensorimotor cortices. Exp Brain Res 2007;180:667–675.
108. Tupak SV, Dresler T, Badewien M, et al. Inhibitory transcranial magnetic theta burst stimulation attenuates prefrontal cortex oxygenation. Hum Brain Mapp 2013;34:150–157.
109. Nyffeler T, Cazzoli D, Hess CW, Muri RM. One session of repeated parietal theta burst stimulation trains induces long-lasting improvement of visual neglect. Stroke 2009;40:2791–2796.
110. Chung HK, Tsai CH, Lin YC, et al. Effectiveness of theta-burst repetitive transcranial magnetic stimulation for treating chronic tinnitus. Audiol Neurootol 2012;17:112–120.
111. Soekadar SR, Arfeller C, Rilk A, et al. Theta burst stimulation in the treatment of incapacitating tinnitus accompanied by severe depression. CNS Spectr 2009;14:208–211.
112. Antal A, Paulus W. Effects of transcranial theta-burst stimulation on acute pain perception. Restor Neurol Neurosci 2010;28:477–484.
113. Holzer M, Padberg F. Intermittent theta burst stimulation (iTBS) ameliorates therapy-resistant depression: a case series. Brain Stimul 2010;3:181–183.
114. Li CT, Chen MH, Juan CH, et al. Efficacy of prefrontal theta-burst stimulation in refractory depression: a randomized sham-controlled study. Brain 2014;137:2088–2098.
115. Plewnia C, Pasqualetti P, Grosse S, et al. Treatment of major depression with bilateral theta burst stimulation: a randomized controlled pilot trial. J Affect Disord 2014;156:219–223.
116. Sweeney JA, Strojwas MH, Mann JJ, Thase ME. Prefrontal and cerebellar abnormalities in major depression: evidence from oculomotor studies. Biol Psychiatry 1998;43:584–594.
117. Franke P, Maier W, Hardt J, et al. Assessment of frontal lobe functioning in schizophrenia and unipolar major depression. Psychopathology 1993;26:76–84.
118. Grimm S, Beck J, Schuepbach D, et al. Imbalance between left and right dorsolateral prefrontal cortex in major depression is linked to negative emotional judgment: an fMRI study in severe major depressive disorder. Biol Psychiatry 2008;63:369–376.
119. Chistyakov AV, Rubicsek O, Kaplan B, et al. Safety, tolerability and preliminary evidence for antidepressant efficacy of theta-burst transcranial magnetic stimulation in patients with major depression. Int J Neuropsychopharmacol 2010;13:387–393.
120. Fitzgerald PB, Benitez J, de Castella A, et al. A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. Am J Psychiatry 2006;163:88–94.
121. Rossi S, Hallett M, Rossini PM, et al. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 2009;120:2008–2039.
122. Oberman L, Edwards D, Eldaief M, Pascual-Leone A. Safety of theta burst transcranial magnetic stimulation: a systematic review of the literature. J Clin Neurophysiol 2011;28:67–74.
123. Oberman LM, Pascual-Leone A. Report of seizure induced by continuous theta burst stimulation. Brain Stimul 2009;2:246–247.
124. Wu SW, Shahana N, Huddleston DA, et al. Safety and tolerability of theta-burst transcranial magnetic stimulation in children. Dev Med Child Neurol 2012;54:636–639.

CHAPTER FOUR

TMS-EEG and its utility in tracking neuromodulatory changes

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Preamble to review paper

In the previous chapter (Chapter 3), TBS and its potential use in the treatment of depression were introduced. The constraints in the wide use of this technique in clinical settings are due in part to the limited knowledge of the effect of TBS in the prefrontal cortex. Advances in methodological techniques, such as TMS-EEG, have recently allowed for in-depth exploration of the effect of NIBS in non-motor brain regions. In the following published review paper, an overview is provided of the cortical properties that can be assessed using TMS-EEG. The review also discusses studies to date that have used this technique to probe the changes resulting from different neuromodulatory paradigms to examine the utility of the method and to predict anticipated outcomes.

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Review

Measuring Brain Stimulation Induced Changes in Cortical Properties Using TMS-EEG

Sung Wook Chung [a], Nigel C. Rogasch [b], Kate E. Hoy [a], Paul B. Fitzgerald [a,*]

[a] Monash Alfred Psychiatry Research Centre, Central Clinical School, The Alfred and Monash University, Melbourne, Australia
[b] Brain and Mental Health Laboratory, School of Psychological Sciences and Monash Biomedical Imaging, Monash University, Melbourne, Australia

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ABSTRACT

Neuromodulatory brain stimulation can induce plastic reorganization of cortical circuits that persist beyond the period of stimulation. Most of our current knowledge about the physiological properties has been derived from the motor cortex. The integration of transcranial magnetic stimulation (TMS) and electroencephalography (EEG) is a valuable method for directly probing excitability, connectivity and oscillatory dynamics of regions throughout the brain. Offering in depth measurement of cortical reactivity, TMS-EEG allows the evaluation of TMS-evoked components that may act as a marker for cortical excitation and inhibition. A growing body of research is using concurrent TMS and EEG (TMS-EEG) to explore the effects of different neuromodulatory techniques such as repetitive TMS and transcranial direct current stimulation on cortical function, particularly in non-motor regions. In this review, we outline studies examining TMS-evoked potentials and oscillations before and after, or during a single session of brain stimulation. Investigating these studies will aid in our understanding of mechanisms involved in the modulation of excitability and inhibition by neuroplasticity following different stimulation paradigms.

Introduction

Neuromodulatory brain stimulation can induce plastic reorganization of cortical circuits which persist beyond the period of stimulation [1]. A variety of neuromodulation techniques are currently used to modulate brain activity, the most common of which are repetitive Transcranial Magnetic Stimulation (rTMS) and transcranial Direct Current Stimulation (tDCS). Traditionally measuring the cortical effect of these techniques has been restricted to the motor cortex, namely due to the easily measureable output of motor evoked potentials (MEPs) which occurs in response to single and paired pulse TMS. As such there is a large body of existing work which has used this non-repetitive TMS over the motor cortex to track changes in cortical activity resulting from neuromodulatory brain stimulation paradigms, specifically looking at corticomotor excitability and cortical inhibition [2–5]. To expand the brain regions and range of variables that can be measured before and after neuromodulation, researchers have increasingly combined this single and paired pulse TMS with electroencephalogram (EEG). Concurrent use of TMS and EEG (TMS-EEG) allows a method for probing varied superficial cortical brain regions to study intracortical neural circuits [6]. Furthermore, TMS-EEG captures additional cortical properties such as the generation of oscillatory brain activity and the propagation of signals to other cortical regions [7]. In this review, we summarize the impact of the most commonly applied neuromodulatory techniques on motor cortical excitability determined using MEPs. We then examine the cortical properties that can be assessed using TMS-EEG and explore how these measures compliment and extend information gained from MEPs. Finally, we outline the studies that have used this approach to assess changes in cortical properties resulting from neuromodulatory paradigms in both motor and non-motor regions, particularly looking at TMS-evoked potentials (TEPs) and oscillations before and after, or during one single session of brain stimulation.

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* Corresponding author. Monash Alfred Psychiatry Research Centre, Level 4, 607 St Kilda Road, Melbourne, Victoria 3004, Australia. Tel.: +61 3 9076 6552; fax: +61 3 9076 8545.
E-mail address: paul.fitzgerald@monash.edu (P.B. Fitzgerald).

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Effects of neuromodulatory brain stimulation on brain function

Neuromodulatory paradigms can influence neural activity in humans in different ways, either increasing or decreasing cortical excitability depending on the stimulation parameters [8–11]. This unique ability to safely modulate cortical activity has led to many experimental and therapeutic applications using these techniques. However, inter-individual variability and state-dependency of neuromodulatory brain stimulation approaches need to be taken into account when efficacy and reliability of these paradigms are investigated [12]. In this section, we briefly overview the effects of four of the main neuromodulatory brain stimulation paradigms on corticomotor excitability derived from motor cortex studies using MEPs as the outcome measure.

rTMS

TMS can be used either to measure cortical properties, including excitation and inhibition, or temporarily alter the organization of cortical circuits [13]. When TMS is given repetitively, it has been shown to have a neuromodulatory effect. Repetitive TMS involves delivery of repeated single pulse stimulation to a specific brain region [14], and has been shown to alter cortical excitability that outlasts the period of the stimulation [9]. Depending on the frequency of stimulation, the after-effects can either increase or decrease cortical excitability [15]. However, these outcomes can vary between subjects, and can be affected by the initial activation state of the targeted neural population [16]. Despite intra- and interindividual variability of responses to rTMS [17], low-frequency rTMS (~1 Hz) has been shown to reduce cortical excitability, while high-frequency rTMS (5–20 Hz) has shown to increase excitability [18]. Believed to mimic the effects of long-term potentiation (LTP) and long-term depression (LTD), rTMS has been used both to study plasticity and as a therapeutic tool in various neurological and psychiatric disorders [19–22].

TBS

Theta burst stimulation (TBS) is a modified form of rTMS, involving pulses applied in bursts of three at 50 Hz with an interburst interval at 5 Hz [8]. Two different paradigms of TBS are commonly used; continuous TBS (cTBS), and intermittent TBS (iTBS). Briefly, cTBS involves either 300 or 600 pulses of uninterrupted TBS delivery, and has shown to reduce cortical excitability for up to 60 min. Intermittent TBS comprises of 2 s of TBS trains repeated every 10 s, with a total number of 600 pulses applied, and has shown to increase cortical excitability for at least 15 min [8]. Even though relatively reproducible effects of iTBS [23] and cTBS [24] have been described, variable effects between subjects have also been demonstrated [25]. Nevertheless, due to shorter duration of stimulation (1–3 min) and lower intensity used compared to conventional rTMS, TBS may prove to be more effective way of modifying brain activity. TBS has been employed with therapeutic intent, but widespread use of clinical use of TBS is yet to emerge [26].

PAS

Paired associative stimulation (PAS) protocols consist of pairing of electrical stimulation of median nerve and cortical TMS over the contralateral motor cortex (M1) [11]. Effects resembling spike-time dependent plasticity (STDP), LTD-like or LTP-like plasticity of corticospinal neurons are observed depending on the interstimulus interval (ISI) of the paired stimulation [27]. PAS with ISI of 10 ms has shown to reduce cortical excitability, and ISI of 25 ms has shown to increase cortical excitability [28]. Bidirectional Hebbian-like plasticity has also been displayed between interconnected cortical areas [29,30]. Similar to other neuromodulatory paradigms, inter-individual variability and age-dependency of PAS have been described [31].

tDCS

Plastic reorganization can also be induced by passing a small current across the scalp, a brain stimulation method known as transcranial direct current stimulation. The underlying mechanisms resulting in changes from tDCS are different to that of TMS. Unlike TMS, tDCS modulates the likelihood of neural firing by changing neuronal membrane potentials [32]. tDCS involves delivery of a weak current (1 or 2 mA) to the scalp with a pair of electrodes, inducing subthreshold modulation of resting membrane potential [33]. Depending on the polarity of the current flow, stimulation intensity and duration, tDCS can lead to increase or decrease in cortical excitability [34]. Anodal tDCS, which involves placing the anode over the stimulation target and the cathode to a reference site, has shown to increase cortical excitability under the anode. On the other hand, cathodal tDCS employs the opposite arrangement to the anodal tDCS, and has shown to reduce cortical excitability at the site of cathodal stimulation [35]. tDCS is attracting considerable research attention as a technique for potentially improving aspects of cognition such as learning, memory, attention and decision-making [37–41]. In addition, tDCS has demonstrated potential therapeutic effects in neurological [42,43] and psychiatric conditions [44,45]. However, a recent meta-analysis has reported that tDCS does not produce reliable changes in many of these measures (with the exception of MEP sizes), bringing into question the general efficacy of the technique [36]. Therefore, further studies directly assessing the neural and behavioral effects of tDCS in non-motor regions are required.

Combining TMS and EEG to measure cortical properties

Despite the wealth of information gained from motor cortex studies on neuromodulatory brain stimulation, recordings of TMS-induced physiological effects (e.g. muscle twitch and MEPs) have not traditionally been accessible in non-motor cortical regions. In brain regions other than motor cortex, other measurable effects such as the perception of phosphenes with TMS [46] and behavioral outcome (task performance) have been investigated although these effects can be limited by either subjectivity or variable effects. A growing body of research is now exploring the after-effects of different neuromodulation techniques by recording EEG concurrently to TMS [29,47–49].

EEG is a commonly-used technique which measures the electrical activity of neurones and allows for non-invasive measurement of spontaneous and event-related brain activity from the entire surface of the brain [50]. Electrophysiological responses induced by a single pulse TMS can be illustrated with waveforms and topographic representation of TMS-evoked potentials (TEPs), providing a direct measure of brain activity [51]. This measure is cortical in nature and not influenced by non-cortical confounds such as spinal cord excitability, which can limit MEP-based measures of cortical excitability. In addition to being able to look at TEPs in non-motor brain regions, the combination of TMS with EEG also allows for more detailed assessment of cortical activity, specifically 1) cortical excitation/inhibition balance by measuring TEPs, 2) cortical connectivity by analyzing that spatiotemporal propagation of activity following TMS and 3) the intrinsic ability of the stimulated region to generate oscillatory activity (Fig. 1).

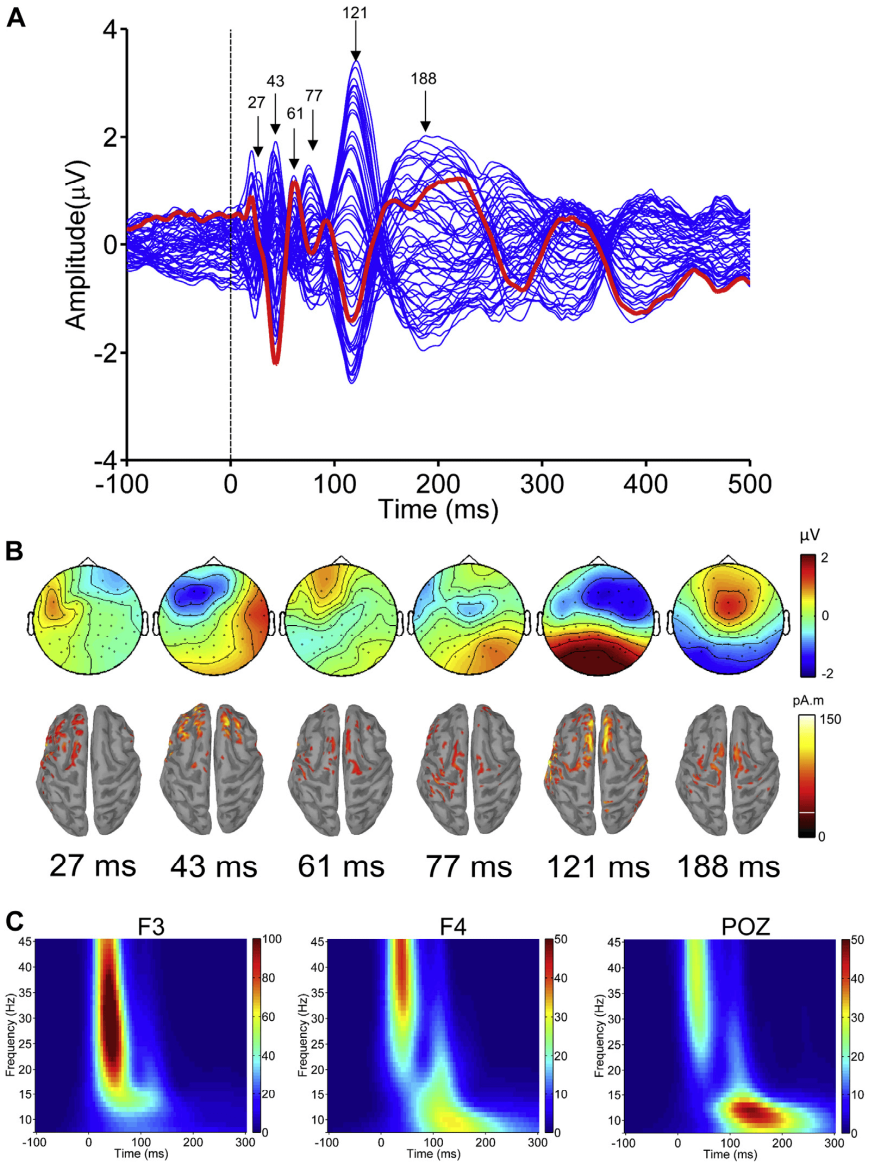

Figure 1. TMS-evoked cortical activity following stimulation of the left dorsolateral prefrontal cortex. A) TMS-evoked potentials from all electrodes averaged across 30 participants. The red line represents the electrode under the coil. B) TMS-evoked cortical connectivity measured by assessing the spatiotemporal propogation of activity following TMS both on the scalp (upper topoplots) and following source reconstruction (bottom plots). C) TMS-evoked oscillatory activity measured from three different electrodes. (Adapted from NeuroImage, 1(101), Rogasch et al., Removing artefacts from TMS-EEG recordings using independent component analysis: importance for assessing prefrontal and motor cortex network properties, 425-39, Copyright (2014), with permission from Elsevier.) (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

TMS-evoked potentials

TEPs represent shifts in the inhibition-excitation balance in cortical circuits following a single TMS pulse [52]. Several studies have shown that TEPs are highly reproducible over time and are sensitive to changes in stimulation parameters such as intensity, location, coil angle and current direction [29,53–59]. TEPs following stimulation of the motor cortex consist of a series of negative and positive deflections lasting up to 300 ms, and these peaks are usually defined as N15, P30, N45, P55, N100, P180 and N280 [60]. Studies have suggested that early peaks reflect excitatory activity due to a positive correlation between peak-to-peak amplitude of N15–P30 component and MEP amplitude [61–63], and that N15–P30 amplitude varies depending on the angle of the TMS coil [53]. Premoli and colleagues (2014) [64] demonstrated that the generation of N45 potential is mediated by activation of

gamma-aminobutryic acid (GABA)–A receptor, and N100 potential by GABA-B activity. Initially, N100 and P180 were believed to be associated with coil click sound [62]. Studies using sound masking protocol (e.g. white noise) have found that cortical activation by TMS contribute to the change in amplitude of N100–P180 complex [65–67]. Several studies have now identified the N100 component to be linked to cortical inhibitory processes [62,63,65,68–70]. Peaks with similar latencies have also been observed from non-motor regions. The physiological origin and functional significance of peaks from non-motor regions are yet to be fully elucidated, although the N100 over prefrontal cortex is also consistent with GABA-B mediated inhibition [70,71]. Modulation of short-latency potentials (P5 and P8) have recently been described to evaluate the reactivity of the stimulated cortex [72,73], but is still in debate as these peaks possibly reflect muscle artifacts [74,75].

TMS-evoked connectivity

Analyzing the latencies and cortical distribution of TEPs, either on the scalp or by using source localization can be used to infer the propagation of activity from the site of stimulation to anatomically connected regions [53,76]. Ipsilateral spreading via association fibers and contralateral propagation through transcallosal and subcortical pathways have been described in various studies [6,56,62,77,78], allowing the investigation of cortico-cortical and cortico-subcortical interactions. A recent diffusion tensor imaging study supported transcallosally mediated TMS-induced inter-hemispheric signal propagation, suggesting that the corpus callosum is involved in the spreading of cortical potentials, and the level of activation is dependent on the intensity of TMS [79].

TMS-evoked oscillations

TMS-evoked responses can also be examined in the frequency domain, revealing information on the intrinsic ability of the stimulated region to generate or entrain oscillations in discrete frequency bands [49,80–84]. Such synchronous activity of neurons in specific rhythms are fundamental for neuronal network communication and information processing [85]. The oscillatory patterns are categorized into bands of frequencies based on the physiological properties, ranging from delta to gamma (delta (0–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz) and gamma (30–70 Hz)) [86]. Delta-band oscillations are prominent in sleep [87], and are linked to motivational drive [88,89]. Theta waves are associated with memory processes [90], and alpha waves are involved in cognitive inhibition [91]. In early studies, alpha-band oscillations were believed to originate from idle brain regions [92]. However, recent studies have proposed alpha to reflect functional inhibition via event-related synchronization, instead of neural inactivity [91,93,94]. Beta-band oscillations are prominent during normal state of wakefulness with open eyes, and are associated with motor control [95,96]. Lastly, gamma-band oscillations are involved in a variety of behavioral components, such as working-memory [97], visual perception [98] and attention [99]. Reduced gamma oscillations have been described in the frontal cortex in schizophrenia patients using TMS-EEG [100,101].

Single-pulse TMS over motor cortex can lead to a brief period of synchronization in beta bands which are thought to reflect a phase-resetting of ongoing oscillations which are amplified by the thalamus [81,84]. In addition, natural frequency preservation of each cortical area has been demonstrated. Stimulation of different cortical regions results in oscillations at different frequencies – alpha-band oscillations (8–12 Hz) in the occipital cortex, beta-band oscillations (13–20 Hz) in the parietal cortex, and fast beta/gamma-band oscillations (21–50 Hz) in the frontal cortex [82], which may provide a guideline to explore the physiological mechanisms involved in generation of oscillations. Therefore, concurrent use of TMS and EEG offers dynamic measures of brain responses and functionality both in healthy and pathological conditions.

Probing brain stimulation-induced changes in cortical properties using TMS-EEG

As described above, TMS-EEG provides additional information on cortical properties than studies of only motor cortex output. Cortical reactivity can also be explored in depth by investigating changes in latency, amplitude, distribution and waveforms of TEPs, which can act as quantifiable markers in a similar manner to MEPs, allowing study of cortical properties outside of the motor cortex. The plasticity inducing properties of non-invasive brain stimulation allows temporary modification of cortical activity in a targeted brain region, which then can be propagated to induce remote or global changes in excitability [102–104]. Different measures are used in different studies and indexes of global and local cortical excitability can be determined by examining: (1) local TEPs with peaks measured from single electrodes, (2) global TEPs with peaks measured using Global Mean Field Power (GMFP) analysis, and (3) TMS-evoked oscillations. To date, a limited number of studies have looked at the excitability changes following neuromodulatory paradigms using TMS-EEG, with rTMS studied the most.

Effects of rTMS using TMS-EEG

Investigation of the direct effects of neuromodulation on cortical excitability using TMS-EEG can be approached using two methods; (1) off-line method with single pulse TMS-EEG recorded before and after neuromodulation to examine the short-term and long-term after-effects, and (2), on-line method with EEG recorded during modulation to examine the on-going TMS-evoked changes. Below we review studies of both off-line and on-line methods for low frequency and high frequency rTMS. The reviewed studies are further summarized in Table 1.

Effects of low frequency rTMS

Recently, Casula and colleagues (2014) [105] showed a site-specific modulation in excitability using single pulse TMS-EEG measured only from M1 when 1 Hz rTMS was applied on both M1 and primary visual cortex (V1). Increases in the amplitude of the P60 and N100 TEPs was seen with M1 stimulation but not V1, and sustained increase in the late local TEPs was more pronounced in the same hemisphere [105], suggesting that 1 Hz rTMS increases inhibitory drive.

Helfrich and colleagues (2012) [47] reported what appears to be a contradictory finding in children with attention deficit hyperactivity disorder (ADHD), observing a reduction in the TMS-evoked N100 amplitude following 1 Hz rTMS over M1. On-line analysis during the study showed a more pronounced decrease in N100 amplitude during the first half of 900 rTMS pulses, and demonstrated a saturation effect of rTMS on cortical excitability [47]. There may be a limit to pulses applied for maximal excitability change at a given time, and an exploration of optimal parameters would allow for more systemic assessment and comparison. A limitation of this study was having no active auditory masking (i.e. white noise) as such auditory evoked potentials may have masked the N100 TEP [67,106,107]. However, reduction in amplitude of N100 has been illustrated in other recent TMS-EEG studies on children with ADHD compared to healthy individuals [108,109], with this finding possibly reflecting the pathophysiology of the illness. In conjunction with direct evidence linking N100 component to GABA-B

Table 1
TMS-EEG measuring neural plasticity pre/post (off-line) and during (on-line) rTMS.

Neuro-modulation	Authors	Subjects	Stimulation parameters	EEG recording	Measurement (examined TEPs)	After effects
rTMS (LF-rTMS)	Van Der Werf and Paus (2006) [84]	$N = 12$ Mean age: 29.4 Healthy	M1 (left) & Dorsal Premotor Cortex (Left) 0.6 Hz, 90% rMT, 560 pulses (15 min)	M1 (left) spTMS (Pre & Post rTMS at 0, 10, 20 & 30 min) ISI: 4–6 s 115% rMT, 50 pulses 8 scalp channels Auditory masking: white noise (80 dB)	Global TEPs (P30, N45, N100, P200) TMS-evoked oscillations	↓ N45 following M1 rTMS but NOT PMC stimulation – Reduction at 0 min before returning to baseline (10 min), and increasing (20 & 30 min) ↓ amplitude of theta oscillation after both M1 and PMC conditioning
	Brignani et al. (2008) [80]	$N = 6$ Mean age: 34 Healthy	M1 (left) 1 Hz, 110% rMT, 600 pulses (10 min)	On-line (During rTMS) 19 scalp channels Auditory masking: Earplugs	TMS-evoked oscillations	↑ power synchronization in the alpha band from 1st to 3rd block of stimulation, and inversely correlated with MEPs amplitude. 1st block: 1–200 pulses 2nd block: 201–400 pulses 3rd block: 401–600 pulses
	Helfrich et al. (2012) [47]	$N = 25$ Mean age: 11.0 ADHD	M1 (left) 1 Hz, 80% rMT, 900 pulses (15 min)	On-line (During rTMS) & M1 (left) spTMS (Pre & Post rTMS) ISI: 6–10 s 110% rMT, 20 pulses 64 scalp channels Auditory masking: Hearing protection	Local TEPs (N100)	↓ N100 amplitude following rTMS (more pronounced decrease during the first half) but not with sham
	Veniero et al. (2012) [73]	$N = 13$ Age: 18–30 Healthy	M1 (left) & PMC (left) 1 Hz, 70% rMT, 900 pulses (3 × 300 pulses with 1 min interval)	M1 (left) spTMS (Pre & Post rTMS) ISI: 1.4–5 s 110% rMT, 200 pulses 70 scalp channels Auditory masking: earplugs	Local TEPs (P5, N8)	Group analysis showed no significance. ↓ amplitude of P5 & N8 in 6 participants, ↑ in 2 participants after PMC conditioning (but not M1 conditioning) ↓ P5 & N8 amplitude showed ↑ MEPs ↑ P5 & N8 amplitude showed ↓ MEPs
	Casula et al. (2014) [105]	$N = 15$ Mean age: 25 Healthy	M1 (left) and V1 (left) 1 Hz, 90% rMT, 1200 pulses (20 min)	M1 (left) spTMS (Pre & Post rTMS) ISI: 4–6 s 120% rMT, 50 pulses 31 scalp channels Auditory masking: white noise (~90 dB)	Local TEPs (P30, N45, P60, N100, P180)	↑ amplitude of P60 & N100 after M1 conditioning (but not V1 conditioning) Sustained ↑ in the late TEPs, especially in the stimulated hemisphere
rTMS (HF-rTMS)	Esser et al. (2006) [113]	$N = 7$ Mean age: 26 Healthy	M1 (left) 5 Hz, 90% rMT, 1500 pulses (50 pulses in 10 s burst, 6 bursts a train with 5 s interval, 5 trains in total with 60 s interval)	M1 (left) spTMS (Pre & Post rTMS) ISI: 0.5–0.7 s 90% rMT, 200 pulses 60 scalp channels Auditory masking: white noise (~90 dB)	Global TEPs (~5, ~18, ~35, ~55, ~84 ms)	↑ EEG response following rTMS – Significant at 2nd (~18 ms), 3rd (~35 ms) and 4th (~55 ms) peak in premotor cortex, bilaterally.
	Veniero et al. (2010) [72]	$N = 16$ Mean age: 23.4 Healthy	M1 (left) 20 Hz, 100% rMT, 400 pulses (10 pulses per train, 40 trains total with 14.55 s inter-train interval)	On-line (During rTMS) 29 scalp channels Auditory masking: white noise (~90 dB)	Local TEPs (P5, N8, P30, N45)	↑ amplitude and ↓ latency in early TMS-evoked responses (P5 & N8), but no significant change in P30 or N45
	Hamidi et al. (2010) [114]	$N = 16$ Mean age: 22.5 Healthy	SPL (left) & PCG (left) 10 Hz, 110% rMT, 2880 pulses (30 pulses per train with minimum of 17.1 s inter-train interval)	On-line (During rTMS) 60 scalp channels Auditory masking: white noise	Global TEPs (~4, ~26, ~42, ~60, ~84 ms)	A series of 5 evoked brain potentials occurring at approximately 4, 26, 42, 60 & 84 ms after each TMS pulse Except for the 1st peak, amplitude of TMS-evoked response ↓ and ↑ during a train (quadratic relationship), at both SPL and PCG.

ADHD – Attention deficit hyperactivity disorder; EEG – Electroencephalogram; ISI – Interstimulus interval; LF/HF – Low/high frequency; M1 – Primary motor cortex; MEPs – Motor evoked potentials; PCG – Postcentral gyrus; PMC – Premotor area; rMT – Resting motor threshold; rTMS – Repetitive transcranial magnetic stimulation; SPL – Superior parietal lobule; spTMS – Single-pulse TMS; TEPs – TMS-evoked potentials; V1 – Primary visual cortex.

mediated inhibition [63,64,70], TMS-evoked N100 may be a reliable marker for cortical inhibition.

Another on-line study by Brignani and colleagues (2008) [80] showed that 1 Hz rTMS on M1 increased even-related alpha and beta synchronization, preferentially in the stimulated hemisphere. The modulation in alpha oscillations increased with duration of stimulation and was inversely correlated with MEPs amplitude [80], possibly reflecting another marker for cortical inhibition using TMS-EEG. It is worth noting that alpha oscillations (~10 Hz) and the N100 (peak at 100 ms – i.e. one 10 Hz cycle) may reflect similar mechanisms.

With respect to off-line studies, Van Der Werf and Paus (2006) [84] applied 0.6 Hz rTMS over both primary motor cortex (M1) and dorsal premotor cortex (PMC) in separate sessions, and recorded changes in cortical excitability following rTMS using single-pulse TMS-EEG over M1. There was a decrease in the N45 component of TMS-evoked response immediately after M1 rTMS and returned to baseline 10-min post stimulation [84]. No change in M1 was observed after PMC conditioning, demonstrating a site-specific TMS-EEG response, even though other rTMS studies stimulating PMC showed changes in M1 excitability [110–112]. M1 and PMC rTMS resulted in the reduction of theta oscillation amplitudes in this study, which was regarded as an auditory habituation to the click of single-pulse TMS. Despite TMS-EEG studies in deaf showing the presence of an N100 component [66,67], modulation of N100 was interpreted as an auditory neural response to the TMS coil click [84]. This, together with using different stimulation frequency (0.6 Hz) may explain the discrepancy in results from the study done by Casula and colleagues (2014) [105].

Veniero and colleagues (2012) [73] examined the modulation in short-latency TMS-evoked potentials using single-pulse TMS-EEG over M1 before and after 1 Hz rTMS was applied on both M1 and PMC in separate sessions, but no statistically significant differences in the amplitudes of both MEPs and TEPs were observed with either type of stimulation. However, single subject analysis showed a reduction in peak-to-peak amplitude of the P5-N8 complex after PMC conditioning, which was negatively correlated with MEP amplitude changes [73]. Even though these early TEP components may be informative for cortical excitability changes, one should be cautious on interpreting the results, as P5-N8 complex has been shown to largely reflect muscular activation [74,75].

Effects of high frequency rTMS

Esser and colleagues (2006) [113] recorded single-pulse TMS-EEG before and after the application of high frequency 5 Hz rTMS to left M1. Source localization revealed predominant activation in premotor cortex which suggests that connections between M1 and premotor cortex were strengthened. Global TEPs showed significant increase in TMS-evoked responses following 5 Hz rTMS compared to sham, except for the first peak (~5 ms) and the last peak (~84 ms) [113]. It was suggested that first peak primarily corresponded to motor cortical activity where no potentiation was observed, and late component may result from different sources than the earlier components [113]. Similar results were seen with Hamidi and colleagues (2010) [114], when 10 Hz rTMS was applied to both superior parietal lobule (SPL) and postcentral gyrus (PCG) while EEG was recorded simultaneously. This on-line analysis showed amplitude changes in both stimulated area in TMS-evoked peaks (4, 26, 42, 60, and 94 ms post-pulse) with exception to the first peak in global field power [114]. Another on-line study using 20 Hz rTMS by Veniero and colleagues (2010) [72] reported a contradictory finding, showing increased amplitudes in early peaks (P5 & N8) of TMS-evoked response, but not in the later peaks (P30 & N45). This is particularly interesting because high-frequency rTMS paradigms induce cortical potentiation, but different frequencies result in different on-line effects on TEPs. The two paradigms might result in a similar cumulative effect on cortical excitability through different interacting mechanisms. However, given insufficient number of studies, it is too early to speculate on the exact mechanism or specific neuronal populations that are involved in eliciting cortical excitability using different frequency, and further studies are required to contrast different stimulation protocols.

Effects of other modulatory techniques using TMS-EEG

There are only a few studies exploring the effects of other neuromodulation techniques using TMS-EEG, and this makes direct comparison problematic. More studies of this nature would allow for more systemic analysis of temporal variation and spatial distribution of TMS-evoked responses and aid in better understanding of physiological changes with different modulation paradigms. We review the research that has been conducted below, with the studies further summarized in Table 2.

PAS

Huber and colleagues (2008) [115] demonstrated changes in amplitude of global TEPs following two different forms of PAS on M1 that correlated with MEPs. PAS ISI 10 ms showed significant change at 75 ms post-pulse, and PAS ISI 25 ms at 70, 84, 139 and 168 ms post-pulse. The authors noted that the correlation was weak and MEPs may not be considered the only indicator of cortical excitability change [115]. Similar to interindividual variability seen in MEPs amplitude, TMS-evoked responses measured using EEG also showed variability after PAS. However, PAS resulted in both local and contralateral changes in the amplitude of TMS-evoked responses that indicated change in sensorimotor excitability [115].

Rajji and colleagues (2013) [116] recently showed PAS-induced potentiation of cortical-evoked activity on Dorsolateral Prefrontal Cortex (DLPFC), which was site and frequency specific. Frequency-specific potentiation of cortical excitability was demonstrated within gamma, theta as well as delta frequency bands, but not within the alpha and beta bands. Modulation of theta and gamma coupling shown in this study suggested PAS-induced potentiation produces synaptic effect and may have an impact on a wide range of cognitive functions [116].

Veniero and colleagues (2013) [29] showed increased connectivity in alpha and beta bands between posterior parietal cortex (PPC) and M1 following cortico-cortical PAS. Three different PAS methods with 5 ms interval were used in separate sessions: (1) PPC following M1, (2) PPC preceding M1, and (3) PPC following M1 (with different coil angle). Single-pulse TMS-EEG was recorded before and after each stimulation at both sites. Spread of activation was more evident after M1 stimulation, including contralateral site, and lack of PPC response to PAS was postulated to be affected by insufficient stimulation intensity and target-dependent modulation [29]. Nonetheless, global TEPs amplitude revealed modulation of M1 reactivity, particularly in peak 1 (~20 ms) and peak 4 (~175 ms), and the ability to selectively manipulate the functional connectivity between two cortical regions was demonstrated [29].

TBS

To date, only one study has investigated the effect of TBS using concurrent TMS-EEG. Vernet and colleagues (2013) [49] used a slightly modified cTBS protocol from the original paradigm and applied this to the motor cortex. Inhibition of P30 TEPs was observed, which was closely related to the changes in MEPs, and low variance to individual TEPs was discussed. A combination of the

Table 2
TMS-EEG measuring neural plasticity pre/post (off-line) and during (on-line) other modulation techniques.

Neuro-modulation	Authors	Subjects	Stimulation parameters	EEG recording	Measurement (examined TEPs)	After effects
PAS	Huber et al. (2008) [115]	$N = 19$ Mean age: 25.2 Healthy	90 stimuli of right median nerve at the wrist (0.5 ms) M1 (left) 130% rMT, every 15 s ISI: 10 ms & 25 ms (22.5 min)	M1 (left) spTMS (Pre & Post PAS) ISI: 0.5–0.7 s 90% rMT, 200 pulses 60 scalp channels Auditory masking: Noise masking	Global TEPs (~32, ~74, ~138, ~170 ms)	Distinct peaks with similar latencies (~32, ~74 & ~170 ms): ↑ amplitude after PAS ISI 25 ms ↓ amplitude after PAS ISI 10 ms Local and contralateral site
	Rajji et al. (2013) [116]	$N = 15$ Age: 18–50 Healthy	180 stimuli of right median nerve DLPFC (left) Intensity needed for MEP amplitude of 1 mV (SI_{1mv}), every 10 s ISI: 25 ms (15 subjects) & 100 ms (9 control subjects) (30 min)	DLPFC (left) spTMS (Pre & Post PAS at 0, 15 & 30 min) ISI: 10 s SI_{1mv}, 100 pulses 64 scalp channels	– TMS-evoked oscillations	↑ cortical-evoked activity after PAS (25 ms) at the target site and across left frontal area, but not contralaterally or globally Potentiation within gamma, theta & delta, but not in alpha or beta frequency bands.
	Veniero et al. (2013) [29]	$N = 13$ Mean age: 27.6 Healthy	100 pairs of stimuli 1. PPC → $M1_{(P-A)}$ (left) 2. $M1_{(P-A)}$ → PPC (left) 3. PPC → $M1_{(A-P)}$ (left) 90% rMT, every 5 s (~8.3 min) ISI: 5 ms	M1 (left) & PPC (left) spTMS (Pre & Post PAS) ISI: ~4 s SI_{1mv} (~130% rMT), 80 pulses 20 scalp channels Auditory masking: earplugs	Global TEPs (~18, ~53, ~108, ~186 ms) TMS-evoked oscillations	1. PPC → $M1_{(P-A)}$: ↑ amplitude of Peak 1 (~18 ms) with ↓ MEPs after stimulating M1, but not PPC 2. $M1_{(P-A)}$ → PPC: ↓ amplitude of Peak 1 & Peak 4 (~186 ms) with ↑ MEPs after stimulating M1, but not PPC 3. PPC → $M1_{(A-P)}$: ↓ amplitude of Peak 1 & Peak 4 with ↑ MEPs after stimulating M1, but not PPC ↑ alpha-band coherence with ↑ MEPs ↑ beta band coherence with ↓ MEPs
TBS	Vernet et al. (2013) [49]	$N = 10$ Mean age: 21 Healthy	M1 (left) cTBS – 3 bursts of pulses at 50 Hz every 240 ms (4.17 Hz) 80% aMT, 600 pulses	M1 (left) spTMS (Pre & Post TBS at 0, 5, 10, 20, 30, 40, 50 & 60 min) ISI: 5–8 s 120% rMT, 10–30 pulses 60 scalp channels Auditory masking: Earplugs	Local TEPs (P30, N45, P55, N100) TMS-evoked oscillations	↓ amplitude of P30 with ↓ MEPs ↓ alpha & theta oscillation ↑ beta oscillation
tDCS	Pellicciari et al. (2013) [35]	$N = 16$ Mean age: 23.2 Healthy	Anodal & Cathodal tDCS Intensity of 1 mA, 13 min Size: 25 cm^2 Current density: 0.04 mA/cm^2 Active: M1 Reference: right frontopolar cortex 8 s fade-in/fade-out	M1 (left) spTMS (Pre & Post tDCS at 0 & 30 min) ISI: 2–4 s 110% rMT, 100 pulses 14 scalp channels Auditory masking: earplugs	Local TEPs (16–40 ms, 59–105 ms, 182–264 ms) Oscillations	Anodal tDCS – ↑ cortical-evoked activity over both hemisphere Left (↑): 0 min: 20–27 ms, 51–72 ms & 258–265 ms 30 min: 15–33 ms & 54–75 ms Right (↑): 0 min: 10–16 ms, 86–96 ms & 209–231 ms 30 min: 86–96 ms & 205–233 ms Cathodal tDCS – ↓ cortical-evoked activity over stimulated hemisphere, ↑ over contralateral Left (↓): 0 min: 206–238 ms 30 min: 201–217 ms Right (↑): 0 min: 37–41 ms & 124–152 ms 30 min: 34–39 ms, 124–131 ms ↑ theta & alpha power after anodal and cathodal tDCS

Romero Lauro et al. (2014) [48]	$N = 14$ Mean age: 27 Healthy	Anodal tDCS & Sham Intensity of 0.75 mA, 15 min Anode (right PPC): Size: 9 cm^2 Current density: 0.08 mA/cm^2 Cathode (left supraorbital): Size: 25 cm^2 Current density: 0.03 mA/cm^2 8 s fade-in/fade-out For sham tDCS, stimulator turned off after 30 s	PPC (left) spTMS (During, Pre & Post tDCS at 15 min) ISI: 2–2.3 s 60–78 % rMT, ~180 pulses 60 scalp channels Auditory masking: Noise masking	Global TEPs (0–50 ms, 50–100 ms, 100–150 ms) Local TEPs (0–50 ms, 50–100 ms, 100–150 ms)	↑ cortical reactivity at 0–100 ms both during and after 15 min anodal tDCS ↑ cortical reactivity at 0–50 ms in the right PPC, contralateral area & bilateral frontal regions after 15 min anodal tDCS

A-P – Anterior-posterior; DLPFC – Dorsolateral prefrontal cortex; ISI – Interstimulus interval; M1 – Primary motor cortex; MEPs – Motor evoked potentials; P-A – Posterior-anterior; PAS – Paired associative stimulation; PPC – Posterior parietal cortex; rMT – Resting motor threshold; spTMS – Single-pulse TMS; cTBS – Continuous theta burst stimulation; tDCS – Transcranial direct current stimulation; TEPs – TMS-evoked potentials.

different TEPs appeared to be the main factor predicting amplitude of MEPs, and more studies are required to clarify the observation to the individual level [49]. Additionally, the pattern of TMS-induced oscillations was modified, with decrease in low-frequencies (theta and alpha) and increase in high-frequency (high beta) followed by cTBS [49]. With more TMS-EEG studies, TEPs and oscillations could provide important information about the plasticity in the brain regions other than motor cortex.

tDCS

Pellicciari and colleagues (2013) [35] measured cortical reactivity using TMS-EEG following anodal and cathodal tDCS and found polarity-dependent and site-specific modulation of neuronal activity induced by TMS. The anodal tDCS induced an increase in cortical-evoked activity in both hemispheres, while the cathodal tDCS induced a decrease in stimulated but not in non-stimulated hemisphere (see Table 2). However, both stimulation paradigms showed general increase in theta and alpha power. It was suggested that these cortical responses to the TMS could be physiological markers for cortical excitability, with TEPs being more sensitive than the EEG power density [35]. Supporting this study, Romero and colleagues (2014) [48] studied the effects of anodal tDCS to right posterior parietal cortex (PPC) and observed a shift in cortical excitability within ipsilateral and contralateral hemispheres. Earlier components of TEPs (~50 ms) were significantly modulated shown by both global TEPs and local TEPs which reflect the excitability of stimulated and interconnected areas [48].

Conclusion

TMS-EEG studies of different neuromodulatory techniques have shown that there are distinctive changes in TEPs before and after brain stimulation. In particularly, peaks occurring approximately at 30 ms, 45 ms and 100 ms following motor cortex stimulation seem more frequently affected by neuromodulation, and change in alpha and theta frequencies are most prevalent in the studies investigated. Even though peaks occurring at different time points and changes in various frequency bands have been illustrated, until more studies of this nature are conducted, it is too early to pinpoint the origin of the TEPs induced by different stimulation techniques. In particular, it is important to note that TEPs from different brain regions can have different latencies, topographies and amplitudes [55], and may reflect different underlying neurophysiological mechanisms. Therefore, judgments about the capacity to generalize the effect of stimulation techniques on TEP components to inform studies in the motor cortex to other brain regions needs further investigation. Additionally, the heterogeneity in stimulation parameters, EEG recording and signal processing methods, as well as strategy of each study in controlling confounds needs to be considered for a more systematic comparison.

TMS-EEG offers a highly sensitive measurement of cortical activity from both the stimulated region and connected, but remote cortical areas. In particular, TMS-EEG enables the evaluation of TEPs that may act as a marker for cortical excitation and inhibition, and provides valuable information from cortical areas not traditionally assessed using TMS. Recording neuronal responses in the millisecond time frame, the dynamics of neural connections can be mapped to investigate functional interactions in the human brain. In addition, TMS-evoked oscillations allow examination of brain oscillatory activity to help clarify the mechanisms involved in processing and transfer of information between brain areas. However, the physiological origin and functional significance of some of the TMS-evoked components

remain to be defined. With carefully designed experimental approaches, many of technical challenges of TMS-EEG can be overcome, and exploring the modification of cortical activity by different neuromodulatory techniques can contribute to unraveling the mechanisms involved in modulation of excitability and inhibition by neuroplasticity, both in healthy and neuropsychiatric population.

References

[1] Wagner T, Rushmore J, Eden U, Valero-Cabre A. Biophysical foundations underlying TMS: setting the stage for an effective use of neurostimulation in the cognitive neurosciences. Cortex 2009;45(9):1025–34.
[2] Chen R, Classen J, Gerloff C, et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology 1997;48(5):1398–403.
[3] Ilic TV, Meintzschel F, Cleff U, Ruge D, Kessler KR, Ziemann U. Short-interval paired-pulse inhibition and facilitation of human motor cortex: the dimension of stimulus intensity. J Physiol 2002;545(Pt 1):153–67.
[4] Kobayashi M, Hutchinson S, Theoret H, Schlaug G, Pascual-Leone A. Repetitive TMS of the motor cortex improves ipsilateral sequential simple finger movements. Neurology 2004;62(1):91–8.
[5] Munchau A, Bloem BR, Irlbacher K, Trimble MR, Rothwell JC. Functional connectivity of human premotor and motor cortex explored with repetitive transcranial magnetic stimulation. J Neurosci 2002;22(2):554–61.
[6] Ilmoniemi RJ, Kicic D. Methodology for combined TMS and EEG. Brain Topogr 2010;22(4):233–48.
[7] Frantseva M, Cui J, Farzan F, Chinta LV, Perez Velazquez JL, Daskalakis ZJ. Disrupted cortical conductivity in schizophrenia: TMS-EEG study. Cereb Cortex 2014;24(1):211–21.
[8] Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron 2005;45(2):201–6.
[9] Maeda F, Keenan JP, Tormos JM, Topka H, Pascual-Leone A. Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation. Clin Neurophysiol 2000;111(5):800–5.
[10] Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol 2000;527(Pt 3):633–9.
[11] Stefan K, Kunesch E, Cohen LG, Benecke R, Classen J. Induction of plasticity in the human motor cortex by paired associative stimulation. Brain 2000;123(Pt 3):572–84.
[12] Lopez-Alonso V, Cheeran B, Rio-Rodriguez D, Fernandez-Del-Olmo M. Inter-individual variability in response to non-invasive brain stimulation paradigms. Brain Stimul 2014;7(3):372–80.
[13] Todd G, Taylor JL, Butler JE, Martin PG, Gorman RB, Gandevia SC. Use of motor cortex stimulation to measure simultaneously the changes in dynamic muscle properties and voluntary activation in human muscles. J Appl Physiol (1985) 2007;102(5):1756–66.
[14] Hallett M, Wassermann EM, Pascual-Leone A, Valls-Sole J. Repetitive transcranial magnetic stimulation. The International Federation of Clinical Neurophysiology. Electroencephalogr Clin Neurophysiol Suppl 1999;52:105–13.
[15] Pascual-Leone A, Tormos JM, Keenan J, Tarazona F, Canete C, Catala MD. Study and modulation of human cortical excitability with transcranial magnetic stimulation. J Clin Neurophysiol 1998;15(4):333–43.
[16] Silvanto J, Pascual-Leone A. State-dependency of transcranial magnetic stimulation. Brain Topogr 2008;21(1):1–10.
[17] Fitzgerald PB, Fountain S, Daskalakis ZJ. A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. Clin Neurophysiol 2006;117(12):2584–96.
[18] Gorsler A, Baumer T, Weiller C, Munchau A, Liepert J. Interhemispheric effects of high and low frequency rTMS in healthy humans. Clin Neurophysiol 2003;114(10):1800–7.
[19] Fitzgerald PB, Benitez J, de Castella A, Daskalakis ZJ, Brown TL, Kulkarni J. A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. Am J Psychiatry 2006;163(1):88–94.
[20] Kimura H, Kurimura M, Kurokawa K, et al. A comprehensive study of repetitive transcranial magnetic stimulation in Parkinson's disease. ISRN Neurol 2011;2011:845453.
[21] Leung A, Donohue M, Xu R, et al. rTMS for suppressing neuropathic pain: a meta-analysis. J Pain 2009;10(12):1205–16.
[22] Paes F, Machado S, Arias-Carrion O, et al. The value of repetitive transcranial magnetic stimulation (rTMS) for the treatment of anxiety disorders: an integrative review. CNS Neurol Disord Drug Targets 2011;10(5):610–20.
[23] Hinder MR, Goss EL, Fujiyama H, et al. Inter- and intra-individual variability following intermittent theta burst stimulation: implications for rehabilitation and recovery. Brain Stimul 2014;7(3):365–71.
[24] Vernet M, Bashir S, Yoo WK, et al. Reproducibility of the effects of theta burst stimulation on motor cortical plasticity in healthy participants. Clin Neurophysiol 2014;125(2):320–6.
[25] Hamada M, Murase N, Hasan A, Balaratnam M, Rothwell JC. The role of interneuron networks in driving human motor cortical plasticity. Cereb Cortex 2013;23(7):1593–605.
[26] Chung SW, Hoy KE, Fitzgerald PB. Theta-burst stimulation: a new form of TMS treatment for depression? Depress Anxiety 2015;32(3):182–92.
[27] Muller-Dahlhaus F, Ziemann U, Classen J. Plasticity resembling spike-timing dependent synaptic plasticity: the evidence in human cortex. Front Synaptic Neurosci 2010;2:34.
[28] Wolters A, Sandbrink F, Schlottmann A, et al. A temporally asymmetric Hebbian rule governing plasticity in the human motor cortex. J Neurophysiol 2003;89(5):2339–45.
[29] Veniero D, Ponzo V, Koch G. Paired associative stimulation enforces the communication between interconnected areas. J Neurosci 2013;33(34):13773–83.
[30] Buch ER, Johnen VM, Nelissen N, O'Shea J, Rushworth MF. Noninvasive associative plasticity induction in a corticocortical pathway of the human brain. J Neurosci 2011;31(48):17669–79.
[31] Muller-Dahlhaus JF, Orekhov Y, Liu Y, Ziemann U. Interindividual variability and age-dependency of motor cortical plasticity induced by paired associative stimulation. Exp Brain Res 2008;187(3):467–75.
[32] Nitsche MA, Cohen LG, Wassermann EM, et al. Transcranial direct current stimulation: state of the art 2008. Brain Stimul 2008;1(3):206–23.
[33] Kuo MF, Nitsche MA. Exploring prefrontal cortex functions in healthy humans by transcranial electrical stimulation. Neurosci Bull 2015;31(2):198–206.
[34] Batsikadze G, Moliadze V, Paulus W, Kuo MF, Nitsche MA. Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. J Physiol 2013;591(Pt 7):1987–2000.
[35] Pellicciari MC, Brignani D, Miniussi C. Excitability modulation of the motor system induced by transcranial direct current stimulation: a multimodal approach. Neuroimage 2013;83:569–80.
[36] Horvath JC, Forte JD, Carter O. Evidence that transcranial direct current stimulation (tDCS) generates little-to-no reliable neurophysiologic effect beyond MEP amplitude modulation in healthy human subjects: a systematic review. Neuropsychologia 2015;66:213–36.
[37] Boggio PS, Campanha C, Valasek CA, Fecteau S, Pascual-Leone A, Fregni F. Modulation of decision-making in a gambling task in older adults with transcranial direct current stimulation. Eur J Neurosci 2010;31(3):593–7.
[38] Coffman BA, Clark VP, Parasuraman R. Battery powered thought: enhancement of attention, learning, and memory in healthy adults using transcranial direct current stimulation. Neuroimage 2014;85(Pt 3):895–908.
[39] Giglia G, Brighina F, Rizzo S, et al. Anodal transcranial direct current stimulation of the right dorsolateral prefrontal cortex enhances memory-guided responses in a visuospatial working memory task. Funct Neurol 2014;29(3):189–93.
[40] Nelson JT, McKinley RA, Golob EJ, Warm JS, Parasuraman R. Enhancing vigilance in operators with prefrontal cortex transcranial direct current stimulation (tDCS). Neuroimage 2014;85(Pt 3):909–17.
[41] Ohn SH, Park CI, Yoo WK, et al. Time-dependent effect of transcranial direct current stimulation on the enhancement of working memory. Neuroreport 2008;19(1):43–7.
[42] Floel A. tDCS-enhanced motor and cognitive function in neurological diseases. Neuroimage 2014;85(Pt 3):934–47.
[43] Khedr EM, Gamal NF, El-Fetoh NA, et al. A double-blind randomized clinical trial on the efficacy of cortical direct current stimulation for the treatment of Alzheimer's disease. Front Aging Neurosci 2014;6:275.
[44] Brunoni AR, Kemp AH, Shiozawa P, et al. Impact of 5-HTTLPR and BDNF polymorphisms on response to sertraline versus transcranial direct current stimulation: implications for the serotonergic system. Eur Neuropsychopharmacol 2013;23(11):1530–40.
[45] Boggio PS, Rigonatti SP, Ribeiro RB, et al. A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. Int J Neuropsychopharmacol 2008;11(2):249–54.
[46] Meyer BU, Diehl R, Steinmetz H, Britton TC, Benecke R. Magnetic stimuli applied over motor and visual cortex: influence of coil position and field polarity on motor responses, phosphenes, and eye movements. Electroencephalogr Clin Neurophysiol Suppl 1991;43:121–34.
[47] Helfrich C, Pierau SS, Freitag CM, Roeper J, Ziemann U, Bender S. Monitoring cortical excitability during repetitive transcranial magnetic stimulation in children with ADHD: a single-blind, sham-controlled TMS-EEG study. PLoS One 2012;7(11):e50073.
[48] Romero Lauro LJ, Rosanova M, Mattavelli G, et al. TDCS increases cortical excitability: direct evidence from TMS-EEG. Cortex 2014;58:99–111.
[49] Vernet M, Bashir S, Yoo WK, Perez JM, Najib U, Pascual-Leone A. Insights on the neural basis of motor plasticity induced by theta burst stimulation from TMS-EEG. Eur J Neurosci 2013;37(4):598–606.
[50] Siebner HR, Bergmann TO, Bestmann S, et al. Consensus paper: combining transcranial stimulation with neuroimaging. Brain Stimul 2009;2(2):58–80.
[51] Rogasch NC, Thomson RH, Farzan F, et al. Removing artefacts from TMS-EEG recordings using independent component analysis: importance for assessing prefrontal and motor cortex network properties. Neuroimage 2014;101:425–39.
[52] Rogasch NC, Fitzgerald PB. Assessing cortical network properties using TMS-EEG. Hum Brain Mapp 2013;34(7):1652–69.

[53] Bonato C, Miniussi C, Rossini PM. Transcranial magnetic stimulation and cortical evoked potentials: a TMS/EEG co-registration study. Clin Neurophysiol 2006;117(8):1699–707.
[54] Kahkonen S, Komssi S, Wilenius J, Ilmoniemi RJ. Prefrontal TMS produces smaller EEG responses than motor-cortex TMS: implications for rTMS treatment in depression. Psychopharmacol Berl 2005;181(1):16–20.
[55] Kahkonen S, Wilenius J, Komssi S, Ilmoniemi RJ. Distinct differences in cortical reactivity of motor and prefrontal cortices to magnetic stimulation. Clin Neurophysiol 2004;115(3):583–8.
[56] Komssi S, Aronen HJ, Huttunen J, et al. Ipsi- and contralateral EEG reactions to transcranial magnetic stimulation. Clin Neurophysiol 2002;113(2):175–84.
[57] Komssi S, Kahkonen S, Ilmoniemi RJ. The effect of stimulus intensity on brain responses evoked by transcranial magnetic stimulation. Hum Brain Mapp 2004;21(3):154–64.
[58] Casarotto S, Romero Lauro LJ, Bellina V, et al. EEG responses to TMS are sensitive to changes in the perturbation parameters and repeatable over time. PLoS One 2010;5(4):e10281.
[59] Lioumis P, Kicic D, Savolainen P, Makela JP, Kahkonen S. Reproducibility of TMS-Evoked EEG responses. Hum Brain Mapp 2009;30(4):1387–96.
[60] Komssi S, Kahkonen S. The novelty value of the combined use of electroencephalography and transcranial magnetic stimulation for neuroscience research. Brain Res Rev 2006;52(1):183–92.
[61] Maki H, Ilmoniemi RJ. The relationship between peripheral and early cortical activation induced by transcranial magnetic stimulation. Neurosci Lett 2010;478(1):24–8.
[62] Ferreri F, Pasqualetti P, Maatta S, et al. Human brain connectivity during single and paired pulse transcranial magnetic stimulation. Neuroimage 2011;54(1):90–102.
[63] Rogasch NC, Daskalakis ZJ, Fitzgerald PB. Mechanisms underlying long-interval cortical inhibition in the human motor cortex: a TMS-EEG study. J Neurophysiol 2013;109(1):89–98.
[64] Premoli I, Castellanos N, Rivolta D, et al. TMS-EEG signatures of GABAergic neurotransmission in the human cortex. J Neurosci 2014;34(16):5603–12.
[65] Bender S, Basseler K, Sebastian I, et al. Electroencephalographic response to transcranial magnetic stimulation in children: evidence for giant inhibitory potentials. Ann Neurol 2005;58(1):58–67.
[66] Bikmullina R, Kicic D, Carlson S, Nikulin VV. Electrophysiological correlates of short-latency afferent inhibition: a combined EEG and TMS study. Exp Brain Res 2009;194(4):517–26.
[67] Ter Braack EM, de Vos CC, van Putten MJ. Masking the auditory evoked potential in TMS-EEG: a comparison of various methods. Brain Topogr 2015 May;28(3):520–8. http://dx.doi.org/10.1007/s10548-013-0312-z. Epub 2013 Sep 1.
[68] Bonnard M, Spieser L, Meziane HB, de Graaf JB, Pailhous J. Prior intention can locally tune inhibitory processes in the primary motor cortex: direct evidence from combined TMS-EEG. Eur J Neurosci 2009;30(5):913–23.
[69] Kicic D, Lioumis P, Ilmoniemi RJ, Nikulin VV. Bilateral changes in excitability of sensorimotor cortices during unilateral movement: combined electroencephalographic and transcranial magnetic stimulation study. Neuroscience 2008;152(4):1119–29.
[70] Farzan F, Barr MS, Hoppenbrouwers SS, et al. The EEG correlates of the TMS-induced EMG silent period in humans. Neuroimage 2013;83:120–34.
[71] Rogasch NC, Daskalakis ZJ, Fitzgerald PB. Cortical inhibition of distinct mechanisms in the dorsolateral prefrontal cortex is related to working memory performance: a TMS-EEG study. Cortex 2015;64:68–77.
[72] Veniero D, Maioli C, Miniussi C. Potentiation of short-latency cortical responses by high-frequency repetitive transcranial magnetic stimulation. J Neurophysiol 2010;104(3):1578–88.
[73] Veniero D, Bortoletto M, Miniussi C. Cortical modulation of short-latency TMS-evoked potentials. Front Hum Neurosci 2012;6:352.
[74] Mutanen T, Maki H, Ilmoniemi RJ. The effect of stimulus parameters on TMS-EEG muscle artifacts. Brain Stimul 2013;6(3):371–6.
[75] Rogasch NC, Thomson RH, Daskalakis ZJ, Fitzgerald PB. Short-latency artifacts associated with concurrent TMS-EEG. Brain Stimul 2013;6(6):868–76.
[76] Miniussi C, Thut G. Combining TMS and EEG offers new prospects in cognitive neuroscience. Brain Topogr 2010;22(4):249–56.
[77] Ilmoniemi RJ, Virtanen J, Ruohonen J, et al. Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity. Neuroreport 1997;8(16):3537–40.
[78] Iwahashi M, Arimatsu T, Ueno S, Iramina K. Differences in evoked EEG by transcranial magnetic stimulation at various stimulus points on the head. Conf Proc IEEE Eng Med Biol Soc 2008;2008:2570–3.
[79] Voineskos AN, Farzan F, Barr MS, et al. The role of the corpus callosum in transcranial magnetic stimulation induced interhemispheric signal propagation. Biol Psychiatry 2010;68(9):825–31.
[80] Brignani D, Manganotti P, Rossini PM, Miniussi C. Modulation of cortical oscillatory activity during transcranial magnetic stimulation. Hum Brain Mapp 2008;29(5):603–12.
[81] Paus T, Sipila PK, Strafella AP. Synchronization of neuronal activity in the human primary motor cortex by transcranial magnetic stimulation: an EEG study. J Neurophysiol 2001;86(4):1983–90.
[82] Rosanova M, Casali A, Bellina V, Resta F, Mariotti M, Massimini M. Natural frequencies of human corticothalamic circuits. J Neurosci 2009;29(24):7679–85.
[83] Thut G, Veniero D, Romei V, Miniussi C, Schyns P, Gross J. Rhythmic TMS causes local entrainment of natural oscillatory signatures. Curr Biol 2011;21(14):1176–85.
[84] Van Der Werf YD, Paus T. The neural response to transcranial magnetic stimulation of the human motor cortex. I. Intracortical and cortico-cortical contributions. Exp Brain Res 2006;175(2):231–45.
[85] Ward LM. Synchronous neural oscillations and cognitive processes. Trends Cogn Sci 2003;7(12):553–9.
[86] Basar E, Basar-Eroglu C, Guntekin B, Yener GG. Brain's alpha, beta, gamma, delta, and theta oscillations in neuropsychiatric diseases: proposal for biomarker strategies. Suppl Clin Neurophysiol 2013;62:19–54.
[87] Rasch B, Born J. About sleep's role in memory. Physiol Rev 2013;93(2):681–766.
[88] Knyazev GG. Motivation, emotion, and their inhibitory control mirrored in brain oscillations. Neurosci Biobehav Rev 2007;31(3):377–95.
[89] Knyazev GG. EEG delta oscillations as a correlate of basic homeostatic and motivational processes. Neurosci Biobehav Rev 2012;36(1):677–95.
[90] Klimesch W. EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. Brain Res Brain Res Rev 1999;29(2–3):169–95.
[91] Klimesch W, Sauseng P, Hanslmayr S. EEG alpha oscillations: the inhibition-timing hypothesis. Brain Res Rev 2007;53(1):63–88.
[92] Pfurtscheller G, Stancak Jr A, Neuper C. Event-related synchronization (ERS) in the alpha band–an electrophysiological correlate of cortical idling: a review. Int J Psychophysiol 1996;24(1–2):39–46.
[93] Jensen O, Mazaheri A. Shaping functional architecture by oscillatory alpha activity: gating by inhibition. Front Hum Neurosci 2010;4:186.
[94] Klimesch W. alpha-band oscillations, attention, and controlled access to stored information. Trends Cogn Sci 2012;16(12):606–17.
[95] Neuper C, Pfurtscheller G. Event-related dynamics of cortical rhythms: frequency-specific features and functional correlates. Int J Psychophysiol 2001;43(1):41–58.
[96] Pfurtscheller G, Zalaudek K, Neuper C. Event-related beta synchronization after wrist, finger and thumb movement. Electroencephalogr Clin Neurophysiol 1998;109(2):154–60.
[97] Howard MW, Rizzuto DS, Caplan JB, et al. Gamma oscillations correlate with working memory load in humans. Cereb Cortex 2003;13(12):1369–74.
[98] Beauchamp MS, Sun P, Baum SH, Tolias AS, Yoshor D. Electrocorticography links human temporoparietal junction to visual perception. Nat Neurosci 2012;15(7):957–9.
[99] Jensen O, Kaiser J, Lachaux JP. Human gamma-frequency oscillations associated with attention and memory. Trends Neurosci 2007;30(7):317–24.
[100] Ferrarelli F, Massimini M, Peterson MJ, et al. Reduced evoked gamma oscillations in the frontal cortex in schizophrenia patients: a TMS/EEG study. Am J Psychiatry 2008;165(8):996–1005.
[101] Levit-Binnun N, Litvak V, Pratt H, Moses E, Zaroor M, Peled A. Differences in TMS-evoked responses between schizophrenia patients and healthy controls can be observed without a dedicated EEG system. Clin Neurophysiol 2010;121(3):332–9.
[102] Carson RG, Kennedy NC. Modulation of human corticospinal excitability by paired associative stimulation. Front Hum Neurosci 2013;7:823.
[103] Lee L, Siebner H, Bestmann S. Rapid modulation of distributed brain activity by Transcranial Magnetic Stimulation of human motor cortex. Behav Neurol 2006;17(3–4):135–48.
[104] Sehm B, Kipping J, Schafer A, Villringer A, Ragert P. A comparison between uni- and bilateral tDCS effects on functional connectivity of the human motor cortex. Front Hum Neurosci 2013;7:183.
[105] Casula EP, Tarantino V, Basso D, et al. Low-frequency rTMS inhibitory effects in the primary motor cortex: Insights from TMS-evoked potentials. Neuroimage 2014;98:225–32.
[106] Michalewski HJ, Starr A, Zeng FG, Dimitrijevic A. N100 cortical potentials accompanying disrupted auditory nerve activity in auditory neuropathy (AN): effects of signal intensity and continuous noise. Clin Neurophysiol 2009;120(7):1352–63.
[107] Tiitinen H, Virtanen J, Ilmoniemi RJ, et al. Separation of contamination caused by coil clicks from responses elicited by transcranial magnetic stimulation. Clin Neurophysiol 1999;110(5):982–5.
[108] Bruckmann S, Hauk D, Roessner V, et al. Cortical inhibition in attention deficit hyperactivity disorder: new insights from the electroencephalographic response to transcranial magnetic stimulation. Brain 2012;135(Pt 7):2215–30.
[109] D'Agati E, Hoegl T, Dippel G, et al. Motor cortical inhibition in ADHD: modulation of the transcranial magnetic stimulation-evoked N100 in a response control task. J Neural Transm 2014;121(3):315–25.
[110] Gerschlager W, Siebner HR, Rothwell JC. Decreased corticospinal excitability after subthreshold 1 Hz rTMS over lateral premotor cortex. Neurology 2001;57(3):449–55.
[111] Rizzo V, Siebner HR, Modugno N, et al. Shaping the excitability of human motor cortex with premotor rTMS. J Physiol 2004;554(Pt 2):483–95.
[112] Suppa A, Bologna M, Gilio F, Lorenzano C, Rothwell JC, Berardelli A. Preconditioning repetitive transcranial magnetic stimulation of premotor cortex can reduce but not enhance short-term facilitation of primary motor cortex. J Neurophysiol 2008;99(2):564–70.

[113] Esser SK, Huber R, Massimini M, Peterson MJ, Ferrarelli F, Tononi G. A direct demonstration of cortical LTP in humans: a combined TMS/EEG study. Brain Res Bull 2006;69(1):86–94.
[114] Hamidi M, Slagter HA, Tononi G, Postle BR. Brain responses evoked by high-frequency repetitive transcranial magnetic stimulation: an event-related potential study. Brain Stimul 2010;3(1):2–14.
[115] Huber R, Maatta S, Esser SK, et al. Measures of cortical plasticity after transcranial paired associative stimulation predict changes in electroencephalogram slow-wave activity during subsequent sleep. J Neurosci 2008;28(31):7911–8.
[116] Rajji TK, Sun Y, Zomorrodi-Moghaddam R, et al. PAS-induced potentiation of cortical-evoked activity in the dorsolateral prefrontal cortex. Neuropsychopharmacology 2013;38(12):2545–52.

CHAPTER FIVE

Working memory as a behavioural marker

Working memory has a close association with one's ability to learn and perform complex cognitive tasks (Cowan et al., 2005) and hence been regarded as an important part of cognitive processing. Working memory refers to temporary storage of information while simultaneously manipulating and processing the same or other input prior to the execution of cognitive decision (Baddeley, 2010). The effectiveness of working memory is affected by cognitive load and/or distraction which ultimately can lead to loss of information due to the limitation in its capacity (Jeneson and Squire, 2012). The n-back task is one of many measurements of working memory which requires participants to respond to stimuli that have been presented *n* trials earlier (Meule, 2017).

Evidence suggests that NIBS is able to increase the activity of DLPFC and consequently improve working memory performance (Pascual-Leone A., 2012). Such improvement has been observed in healthy subjects (Fregni et al., 2005; Hoy et al., 2016; Zaehle et al., 2011) as well as in clinical populations (Birba et al., 2017; Tortella et al., 2014). A recent meta-analysis supports these findings and demonstrated superior improvement in clinical cohorts compared to healthy individuals (Brunoni and Vanderhasselt, 2014). More recently, there has been a growing interest in using TBS as a cognitive enhancer (Demeter, 2016a) and a limited number of studies have shown modulation of working memory performance following TBS (Hoy et al., 2016; Schicktanz et al., 2015). In addition, these studies provided a strong rationale in measuring neurophysiological changes as a behavioural correlate.

Neuroimaging studies have shown that the frontal and parietal cortical regions are activated during the n-back task (Jansma et al., 2000; Jonides et al., 1993; Owen et al., 2005) and the magnitude of the activation is associated with the memory load (Braver et al., 1997). The use of EEG allows for the measurement of spectral characteristics of n-back task performance (Gevins et al., 1997). For example, midline frontal theta (5 – 7 Hz) frequency increases with increasing task load, which is related to attention and sustained concentration (Miyata et al., 2015). Therefore, the performance measures during the n-back task, such as accuracy and accurate reaction time, can be utilised as behavioural markers of neurophysiological changes.

CHAPTER SIX

Objectives and aims

Summary of the literature review

In summary, NIBS provides an exciting opportunity to investigate neurophysiological applications in humans. In particular, TBS is a promising method of neuromodulatory stimulation which may be applicable to a wide variety of psychiatric and neurological disorders. Its application is highly rapid and efficient compared to conventional rTMS protocols. However, optimal methods of producing cortical after-effects in the prefrontal brain regions have not been well defined. Combining neuroimaging techniques with TMS has allowed researchers to probe cortical activity beyond the motor area. TMS-EEG studies have shown changes in cortical responses to different NIBS techniques.

Research objectives

In the current study, TMS-EEG methods are primarily used to study the responses to a variety of modifications of TBS paradigms and to identify optimal ways of application in the prefrontal cortex. Elucidating the neurobiological effects of TBS and the impact of different stimulation parameters would ultimately improve the protocols for illnesses such as depression. In addition to neurophysiological changes, cognitive assessments are conducted as a secondary measure acting as a behavioural marker because cognitive impairment is one of the key endophenotypes observed in patients with major depression (Hasler et al., 2004).

Study aims

The goal of this thesis was to better understand the mechanisms of TBS in the prefrontal cortex and to identify optimal stimulation parameters for changing the activity in this brain region. To achieve these goals, five specific aims were developed:

Aim 1 was to evaluate the efficacy of TBS in altering corticospinal excitability, and to identify potential stimulation parameters to be investigated in the prefrontal cortex.

Aim 2 was to explore the utility of TMS-EEG in tracking plasticity changes following TBS in the prefrontal cortex.

Aim 3: Having established the validity of the method, the third aim was to examine the effects of different stimulation intensities of iTBS in the prefrontal cortex.

Aim 4 was to examine the effects of repeated application of prefrontal iTBS.

Aim 5 was to examine the effects of frequency of iTBS in the prefrontal cortex.

To achieve these aims, five studies have been completed:

1. A detailed examination of the effects of iTBS and cTBS on the corticospinal excitability and inhibition, and identification of parameters affecting the after-effects such the frequency and the number of pulses of stimulation.
2. A validation of TMS-EEG as a method of tracking TBS-induced changes in the reactivity of prefrontal cortex of healthy individuals via TMS-evoked potentials (TEPs) and TMS-evoked oscillations, and establishment of indices of measurement.

3. A comparison of different stimulation intensities of iTBS to determine the optimal stimulation intensity and to be used in subsequent studies. iTBS-induced changes were assessed using TMS-EEG and working memory performance in healthy individuals.
4. A comparison between single and repeated application of iTBS on TMS-EEG and working memory performance outcomes in healthy individuals.
5. A comparison between the two most commonly applied stimulation methods (30 Hz and 50 Hz) and a new method for individualising the frequency of iTBS in the prefrontal cortex on TMS-EEG, mood and working memory performance outcomes in healthy individuals.

CHAPTER SEVEN

Efficacy of TBS and factors affecting TBS-induced corticospinal excitability

Chung SW, Hill AT, Rogasch NC, Hoy KE, Fitzgerald PB. 2016. Use of theta-burst stimulation in changing excitability of motor cortex: A systematic review and meta-analysis. *Neuroscience & Biobehavioural Reviews.* 63(4):43-64.

Preamble to systematic review and meta-analysis

As discussed in Chapter 4, TMS-EEG provides a direct measure of cortical properties via TMS-evoked potentials and oscillations. This technique is particularly useful in non-motor regions where direct physiological responses resulting from neural activation are not available. Furthermore, TMS-EEG allows researchers to probe plastic changes following neuromodulatory paradigms such as theta burst stimulation. Until recently, a vast majority of the studies investigating plasticity following TBS has been conducted in the motor cortex due to technical limitations. Even though TBS has shown great promise in modulating corticospinal excitability in human since its first induction in 2005 (Huang et al., 2005), recent studies with larger sample sizes have shown substantial variability in response to TBS (Hamada et al., 2013; Hinder et al., 2014). In order to enhance the effect of TBS, several studies have identified beneficial modifications in stimulation parameters such as the frequency at which pulses are given (Goldsworthy et al., 2012b) and repeated applications of the standard TBS protocols following gaps of 10 – 15 mins (Goldsworthy et al., 2012a; Nettekoven et al., 2014). However, the current literature lacks a systematic and collective

comparison of the after-effects of TBS in regards to different stimulation parameters. In this published paper, overall effects of iTBS and cTBS in altering corticospinal excitability were evaluated. In addition, subgroup analyses were conducted on the impact of variables such as stimulation parameters and genetics. A detailed examination of publication bias, a suggestive sign of overestimated effects of TBS in the literature was also provided.

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Review

Use of theta-burst stimulation in changing excitability of motor cortex: A systematic review and meta-analysis

Sung Wook Chung [a,*], Aron T. Hill [a], Nigel C. Rogasch [b], Kate E. Hoy [a], Paul B. Fitzgerald [a]

[a] Monash Alfred Psychiatry Research Centre, Central Clinical School, The Alfred and Monash University, Melbourne, Australia
[b] Brain and Mental Health Laboratory, School of Psychological Sciences and Monash Biomedical Imaging, Monash University, Melbourne, Australia

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ABSTRACT

Noninvasive brain stimulation has been demonstrated to modulate cortical activity in humans. In particular, theta burst stimulation (TBS) has gained notable attention due to its ability to induce lasting physiological changes after short stimulation durations. The present study aimed to provide a comprehensive meta-analytic review of the efficacy of two TBS paradigms; intermittent (iTBS) and continuous (cTBS), on corticospinal excitability in healthy individuals. Literature searches yielded a total of 87 studies adhering to the inclusion criteria. iTBS yielded moderately large MEP increases lasting up to 30 min with a pooled SMD of 0.71 ($p < 0.00001$). cTBS produced a reduction in MEP amplitudes lasting up to 60 min, with the largest effect size seen at 5 min post stimulation (SMD = –0.9, $P < 0.00001$). The collected studies were of heterogeneous nature, and a series of tests conducted indicated a degree of publication bias. No significant change in SICI and ICF was observed, with exception to decrease in SICI with cTBS at the early time point (SMD = 0.42, $P = 0.00036$). The results also highlight several factors contributing to TBS efficacy, including the number of pulses, frequency of stimulation and BDNF polymorphisms. Further research investigating optimal TBS stimulation parameters, particularly for iTBS, is needed in order for these paradigms to be successfully translated into clinical settings.

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* Corresponding author at: Monash Alfred Psychiatry Research Centre, Level 4, 607 St Kilda Road, Melbourne, Victoria 3004, Australia. Fax: + 61 39076 5075.
E-mail address: sung.chung@monash.edu (S.W. Chung).

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1. Introduction

Noninvasive brain stimulation (NIBS) techniques are frequently used in both research and clinical settings due to their ability to induce transient changes in cortical activity. In particular, transcranial magnetic stimulation (TMS) has been extensively used to explore cortical physiology and plasticity. TMS is a commonly used technique in the neurosciences which involves stimulating the brain through the intact scalp (Verdon et al., 2004). Based on Faraday's law of electromagnetic induction, TMS generates a time-varying magnetic field which penetrates unimpeded through the scalp and skull and induces an electrical current in the underlying cortex. The elicited focal current in the brain results in neuronal depolarization and firing within the stimulated region (Kobayashi and Pascual-Leone, 2003). A single TMS pulse produces acute cortical activation and when applied to the primary motor cortex (M1), excitability can be quantified using the measurable output of motor evoked potentials (MEPs) from a contralateral muscle. Repetitive application of TMS pulses can induce plastic changes in cortical circuits which outlast the period of stimulation (Maeda et al., 2000b). Using this characteristic, repetitive TMS (rTMS) is frequently applied to induce ongoing modulation of cortical activity. In particular, a modified form of rTMS known as theta-burst stimulation (TBS), has gained notable attention due to its efficacy following short stimulation durations at low intensities. Briefly, TBS consists of pulses applied in bursts of three at 50 Hz with an inter-burst interval at 5 Hz (Huang et al., 2005). Intermittent TBS (iTBS) involves 2 s of TBS trains repeated every 10 s for a total of 20 cycles (600 pulses), and has been shown to increase cortical excitability for at least 20 min. On the other hand, continuous TBS (cTBS) involves uninterrupted TBS trains for 20 (300 pulses) or 40 s (600 pulses), and has shown to decrease cortical excitability for up to 60 min (Huang et al., 2005).

Differences in stimulation parameters, such as the frequency at which pulses are given, as well as dosage (number of pulses), can influence the strength and duration of after-effects of TBS (Gamboa et al., 2010; Goldsworthy et al., 2012a,b). It has been demonstrated that TBS at 30 Hz may produce a neuroplastic response similar to that of TBS at 50 Hz (Jacobs et al., 2014; Tsang et al., 2014; Wu and Gilbert, 2012), although there has been only one study done on motor cortex that directly compared the two frequencies (Goldsworthy et al., 2012b). Even though 30 Hz TBS produced a more consistent and greater reduction in MEP amplitudes than 50 Hz TBS (Goldsworthy et al., 2012b), more studies are required to validate its reliability.

The peak-to-peak amplitude of MEPs produced from single TMS pulses provide an objective measure of corticospinal excitability. In addition to assessing changes in MEPs, short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) can be measured to determine the effect of neuroplasticity invoking paradigms on the excitability of circuits intrinsic to motor cortex. Specifically, SICI Involves two TMS pulses applied at the same cortical location, separated by a brief interstimulus interval (ISI) of typically between 1 and 4 ms (Ziemann et al., 1996) and its effects are believed to be mediated by the gamma-aminobutyric acid (GABA)—A receptor (Di Lazzaro et al., 2006). ICF is measured with ISI of 10–20 ms (Ziemann et al., 1996), and is believed to be mediated by excitatory inputs from glutamatergic pathways (Liepert et al., 1997).

A recent systematic review of TBS on MEPs has demonstrated efficacy of this technique in modulating cortical excitability (Wischnewski and Schutter, 2015), however recent studies with larger sample sizes ($n > 50$) have revealed substantial inter- and intra-individual variability in response to TBS (Hamada et al., 2013; Hinder et al., 2014; Player et al., 2012). In particular, several factors, such as age, gender, time of day, level of attention and genetic variations appear to influence the variability of response to other TMS paradigms such as rTMS and PAS (Conte et al., 2007; Kleim et al., 2006; Muller-Dahlhaus et al., 2008; Sale et al., 2008; Tecchio et al., 2008; Todd et al., 2010). However, these factors have not been found to directly influence individuals' responses to TBS (Di Lazzaro et al., 2008b; Vernet et al., 2014; Young-Bernier et al., 2014) with the exception of brain-derived neurotrophic factor (BDNF) polymorphisms (Antal et al., 2010; Cheeran et al., 2008; Lee et al., 2013).

BDNF is involved in synaptic plasticity in adults (Lu, 2003), and Val66Met, a single nucleotide polymorphism that codes for the BDNF protein, is often implicated in an altered ability to induce neuroplasticity in humans using non-invasive brain stimulation (Antal et al., 2010; Lee et al., 2013). Val66Val carriers were significantly more susceptible to the effects of TMS compared to 'Met' carriers in these studies. However, other studies have found no difference between different genotypes (Li Voti et al., 2011; Mastroeni et al., 2013; Nakamura et al., 2011). In addition, recent evidence suggests that intrinsic differences in recruitment of I-waves may play role in inter-individual variability (Hamada et al., 2013).

The primary aim of this systematic review and meta-analysis was to evaluate the efficacy of iTBS and cTBS in altering corticospinal excitability, SICI and ICF at M1 in healthy individuals. In addition, as the optimal stimulation parameters and factors affecting after-effects of TBS are still unclear, the secondary aim of this review was to investigate the impact of these variables, particularly frequency, number of pulses and BDNF polymorphisms, on TBS-induced corticospinal excitability changes in healthy individuals. We hypothesized that iTBS would increase, while cTBS would decrease, M1 excitability in healthy individuals and influence both SICI (increase in SICI following iTBS, decrease in SICI following cTBS) and ICF (increase in ICF following iTBS, decrease in ICF following cTBS) accordingly. Furthermore, we also hypothesized that 30 Hz TBS as well as longer applications of TBS would induce more effective changes in corticospinal excitability compared to 50 Hz TBS

and shorter durations of TBS. Finally, we also predicted that Val/Val individuals would be more likely to show a greater response to TBS than Met carriers.

2. Methods

2.1. Protocol and registration

This review adhered to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (Moher et al., 2009) and the protocol was registered in the database of International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD42015017587).

2.2. Search strategy

Comprehensive electronic literature searches were performed using the following resources: PubMed, EMBASE, The Cochrane Library, EBSCO Medline and Ovid Medline, from January 2005 to August 2014. The key search terms included: 'TBS' or 'theta burst stimulation' or 'theta burst transcranial magnetic stimulation' or 'transcranial theta burst stimulation' and 'motor cortex' or 'cortical excitability' or 'motor evoked potentials' or 'MEPs' or 'motor threshold' or 'recruitment curves' or 'cortical inhibition' or 'LICI' or 'long interval cortical inhibition' or 'CSP' or 'cortical silent period'. The addition of search words 'SICI' or 'short interval cortical inhibition' or 'ICF' or 'intracortical facilitation' did not change search results (See result Section 3.1 for more detail).

Two reviewers (SWC and AH) independently assessed the titles and abstracts of the initial search results for relevant studies against the inclusion criteria (see Table 1). Full-text versions were examined in instances where it was unclear form the summary data alone whether the study met the inclusion criteria. Full text versions of potentially eligible studies were then progressed to the next stage of screening by the same reviewers. Discrepancies between the reviewers were solved by consensus.

2.3. Selection criteria

Studies were included on the basis of the inclusion and exclusion criteria outlined in Table 1. Studies were selected if: (1) the intervention used was iTBS or cTBS over M1 in healthy subjects over 18 years of age, (2) MEP amplitudes, SICI or ICF were used as outcome measures, (3) sufficient data was available to compute effect sizes using Hedge's adjusted g (mean, standard deviation, and sample size), (4) studies had before and after measurements, (5) study designs were cross-over or parallel, (5) studies were published in peer-reviewed journals, and (6) articles were written in English. Full-text articles were assessed to exclude studies using a combination of different interventions with TBS, or TBS accompanied by any tasks or stimuli (e.g., movement tasks, emotional or visual stimuli).

2.4. Outcome measures

Studies investigating the effects of iTBS and/or cTBS on MEP amplitudes have been included as the primary outcome measure. Studies evaluating the changes in SICI and ICF were included as secondary outcome measures.

2.5. Data extraction

Total sample sizes were recorded and means and standard deviations of the outcome measures from baseline up to 60 min post-stimulation were obtained from text or tables in the included papers. If numerical values were not available, data were extracted directly from relevant figures using Plot Digitizer software (Huwaldt, 2010). In cases of insufficient or incomplete data being reported, attempts were made to contact the corresponding authors for clarification and additional data.

Table 1
Inclusion and exclusion criteria.

	Inclusion	Exclusion
Participants	Healthy individuals over 18 years of age	Individuals suffering from any type of neurological disease Non-human subjects
Interventions	iTBS or cTBS applied over M1	Combination of different interventions involving behavioural/motor tasks or different stimuli (e.g emotional stimuli, visual attention, mirror visual feedback) before intervention or during measurement
Comparison	Before and after intervention	No baseline measurement
Outcomes	MEP amplitudes measured by single pulse TMS SICI or ICF measured by paired pulse TMS	Other type of measurement (e.g behavioural, fMRI, NIRS, EEG)
Study design	Pre–post studies Cross-over or parallel group	–
Data reported	Data that enables analysis and estimation of the effects of TBS on characteristics of MEPs, SICI and ICF Data collected from stimulated area	Unpublished data Data without SD/SEM Data collected from non-stimulated area
Type of publications	Peer-reviewed journal Written in English	Non-English articles Review articles, case reports, grey literature

EEG – electroencephalogram; fMRI – functional magnetic resonance imaging; iTBS/cTBS – intermittent/continuous TBS; ICF – intracortical facilitation; M1–primary motor cortex; MEPs – motor evoked potentials; NIRS – near-infrared spectroscopy; SICI – short-interval intracortical inhibition; SEM – standard error of mean; SD – standard deviation; TMS – transcranial magnetic stimulation.

2.6. Meta-analysis

2.6.1. Calculating effect sizes

Continuous outcome measures were used in the meta-analysis. The extracted data (number of participants, means and standard deviations) were entered into the MIX 2.0 computer program (Bax, 2010) to conduct the analyses. MIX allows calculation of statistical significance of differences between means (pre versus post intervention) with 95% confidence intervals (CIs). The standardized mean difference (SMD) calculated using Hedge's adjusted g was estimated for the effect sizes of the outcome measures. For SMDs, values of 0.2 were defined small, 0.5 medium and 0.8 large (Cohen, 1988). Hedge's adjusted g is similar to Cohen's d, but includes adjustment for small sample bias (Hedges and Olkin, 1985). Where standard error (SE) values were presented, standard deviation (SD) values were estimated using the formula $SD = SE\ \sqrt{n}$ (n = sample size) (Higgins and Green, 2008).

2.6.2. Test of heterogeneity

Heterogeneity among studies was evaluated using the I^2 statistic (Higgins et al., 2003). I^2 ranges from 0% to 100%, with 0% indicating no observed heterogeneity, and >50% representing substantial heterogeneity. In addition, Galbraith plots were used as a graphical

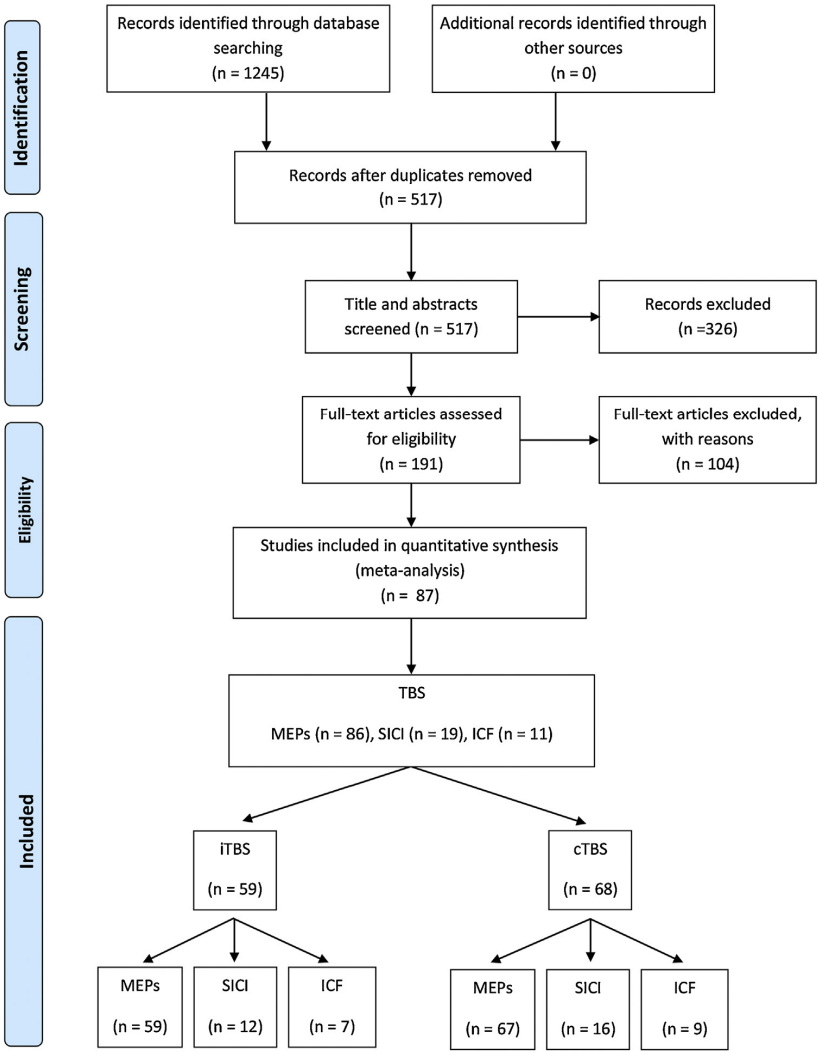

Fig. 1. Flow diagram of selected studies (*n* = number of articles).

representation of the heterogeneity of the study data. It has been described that the test of heterogeneity should not set the basis for which model to use (Borenstein et al., 2010). As the included studies had been performed independently by different researchers, it was highly unlikely that all the studies used identical stimulation parameters, equipment, and populations. Therefore, random-effect models were employed for all analyses regardless of heterogeneity.

2.6.3. Publication bias

Possible publication bias was explored using several methods. First, methods based on funnel asymmetry were employed. These include visually inspecting selectivity funnel plot, the trim and fill method (Duval and Tweedie, 2000), Begg's adjust rank correlation test (Begg and Mazumdar, 1994) and Egger's regression test (Egger et al., 1997). Asymmetry in funnel plots indicates a relationship between effects and study size, suggesting the likelihood of either publication bias or a systematic difference between smaller and larger studies (Sterne et al., 2001). In addition, the trim and fill method aims to correct for publication bias by estimating the number of missing studies, trimming and filling in to maintain the symmetry of the funnel plot (Duval and Tweedie, 2000). These methods have been described to be relatively powerful with large number of studies (Sterne et al., 2000). However, it should be noted that the tests of funnel plot asymmetry have low power in the presence of large between-study heterogeneity (Deeks et al., 2005). Furthermore, the trim and fill method relies on the assumption that the observed asymmetry is solely due to publication bias, and true effect is underestimated when there is no publication bias (Peters et al., 2007). To investigate the contribution of imprecise study samples and effect sizes, cumulative forest plots were examined, sorted in the sequence of largest to smallest (Borenstein et al., 2009). The drifting trend of the estimated effect sizes indicates the impact of small imprecise studies may have on the overall effect. Finally, a Bayesian approach was used to detect and mitigate the effects of publication bias. The Bayesian model has been shown to allow for

the affirmation and falsification of null hypothesis, with inclusion of prior information (Guan and Vandekerckhove, 2015).

3. Results

3.1. Selection of studies

Electronic literature searches identified a total of 1245 studies matching the search terms. Duplicate removal resulted in 517 studies remaining. Initial screening of title and abstract was performed against the selection criteria, and in cases of insufficient information, full-text articles were referred to. After excluding 326 studies from the initial screening, full-text versions of 191 records were screened for eligibility. Insufficient number of studies investigating TBS effects on LICI and CSP led to additional screening of SICI and ICF. A total of 87 studies were included in the systematic review and meta-analysis, of which 86 were appropriate for MEP amplitude analysis, 19 for SICI and 11 for ICF (Fig. 1). Selected studies were then categorized into two groups based on the TBS paradigm used- iTBS (MEPs: 59 studies, SICI: 12 studies, ICF: 7 studies) and cTBS (MEPs: 67 studies, SICI: 16 studies, ICF: 9 studies).

3.2. Intermittent TBS

Table 2 summarizes the characteristics of iTBS studies, with MEPs as outcome measures. Studies of multiple experimental conditions were separated into different datasets depending on the specific stimulation parameter (number of pulses given), BDNF polymorphism and/or number of participants. MEP amplitudes pre-iTBS were compared to post-iTBS at three different time points: early (within 5 min), mid (20–30 min post), and late (50–60 min post).

3.2.1. Effect of iTBS on MEP amplitude

Fig. 2 provides a summary of the pooled data extracted from all studies with iTBS as an intervention, measured at different time points; Fig. 2A—early (within 5 min, 81 datasets, 1071 subjects), Fig. 2B—mid (20–30 min, 65 datasets, 826 subjects), and Fig. 2C—late (50–60 min, 18 datasets, 235 subjects). These include all studies regardless of differences in stimulation parameters or BDNF polymorphism. The effect of iTBS at the early time point yielded a significant and moderately large MEP increase with a pooled SMD of 0.69 (95% CI: 0.54; 0.84, $p < 0.00001$). The test of heterogeneity was significant ($Q = 200.25$, $p < 0.00001$, $I^2 = 60.05\%$). These results remained significant up to the mid time point (SMD = 0.71, 95% CI: 0.54; 0.87, $p < 0.00001$) with significant heterogeneity ($Q = 152.89$, $p < 0.00001$, $I^2 = 58.14\%$). The effect of iTBS on MEP amplitudes at the late time point was not significant (SMD = 0.17, 95% CI: −0.06; 0.4, $p = 0.15$).

3.2.2. Publication bias in iTBS studies

Galbraith plots indicated heterogeneity in the dataset at the early time point (Fig. 3A) and there was also apparent asymmetry in the shape of the selectivity funnel plot at this time point (Fig. 3B). Each line forming the shape of the funnel represents various levels of significance (0.01, 0.05 and 0.1). The trim and fill method estimated the overall effect size at 0.36 (Fig. 3C), which was far smaller than the original value of 0.69. Begg's test (tau = 0.1985, $p = 0.0086$) and Egger's regression test indicated evidence of publication bias (Fig. 3C, $t = 4.5930$, $p = 0.00002$). The cumulative forest plot also showed a shift in the point estimate (Fig. 3E), indicating the presence of bias. Finally, Bayesian analysis yielded a smaller effect size of 0.57 compared to the original outcome (Fig. 3F). These combined analyses indicate a strong possibility of publication bias in this dataset.

Presence of publication bias was less apparent at mid time point. Trim and fill analysis estimated the overall effect size of 0.52, compared to the original value of 0.71. Begg's test indicated no publication bias (tau = 0.1582, $p = 0.0625$). However, Egger's regression test revealed possible publication bias (Fig. 3D, $t = 3.0286$, $p = 0.0036$). Bayesian analysis estimated an overall effect size of 0.62. It is therefore plausible that there was publication bias in this dataset. No publication bias was observed at late time point, in both Begg's test (tau = 0.0327, $p = 0.8498$) and Egger's test ($t = -0.2344$, $p = 0.8176$), and Bayesian analysis estimated overall effect size of 0.17, the same as the original effect size.

3.2.2.1. Subgroup analysis on MEP amplitude for iTBS. Subgroup analysis was performed based on number of pulses (Fig. 4) and BDNF polymorphism (Fig. 5). Frequency was not able to be analysed as only one study was found.

3.2.2.1.1. Number of pulses. Fig. 4 illustrates the impact of number of pulses on MEP amplitude, measured at the different time points. Data sets (Fig. 2) were categorized into two subgroups, 600 pulses and 1200 pulses. At the early time point, both of these subgroups showed similar and moderately large significant MEP increases, with SMDs of 0.68 (95% CI: 0.52; 0.83, $p < 0.00001$) and 0.64 (95% CI: 0.03; 1.25, $p = 0.04$), respectively (Fig. 4A). Moderate differences in effect sizes between the subgroups were observed at the mid time point, with SMD of 0.68 (95% CI: 0.52; 0.84, $p < 0.00001$) for 600 pulses, and 0.84 (95% CI: 0.01; 1.68, $p = 0.047$) for 1200 pulses (Fig. 4B). The effect of iTBS on MEP amplitudes at the late time point following 600 pulses was significant, but with a smaller effect size (SMD = 0.33, 95% CI: 0.12; 0.54, $p = 0.002$) (Fig. 4C). However, 1200 pulses of iTBS failed to produce a significant effect (SMD = − 0.21, 95% CI: − 0.76; 0.35, $p = 0.47$).

3.2.2.1.2. BDNF polymorphism. Fig. 5 depicts forest plots of the influence of the BDNF polymorphism on MEP amplitudes after iTBS. At the early time point, there was a significant increase in MEP amplitudes following iTBS with a moderate effect size in Met carriers (SMD = 0.58, 95% CI: 0.15; 1.02, $p = 0.009$), while a substantially larger effect size was seen in the Val/Val group (SMD = 0.96, 95% CI: 0.54; 1.38, $p < 0.00001$) (Fig. 5A). A non-significant increase in MEP amplitude with a moderately large effect size was observed with Met carriers at the mid time point (SMD = 0.73, 95% CI: −0.22; 1.67, $p = 0.13$). However, the Val/Val group maintained a significant increase in MEP amplitude with a large effect size (SMD = 0.99, 95% CI: 0.65; 1.32, $p < 0.00001$) (Fig. 5B).

3.2.3. Effect of iTBS on SICI

Table 3 summarizes characteristics of iTBS studies with SICI as the outcome measure. SICI at pre-iTBS was compared to post-iTBS at two different time points: early (within 5 min) and mid (20–30 min post). A total of 13 datasets, containing results for 176 subjects, were included in the analysis.

No significant differences were found in SICI for both at the early time point (SMD = −0.02, 95% CI: −0.24; 0.2, $P = 0.88$) (see Supplementary Fig. 1A) and the mid time point (SMD = 0.06, 95% CI: −0.3; 0.43, $P = 0.74$) (Supplementary Fig. 1B). The tests of heterogeneity were not significant for both time points; early ($Q = 6.53$, $p = 0.77$, $I^2 = 0.00\%$), and mid ($Q = 1.25$, $p = 0.94$, $I^2 = 0.00\%$).

3.2.4. Effect of iTBS on ICF

Table 4 outlines characteristics of iTBS studies with ICF as the outcome measure. ICF at pre-iTBS were compared to post-iTBS at two different time points: early (within 5 min) and mid (20–30 min post). A total of 7 datasets, containing the results from 74 subjects, were included in the analysis.

No significant differences were found in ICF at both early (SMD = 0.18, 95% CI: −0.56; 0.93, $P = 0.63$) (see Supplementary Fig. 2A) and mid time point (SMD = −0.18, 95% CI: −0.7; 0.34, $P = 0.49$)

(Supplementary Fig. 2B). The test of heterogeneity was significant

Table 2
MEPs – iTBS.

Studies (no. of experiments)	Sample size (n)	Gender ratio	Mean age ± SD (age range)	iTBS parameters (variable)	iTBS pulse number (interval setting)	Target muscle	Poly-morphism
Antal et al. (2010) (1)	10	3 M: 7F	(21 – 32)	80% aMT, 50 Hz/5 Hz	600	FDI	Val/Val
Antal et al. (2010) (2)	5	2 M: 3F	(20 – 29)	80% aMT, 50 Hz/5 Hz	600	FDI	Val/Met
Belvisi et al. (2013)	14	11 M: 3F	41.9 ± 11.36 (23 – 60)	80% aMT, 50 Hz/5 Hz	600	FDI	–
Brownjohn et al. (2014)	10	9 M: 1F	26.9 ± 4.7 (22- 37)	80% aMT, 50 Hz/5 Hz	600	FDI	–
Cardenas-Morales et al. (2014)	12	7 M: 5F	39 ± 11	70% rMT, 50 Hz/5 Hz	600	APB	–
Cheeran et al. (2008) (1)	9	6 M: 3F	29.3 ± 3	80% aMT, 50 Hz/5 Hz	600	FDI	Val/Val
Cheeran et al. (2008) (2)	9	6 M: 3F	28.7 ± 3	80% aMT, 50 Hz/5 Hz	600	FDI	Val/Met
Conte et al. (2012)	15	–	68.0 ± 7.75 (60 – 85)*	80% aMT, 50 Hz/5 Hz	600	FDI	–
Di Lazzaro et al. (2008a)	12	7 M: 5F	63.2 ± 5.3	80% aMT, 50 Hz/5 Hz	600	FDI	–
Di Lazzaro et al. (2008b)	18	–	51.2 ± 17.9 (25 – 75)	80% aMT, 50 Hz/5 Hz	600	FDI	–
Di Lazzaro et al. (2011)	10	–	26.6 ± 4.1	80% aMT, 50 Hz/5 Hz	600	FDI	–
Doeltgen and Ridding (2011b) (1)	14	4 M: 10F	24.5 ± 3.1	80% aMT, 50 Hz/5 Hz	600	FDI	–
Doeltgen and Ridding (2011b) (2)	9*			80% aMT, 50 Hz/5 Hz	600	FDI	–
Gamboa et al. (2010) (1)	14	7 M: 7F	(21 – 27)	80% aMT, 50 Hz/5 Hz	600	FDI	–
Gamboa et al. (2010) (2)	14			80% aMT, 50 Hz/5 Hz	1200	FDI	–
Gamboa et al. (2011) (1)	10*	10 M: 6F	24.7 ± 1.39 (21 – 27)	80% aMT, 50 Hz/5 Hz	600	FDI	–
Gamboa et al. (2011) (2)	10*			80% aMT, 50 Hz/5 Hz	1200 (600 – 2 min – 600)	FDI	–
Gamboa et al. (2011) (3)	10*			80% aMT, 50 Hz/5 Hz	1200 (600 – 5 min – 600)	FDI	–
Gamboa et al. (2011) (4)	10*			80% aMT, 50 Hz/5 Hz	1200 (600 – 20 min – 600)	FDI	–
Hamada et al. (2013)	52	32 M: 24F	30.3 ± 7.4 (18 – 52)	80% aMT, 50 Hz/5 Hz	600	FDI	–
Hasan et al. (2012)	9	7 M: 2F	30.3 ± 1.5	80% aMT, 50 Hz/5 Hz (with sham tDCS)	600	FDI	–
Hinder et al. (2014)	30	11 M: 19F	25.3 ± 8.7 (18 – 44)	80% aMT, 50 Hz/5 Hz	600	FDI	–
Hsu et al. (2011)	10	5 M: 5F	29.0 ± 7.1	80% aMT, 50 Hz/5 Hz	1200	FDI	–
Huang et al. (2005)	9	–	33.6 ± 7.8 (23- 52)	80% aMT, 50 Hz/5 Hz	600	FDI	–
Huang et al. (2007)	6	1 M: 5F	29 ± 6	80% aMT, 50 Hz/5 Hz (with placebo)	600	FDI	–
Huang et al. (2008)	7	5 M: 2F	32 ± 5	80% aMT, 50 Hz/5 Hz	600	FDI	–
Huang et al. (2010b) (1)	8	1 M: 7F	33.3 ± 10.3	80% aMT, 50 Hz/5 Hz	150	FDI	–
Huang et al. (2010b) (2)	7	4 M: 3F	28.7 ± 3.6	80% aMT, 50 Hz/5 Hz	600	FDI	–
Iezzi et al. (2008) (1)	10	6 M: 4F	35 ± 3	80% aMT, 50 Hz/5 Hz	600	FDI	–
Iezzi et al. (2008) (2)	5*			80% aMT, 50 Hz/5 Hz	600	APB	–
Iezzi et al. (2011)	10	6 M: 4F	32 ± 5.03	80% aMT, 50 Hz/5 Hz	600	FDI	–
Kishore et al. (2012a)	10	8 M: 2F	45.6 ± 7.8	80% aMT, 50 Hz/5 Hz	600	FDI	–
Kishore et al. (2012b)	10	8 M: 2F	45.6 ± 7.8	80% aMT, 50 Hz/5 Hz	600	FDI	–
Koch et al. (2012)	14	9 M: 5F	–	80% aMT, 50 Hz/5 Hz	600	FDI	–
Koch et al. (2014)	10	6 M: 4F	68.3 ± 5.6	80% aMT, 50 Hz/5 Hz	600	FDI	–
Lee et al. (2013) (1)	6	4 M: 2F	29.6 ± 3.6	80% rMT, 50 Hz/5 Hz	600	FDI	Val/Val
Lee et al. (2013) (2)	13	4 M: 9F	32.5 ± 4.7	80% rMT, 50 Hz/5 Hz	600	FDI	Val/Met
Lee et al. (2013) (3)	4	2 M: 2F	31.3 ± 5.3	80% rMT, 50 Hz/5 Hz	600	FDI	Met/Met
Li Voti et al. (2011) (1)	14*	22 M: 16F	27.95 ± 5.57	80% aMT, 50 Hz/5 Hz	600	FDI	Val/Val
Li Voti et al. (2011) (2)	7*			80% aMT, 50 Hz/5 Hz	600	FDI	Met Carriers
López-Alonso et al. (2014)	56	50 M: 6F	20.52 ± 1.52 (19 – 24)	80% aMT, 50 Hz/5 Hz	600	FDI	–
Martin et al. (2006)	8	–	30.6 ± 8.2	80% aMT, 50 Hz/5 Hz	600	FDI & Biceps	–
Mastroeni et al. (2013) (1)	17*	29M	26.0 ± 3.2	80% aMT, 50 Hz/5 Hz	600	FDI	Val/Val
Mastroeni et al. (2013) (2)	12*			80% aMT, 50 Hz/5 Hz	600	FDI	Val/Met
Mastroeni et al. (2013) (3)	17*			80% aMT, 50 Hz/5 Hz	1200 (600 – 30 min – 600)	FDI	Val/Val
Mastroeni et al. (2013) (4)	12*			80% aMT, 50 Hz/5 Hz	1200 (600 – 30 min – 600)	FDI	Val/Met
McAllister et al. (2009)	9	4 M: 5F	28.3 ± 11.1	70% aMT, 50 Hz/5 Hz	600	FDI	–
Moliadze et al. (2014)	12	–	25.7 ± 4.1 (23 – 38)	80% aMT, 50 Hz/5 Hz	600	FDI	Val/Val
Monte-Silva et al. (2011)	12	6 M: 6F	25.75 ± 5.11	80% aMT, 50 Hz/5 Hz (with placebo)	600	FDI	–
Mori et al. (2012)	77	31 M: 46F	38.3 ± 10.2	80% aMT, 50 Hz/5 Hz	600	FDI	–
Mori et al. (2013)	13	8 M: 5F	35.5 ± 9.2	80% aMT, 50 Hz/5 Hz	600	FDI	–
Murakami et al. (2008)	6*	13 M: 15F	27.1 ± 4.8	80% aMT, 50 Hz/5 Hz	600	FDI	–
Murakami et al. (2012) (1)	9	7 M: 2F	29.2 ± 6.9	80% aMT, 50 Hz/4.2 Hz	600	FDI	–

Table 2 (*Continued*)

Studies (no. of experiments)	Sample size (n)	Gender ratio	Mean age ± SD (age range)	iTBS parameters (variable)	iTBS pulse number (interval setting)	Target muscle	Poly-morphism
Murakami et al. (2012) (2)	9	7 M: 2F	29.2 ± 6.9	80% aMT, 50 Hz/4.2 Hz	1200 (600 – 15 min – 600)	FDI	–
Murakami et al. (2012) (3)	8	5 M: 3F	27.4 ± 4.7	70, 80% aMT, 50 Hz/4.2 Hz	600	FDI	–
Nettekoven et al. (2014) (1)	16	7 M: 9F	27 ± 3	70% rMT, 50 Hz/5 Hz	600	APB	–
Nettekoven et al. (2014) (2)	6*			70% rMT, 50 Hz/5 Hz	600	APB	–
Nettekoven et al. (2014) (3)	16			70% rMT, 50 Hz/5 Hz	1200 (600 – 15 min – 600)	APB	–
Nettekoven et al. (2014) (4)	16			70% rMT, 50 Hz/5 Hz	1800 (600 – 15 min – 600 – 15 min – 600)	APB	–
Oberman et al. (2010)	2*	2 M: 3F	38.6 ± 13.8 (22 – 54)	80% aMT, 50 Hz/5 Hz	600	FDI	–
Oberman et al. (2012)	20	16 M: 4F	34.9 ± 16.2	80% aMT, 50 Hz/5 Hz	600	FDI	–
Pichiorri et al. (2012)	11	8 M: 3F	31 ± 8.5	80% aMT, 50 Hz/5 Hz	600	FDI	–
Player et al. (2012) (1)	10*	9 M: 7F	–	80% aMT, 50 Hz/5 Hz	600	FDI	–
Player et al. (2012) (2)	6*			80% aMT, 50 Hz/5 Hz	600	FDI	–
Popa et al. (2013)	14*	8 M: 15F	32.6 ± 6.6	80% aMT, 50 Hz/5 Hz	600	APB & ADM	–
Suppa et al. (2008)	15*	11 M: 7F	31 ± 5 (26 – 45)	80% aMT, 50 Hz/5 Hz	600	FDI	–
Suppa et al. (2011a)	14	11 M: 3F	60 ± 11.28 (49 – 81)	80% aMT, 50 Hz/5 Hz	600	FDI	–
Suppa et al. (2011b)	12	7 M: 5F	30 ± 4.9 (25 – 40)	80% aMT, 50 Hz/5 Hz	600	FDI	–
Suppa et al. (2014a)	20	14 M: 6F	32.8 ± 11.2	80% aMT, 50 Hz/5 Hz	600	FDI	–
Suppa et al. (2014b)	20	10 M: 10F	58.6 ± 11.5 (36 – 81)	80% aMT, 50 Hz/5 Hz	600	FDI	–
Swayne et al. (2009)	10	7 M: 3F	29.6 ± 4.7	80% aMT, 50 Hz/5 Hz (with placebo)	600	FDI	–
Talelli et al. (2007) (1)	10*	9 M: 9F	29.6 ± 3.9	80% aMT, 50 Hz/5 Hz	600	FDI	–
Talelli et al. (2007) (2)	10*			100% aMT, 50 Hz/5 Hz	600	FDI	–
Teo et al. (2007)	6	4 M: 2F	–	80% aMT, 50 Hz/5 Hz (with placebo)	600	FDI	–
Todd et al. (2009)	8	4 M: 4F	27 ± 10	80% aMT, 50 Hz/5 Hz	600	FDI	–
Vallence et al. (2013)	18	9 M: 9F	23.3 ± 2.7	80% aMT, 50 Hz/5 Hz	600	APB	–
Wu and Gilbert (2012)	11	7 M: 4F	27.5 ± 9.0 [± 5]+	80% aMT, 50 Hz/5 Hz	600	FDI	–
Wu et al. (2012)	9*	8 M: 10F	33 ± 9.0	90% rMT, 30 Hz/5 Hz	600	FDI	–
Young-Bernier et al. (2014) (1)	20	7 M: 13F	22.3 ± 3.2	80% aMT, 50 Hz/5 Hz	600	FDI & APB	–
Young-Bernier et al. (2014) (2)	18	9 M: 9F	70.1 ± 5.6	80% aMT, 50 Hz/5 Hz	600	FDI & APB	–
Zafar et al. (2008)	9	4 M: 5F	21.3 (21 – 26)	80% aMT, 50 Hz/5 Hz	600	ADM	–
Zamir et al. (2012)	10	4 M: 6F	63.1 ± 8.8 (50 – 75)	80% aMT, 50 Hz/5 Hz	600	FDI	–

aMT/rMT – active/resting motor threshold; APB – abductor pollicis brevis; ADM – abductor digiti minimi; FDI – first dorsal interosseous; iTBS – intermittent theta burst stimulation; tDCS – transcranial direct current stimulation * indicates numbers that are subset of total recruited subjects, + indicates age used for age-matched group

for ICF measured at early ($Q = 22.80$, $p = 0.0009$, $I^2 = 73.68\%$), but not at mid time point ($Q = 0.48$, $p = 0.49$, $I^2 = 0.00\%$).

3.3. Continuous TBS

Table 5 summarizes the characteristics of cTBS studies using MEPs as the outcome measure. MEP amplitudes pre-cTBS were compared to post-cTBS at three different time points: early (within 5 min), mid (20–30 min post), and late (50–60 min post).

3.3.1. Effect of cTBS on MEP amplitude

Fig. 6 outlines the summary of all included studies with cTBS as an intervention, measured at different time points; Fig. 6A—early (within 5 min, 95 datasets, 1182 subjects), Fig. 6B—mid (20–30 min, 83 datasets, 984 subjects), and Fig. 6C—late (50–60 min, 26 datasets, 291 subjects). At the early time point, cTBS produced a significant and large MEP decrease with a pooled SMD of −0.9 (95% CI: −1.08; −0.71, $P < 0.00001$). The test of heterogeneity was significant ($Q = 383.90$, $p < 0.00001$, $I^2 = 75.51\%$). At the mid time point, a significant but reduced effect size was observed (SMD = −0.69, 95% CI: −0.87; −0.51, $p < 0.00001$), with heterogeneity remaining significant ($Q = 278.29$, $p < 0.00001$, $I^2 = 70.53\%$). The effect of cTBS on MEP amplitudes at the late time point remained significant with a relatively moderate effect size (SMD = −0.43, 95% CI: −0.76; −0.1, $p = 0.01$).

3.3.2. Publication bias in cTBS studies

Heterogeneity at the early time point is displayed in Fig. 7A using a Galbraith plot. Obvious asymmetry in the selectivity funnel plot indicated the presence of publication bias (Fig. 7B). The trim and fill method estimated an overall effect size of −0.48 (Fig. 7C), which was significantly smaller than the original value of −0.90. Publication bias assessed with Begg's test (tau = −0.4085, $p < 0.00001$), and Egger's regression test (Fig. 7D, $t = -5.8606$, $p < 0.00001$) showed a high level of significance. The cumulative forest plot showed shift in the point estimate (Fig. 7E), indicating a presence of bias. Finally, Bayesian analysis yielded smaller effect size of −0.68 compared to the original outcome (Fig. 7F). Overall, the combined analyses are strongly suggestive of a degree of publication bias in this data set.

Presence of publication bias continued to exist at the mid time point. Trim and fill analysis estimated the overall effect size of −0.29, compared to the original value of −0.69. Begg's test (tau = −0.3748, $p < 0.00001$) and Egger's regression test ($t = -5.1970$, $p < 0.00001$) were both highly significant. Bayesian

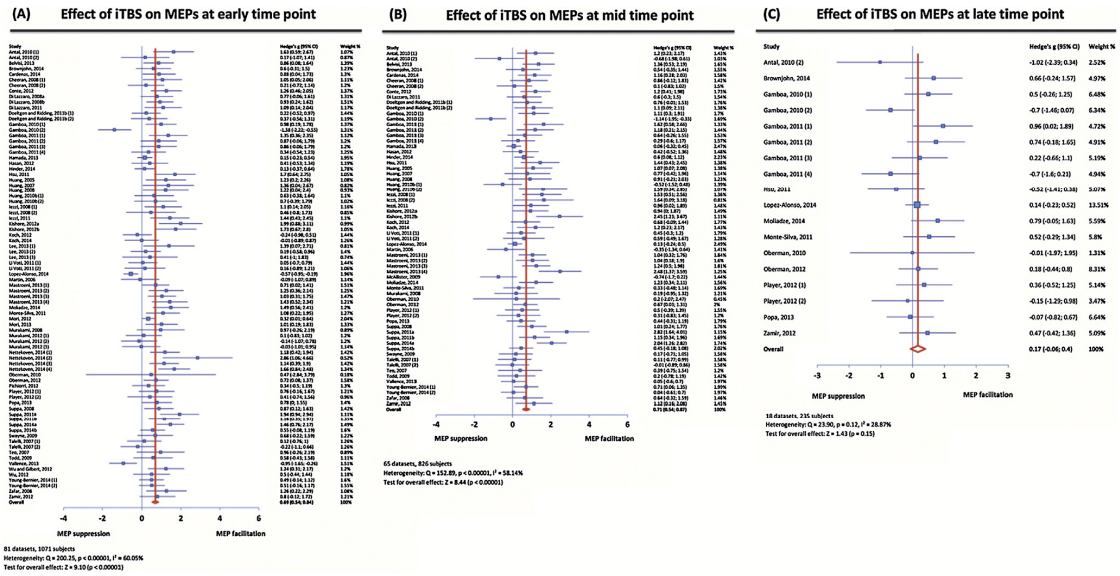

Fig. 2. Forest plot of the Hedge's adjusted g analysis for all studies for MEPs amplitude after iTBS measured post 0–5 min (A), 20–30 min (B) and 50–60 min (C).

Table 3
SICI – iTBS.

Studies (no. of experiments)	Sample size (n)	Gender ratio	Mean age ± SD (age range)	iTBS parameters	SICI ISI	Target muscle
Brownjohn et al. (2014)	9*	9 M: 1F	26.9 ± 4.7 (22- 37)	80% aMT, 50 Hz/5 Hz, 600 pulses	3 ms	FDI
Di Lazzaro et al. (2011)	10	–	26.6 ± 4.1	80% aMT, 50 Hz/5 Hz, 600 pulses	3 ms	FDI
Doeltgen and Ridding (2011b)	14	4 M: 10F	24.5 ± 3.1	80% aMT, 50 Hz/5 Hz, 600 pulses	2 & 3 ms	FDI
Hasan et al. (2012)	9	7 M: 2F	30.3 ± 1.5	80% aMT, 50 Hz/5 Hz, 600 pulses (with sham tDCS)	2 & 3 ms	FDI
Huang et al. (2005)	7*	–	33.6 ± 7.8 (23- 52)	80% aMT, 50 Hz/5 Hz, 600 pulses	2 ms	FDI
Huang et al. (2010b)	6	2 M: 4F	30.3 ± 3.1	80% aMT, 50 Hz/5 Hz, 150 pulses	2 & 3 ms	FDI
Lee et al. (2013)	23	10 M: 13F	31.9 ± 4.4	80% rMT, 50 Hz/5 Hz, 600 pulses	2 ms	FDI
López-Alonso et al. (2014)	56	50 M: 6F	20.52 ± 1.52 (19 – 24)	80% aMT, 50 Hz/5 Hz, 600 pulses	2 ms	
McAllister et al. (2009)	9	4 M: 5F	28.3 ± 11.1	70% aMT, 50 Hz/5 Hz, 600 pulses	3 ms	FDI
Murakami et al. (2008)	6*	13 M: 15F	27.1 ± 4.8	80% aMT, 50 Hz/5 Hz, 600 pulses	2 ms	FDI
Murakami et al. (2012) (1)	9	7 M: 2F	29.2 ± 6.9	80% aMT, 50 Hz/4.2 Hz, 600 pulses	2 ms	FDI
Murakami et al. (2012) (2)	8	5 M: 3F	27.4 ± 4.7	70, 80% aMT, 50 Hz/4.2 Hz, 600 pulses	2 ms	FDI
Zamir et al. (2012)	10	4 M: 6F	63.1 ± 8.8 (50 – 75)	80% aMT, 50 Hz/5 Hz, 600 pulses	2 ms	FDI

aMT – active motor threshold; FDI – first dorsal interosseous; ISI – interstimulus interval; iTBS – intermittent theta burst stimulation; SICI – short interval intracortical inhibition * indicates numbers that are subset of total recruited subjects

analysis estimated overall effect size of −0.54. It is therefore highly likely that there was a degree of publication bias in this dataset also.

There was an indication of possible publication bias at the late time point. Trim and fill method estimated an overall effect size of −0.27 (original = −0.43), and Begg's test (tau = −0.3446, $p = 0.0136$) and Egger's test ($t = -2.8805$, $p = 0.0082$) suggested the presence of bias. Bayesian analysis estimated overall effect size of −0.29.

3.3.2.1. Subgroup analysis on MEPs amplitude for cTBS. Subgroup analysis was performed based on number of pulses (Fig. 8), frequency of stimulation given (Fig. 9) and BDNF polymorphism (Fig. 10).

3.3.2.1.1. Number of pulses. Fig. 8 displays the forest plot of the impact of number of pulses (300 pulses, 600 pulses and 1200 pulses) on MEP amplitude, measured at different time points. At the early time point, both 300 pulses and 1200 pulses resulted in sim-

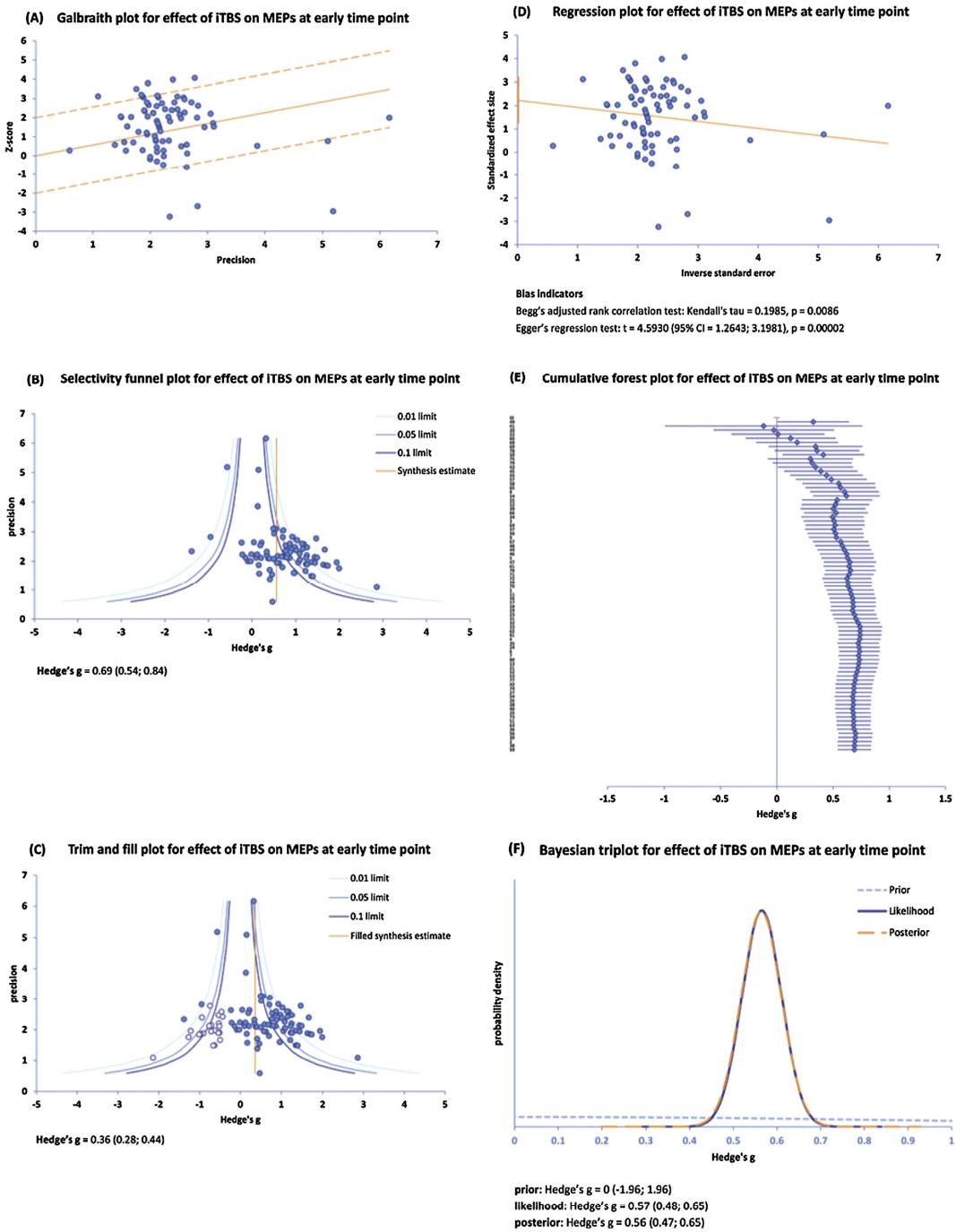

Fig. 3. Series of tests for heterogeneity and publication bias for all studies for MEPs amplitude after iTBS measured post 0–5 min; (A) Galbraith plot, (B) Selectivity funnel plot, (C) Trim and fill plot, (D) Regression plot, (E) Cumulative forest plot and (F) Bayesian triplot.

ilar and highly significant MEP amplitude decreases with SMDs of −1.02 (95% CI: −1.59; −0.46, $P = 0.0004$) and −1.05 (95% CI: −1.69; −0.42, $P = 0.001$), respectively (Fig. 8A). 600 pulses yielded a lower effect size compared to 300 and 1200 pulses, but nevertheless produced a highly significant MEP amplitude reduction (SMD = −0.85, 95% CI: −1.06; −0.65, $P < 0.00001$). However, at the mid time point, two subgroups, 300 pulses and 600 pulses, produced significant and almost identical moderate-to-large effect sizes (SMD = −0.62,

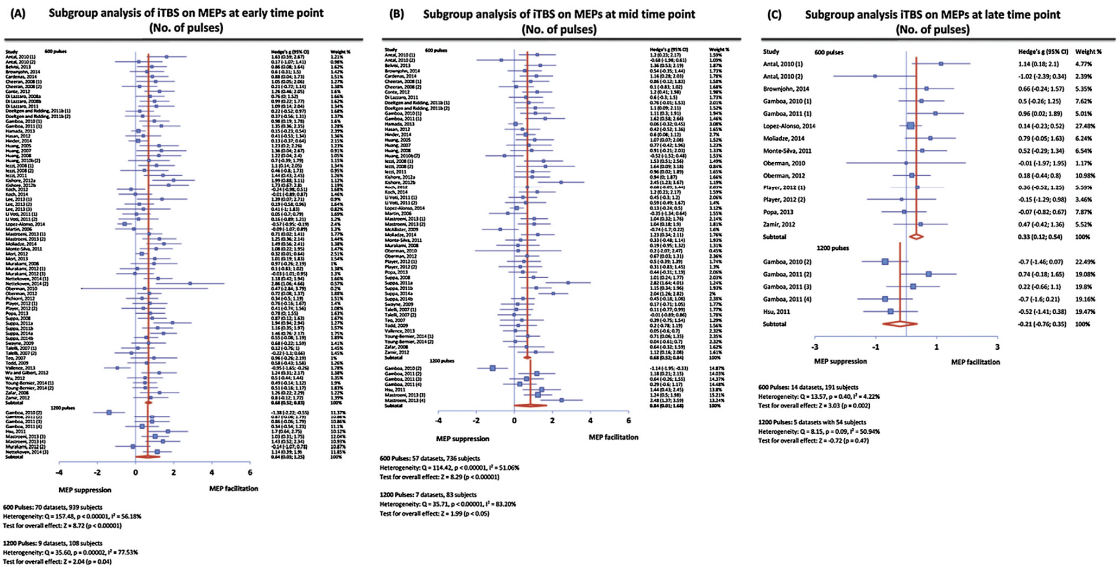

Fig. 4. Forest plot of the Hedge's adjusted g analysis for subgroup studies (no. of pulses) of MEPs amplitude after iTBS measured post 0–5 min (A), 20–30 min (B) and 50–60 min (C).

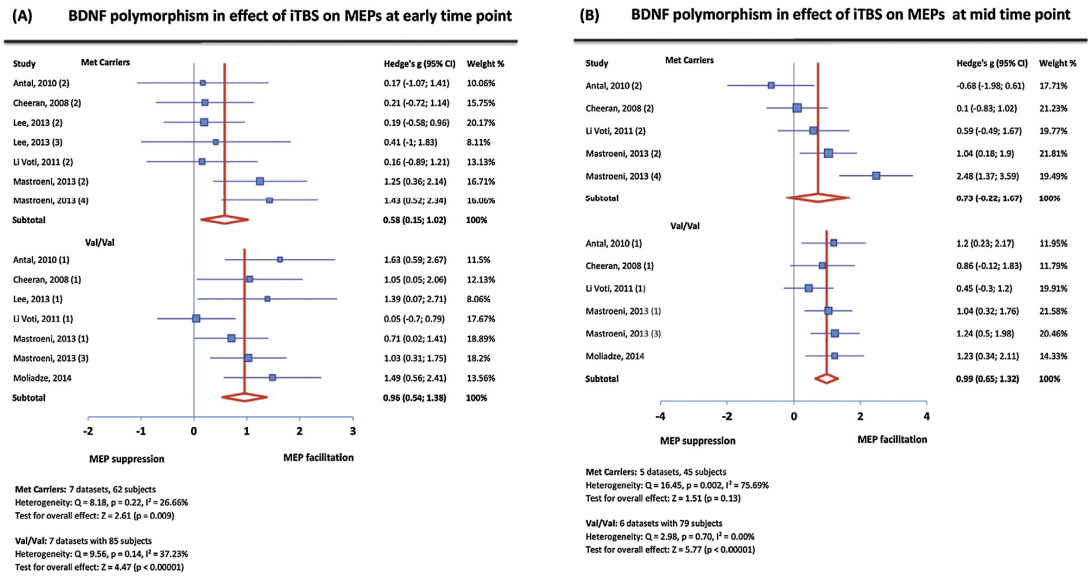

Fig. 5. Forest plot of the Hedge's adjusted g analysis for influence of BDNF polymorphism on MEPs amplitude after iTBS measured post 0–5 min (A) and 20–30 min (B).

95% CI: −0.91; −0.34, $P = 0.00002$ and SMD = −0.62, 95% CI: −0.82; −0.42, $P < 0.00001$, respectively). A considerably larger and significant SMD was seen with 1200 pulses of cTBS compared to the other two subgroups (SMD = −1.14, 95% CI: −1.89; −0.4, $P = 0.003$) (Fig. 8B). At the late time point, the effect of cTBS with 600 pulses produced a non-significant result (SMD = −0.19, 95% CI: −0.44; 0.06, $P = 0.13$). However, the effect of 1200 pulses remained significant and large (SMD = − 1.18, 95% CI: − 2.1; −0.26, $P = 0.01$) (Fig. 8C). There were no studies investigating 300 pulses of cTBS at the late time point.

3.3.2.1.2. Frequency of stimulation. Fig. 9 illustrates the impact of frequency of stimulation (30 Hz vs 50 Hz) on MEP amplitude, measured at different time points. Only studies with 600 pulses were included in this analysis as included studies using 30 Hz stimulation employed 600 pulses, and above analysis showed dose-dependent effect of stimulation at 50 Hz. At the early time point, the 30 Hz subgroup demonstrated a significant and large MEP

Table 4
ICF – iTBS.

Studies (no. of experiments)	Sample size (n)	Gender ratio	Mean age ± SD (age range)	iTBS parameters (variable)	ICF ISI	Target muscle
Di Lazzaro et al. (2011)	10	–	26.6 ± 4.1	80% aMT, 50 Hz/5 Hz, 600 pulses	15 ms	FDI
Hasan et al. (2012)	9	7 M: 2F	30.3 ± 1.5	80% aMT, 50 Hz/5 Hz, 600 pulses (with sham tDCS)	10 & 12 ms	FDI
Huang et al. (2005)	7*	–	33.6 ± 7.8 (23- 52)	80% aMT, 50 Hz/5 Hz, 600 pulses	10 ms	FDI
Huang et al. (2010b)	6	2 M: 4F	30.3 ± 3.1	80% aMT, 50 Hz/5 Hz, 150 pulses	10 & 12 ms	FDI
Lee et al. (2013)	23	10 M: 13F	31.9 ± 4.4	80% rMT, 50 Hz/5 Hz, 600 pulses	15 ms	FDI
McAllister et al. (2009)	9	4 M: 5F	28.3 ± 11.1	70% aMT, 50 Hz/5 Hz, 600 pulses	10 ms	FDI
Zamir et al. (2012)	10	4 M: 6F	63.1 ± 8.8 (50 – 75)	80% aMT, 50 Hz/5 Hz, 600 pulses	10 ms	FDI

aMT – active motor threshold; FDI – first dorsal interosseous; ISI – interstimulus interval; iTBS – intermittent theta burst stimulation; ICF – intracortical facilitation * indicates numbers that are subset of total recruited subjects

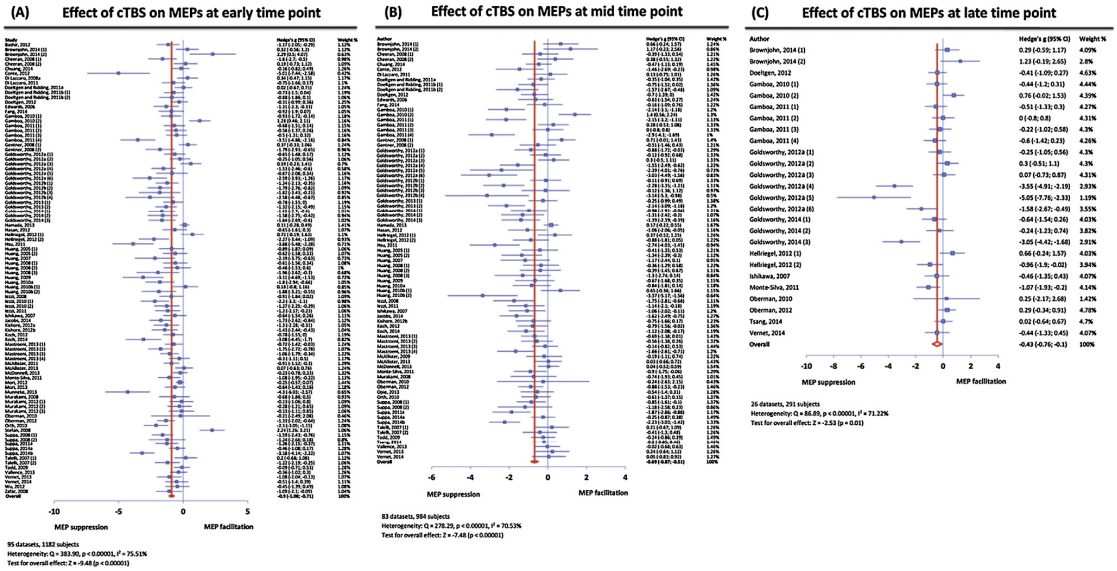

Fig. 6. Forest plots of the Hedge's adjusted g analysis for all studies for MEPs amplitude after cTBS measured post 0–5 min (A), 20–30 min (B) and 50–60 min (C).

decrease with SMD of −1.49 (95% CI: −2.29; −0.68, $p = 0.003$). The 50 Hz subgroup also showed a significant and large effect size (SMD = −0.83, 95% CI: −1.03; −0.63, $p < 0.00001$) (Fig. 9A). A slight increase (SMD = −1.61, 95% CI: −2.82; −0.4, $p < 0.009$) in the effect size and significant result compared to the early time point was produced for 30 Hz cTBS at the mid time point, whereas a significant but decreased effect was found with 50 Hz stimulation (SMD = −0.56, 95% CI: −0.75; −0.36, $p < 0.00001$) over time.

3.3.2.1.3. BDNF polymorphism. The influence of BDNF polymorphism on MEP amplitude after cTBS is displayed in Fig. 10. At the early time point, Met carriers yielded a moderate but non-significant decrease in MEP amplitude (SMD = −0.61, 95% CI: −1.69; 0.48, $P = 0.27$), whereas the Val/Val group revealed a significant and large effect size (SMD = −1.01, 95% CI: −1.47; −0.55, $P = 0.00001$) (Fig. 10A). As shown in Fig. 10B, no change was observed with Met carriers at the mid time point (SMD = −0.61, 95% CI: −1.71; 0.5, $P = 0.28$). However, the Val/Val group had a small-to-medium but non-significant effect size of SMD = −0.4 (95% CI: −0.83; 0.03, $p = 0.065$).

3.3.3. Effect of cTBS on SICI

Characteristics of cTBS studies with SICI as the outcome measure are summarized in Table 6. SICI at pre-cTBS were compared to post-cTBS at two different time points: early (within 5 min) and mid (20–30 min post). A total of 18 datasets, containing results for 174 subjects, were included in the analysis.

Fig. 11 displays the Hedge's adjusted g analysis as forest plots for effect of cTBS on SICI. The pooled SMD for the early time point was 0.42 (95% CI: 0.19; 0.64, $p = 0.00036$), with a significant decrease in SICI (Fig. 11A). However, a non-significant effect size was observed at the mid time point (SMD = 0.22, 95% CI: −0.04; 0.47, $P = 0.096$) (Fig. 11B). The tests of heterogeneity were not significant for both time points; early ($Q = 14.50$, $p = 0.49$, $I^2 = 0.00\%$), and mid ($Q = 9.73$, $p = 0.55$, $I^2 = 0.00\%$).

3.3.4. Effect of cTBS on ICF

Table 7 outlines characteristics of cTBS studies with ICF as the outcome measure. ICF at pre-cTBS was compared to post-cTBS at two different time points: early (within 5 min) and mid (20–30 min

Table 5
MEPs – cTBS.

Studies (no. of experiments)	Sample size (n)	Gender ratio	Mean age ± SD (age range)	cTBS parameters (variable)	cTBS pulse number (interval setting)	Target Muscle	Poly-morphism
Bashir et al. (2012)	12	7 M: 5F	30 ± 14 (19 – 55)	80% aMT, 50 Hz/5 Hz	600	FDI	–
Brownjohn et al. (2014) (1)	10	9 M: 1F	26.9 ± 4.7 (22- 37)	80% aMT, 50 Hz/5 Hz	600	FDI	-
Brownjohn et al. (2014) (2)	5*			80% aMT, 50 Hz/5 Hz	600	FDI	-
Cheeran et al. (2008) (1)	9	6 M: 3F	29.3 ± 3	80% aMT, 50 Hz/5 Hz	600	FDI	Val/Val
Cheeran et al. (2008) (2)	9	6 M: 3F	28.7 ± 3	80% aMT, 50 Hz/5 Hz	600	FDI	Val/Met
Chuang et al. (2014)	18	7 M: 11F	48.6 ± 12.8	80% aMT, 50 Hz/5 Hz	600	FDI	-
Conte et al. (2012)	7*	–	68.0 ± 7.75 (60 – 85)*	80% aMT, 50 Hz/5 Hz	600	FDI	–
Di Lazzaro et al. (2008a)	12	7 M: 5F	63.2 ± 5.3	80% aMT, 50 Hz/5 Hz	600	FDI	–
Di Lazzaro et al. (2011)	10	–	26.6 ± 4.1	80% aMT, 50 Hz/5 Hz	600	FDI	–
Doeltgen and Ridding (2011a)	16	8 M: 8F	25.2 ± 3.5	60, 65, 70% rTM, 50 Hz/5 Hz	300	FDI	–
Doeltgen and Ridding (2011b) (1)	14	4 M: 10F	24.5 ± 3.1	80% aMT. 50 Hz/5 Hz	600	FDI	–
Doeltgen and Ridding (2011b) (2)	9*			80% aMT, 50 Hz/5 Hz	600	FDI	–
Doeltgen et al. (2012)	17	7 M: 10F	23.1 ± 5.1	80% aMT, 50 Hz/5 Hz (with sham tDCS)	600	FDI	–
Edwards et al. (2006)	10	7 M: 3F	43 (26 – 69)	80% aMT, 50 Hz/5 Hz	300	FDI	–
Fang et al. (2014)	9	5 M: 4F	24.2 ± 2.0	80% aMT, 50 Hz/5 Hz	300	FCR	–
Gamboa et al. (2010) (1)	14	7 M: 7F	(21 – 27)	80% aMT, 50 Hz/5 Hz	600	FDI	–
Gamboa et al. (2010) (2)	14			80% aMT, 50 Hz/5 Hz	1200	FDI	–
Gamboa et al. (2011) (1)	12	6 M: 6F	24.7 ± 1.39	80% aMT, 50 Hz/5 Hz	600	FDI	–
Gamboa et al. (2011) (2)	12			80% aMT, 50 Hz/5 Hz	1200 (600 – 2 min – 600)	FDI	–
Gamboa et al. (2011) (3)	12			80% aMT, 50 Hz/5 Hz	1200 (600 – 5 min – 600)	FDI	–
Gamboa et al. (2011) (4)	12			80% aMT, 50 Hz/5 Hz	1200 (600 – 20 min – 600)	FDI	–
Gentner et al. (2008) (1)	16*	14 M: 22F	26.6 ± 7.4 (20–56)	70% rMT, 50 Hz/5 Hz	600	APB	–
Gentner et al. (2008) (2)	9*			70% rMT, 50 Hz/5 Hz	300	APB	–
Goldsworthy et al. (2012a) (1)	12	5 M: 7F	26.3 ± 2.3	80% aMT, 50 Hz/5 Hz	600	FDI	–
Goldsworthy et al. (2012a) (2)	12			70% rMT, 50 Hz/5 Hz (with sham cTBS)	600	FDI	–
Goldsworthy et al. (2012a) (3)	12			80% aMT, 50 Hz/5 Hz	1200 (600 – 10 min – 600)	FDI	–
Goldsworthy et al. (2012a) (4)	12			70% rMT, 50 Hz/5 Hz	1200 (600 – 10 min – 600)	FDI	–
Goldsworthy et al. (2012a) (5)	6	3 M: 3F	29.7 ± 4.0	65% rMT, 50 Hz/5 Hz	1200 (600 – 10 min – 600)	FDI	–
Goldsworthy et al. (2012a) (6)	9	4 M: 5F	22.1 ± 3.7	70% rMT, 50 Hz/5 Hz	1200 (600 – 10 min – 600)	FDI	–
Goldsworthy et al. (2012b) (1)	12	6 M: 6F	23.7 ± 8.1	80% aMT, 50 Hz/5 Hz	600	FDI	–
Goldsworthy et al. (2012b) (2)	12			80% rMT, 30 Hz/6 Hz	600	FDI	–
Goldsworthy et al. (2012b) (3)	5	3 M: 2F	27.0 ± 9.9	80% aMT, 50 Hz/5 Hz	600	FDI	–
Goldsworthy et al. (2012b) (4)	5			80% aMT, 30 Hz/6 Hz	600	FDI	–
Goldsworthy et al. (2013) (1)	14	7 M: 7F	23.8 ± 4.7	70% rMT, 50 Hz/5 Hz (with sham cTBS)	600	FDI	–
Goldsworthy et al. (2013) (2)	14	7 M: 7F	23.4 ± 5.0	70% rMT, 50 Hz/5 Hz	1200 (600 – 10 min – 600)	FDI	–
Goldsworthy et al. (2014) (1)	10	5 M: 5F	23.7 ± 3.1	70% rMT, 50 Hz/5 Hz (with sham cTBS)	600	FDI	–
Goldsworthy et al. (2014) (2)	8	6 M: 2F	23.0 ± 3.5	70% rMT, 50 Hz/5 Hz (with sham cTBS)	600	FDI	–
Goldsworthy et al. (2014) (3)	10	4 M: 6F	24.7 ± 4.0	70% rMT, 50 Hz/5 Hz	1200 (600 – 10 min – 600)	FDI	–
Hamada et al. (2013)	52	32 M: 24F	30.3 ± 7.4 (18 – 52)	80% aMT, 50 Hz/5 Hz	600	FDI	–
Hasan et al. (2012)	9	7 M: 2F	30.3 ± 1.5	80% aMT, 50 Hz/5 Hz (with sham tDCS)	600	FDI	–

Table 5 (*Continued*)

Studies (no. of experiments)	Sample size (n)	Gender ratio	Mean age ± SD (age range)	cTBS parameters (variable)	cTBS pulse number (interval setting)	Target Muscle	Poly-morphism
Hellriegel et al. (2012) (1)	10	–	55.4 ± 18.88 (25 – 71)	30% aMT, 50 Hz/5 Hz	600 (300 – 1 min – 300)	FDI	–
Hellriegel et al. (2012) (2)	10	–		80% aMT, 50 Hz/5 Hz	600 (300 – 1 min – 300)	FDI	–
Hsu et al. (2011)	10	5 M: 5F	29.0 ± 7.1	80% aMT, 50 Hz/5 Hz	1200	FDI	–
Huang et al. (2005) (1)	9	–	33.6 ± 7.8 (23- 52)	80% aMT, 50 Hz/5 Hz	300	FDI	–
Huang et al. (2005) (2)	9			80% aMT, 50 Hz/5 Hz	600	FDI	–
Huang et al. (2007)	6	1 M: 5F	29 ± 6	80% aMT, 50 Hz/5 Hz (with placebo)	300	FDI	–
Huang et al. (2008)(1)	9	6 M: 3F	30.9 ± 6.8	80% aMT, 50 Hz/5 Hz	300	FDI	–
Huang et al. (2008) (2)	7	5 M: 2F	31 ± 7	80% aMT, 50 Hz/5 Hz	300	FDI	–
Huang et al. (2008) (3)	5	2 M: 3F	30 ± 6	80% aMT, 50 Hz/5 Hz	300	Biceps	–
Huang et al. (2009)	8	3 M: 5F	35 ± 14	80% aMT, 50 Hz/5 Hz	300	FDI	–
Huang et al. (2010a)	9	4 M: 5F	42.7 ± 12.1	80% aMT, 50 Hz/5 Hz	300	FDI	–
Huang et al. (2010b) (1)	8	1 M: 7F	33.3 ± 10.3	80% aMT, 50 Hz/5 Hz	150	FDI	–
Huang et al. (2010b) (2)	7	4 M: 3F	28.7 ± 3.6	80% aMT, 50 Hz/5 Hz	300	FDI	–
Iezzi et al. (2008)	10	6 M: 4F	35 ± 3	80% aMT, 50 Hz/5 Hz	300	FDI	–
Iezzi et al. (2010) (1)	11	9 M: 2F	30 ± 5.22	80% aMT, 50 Hz/5 Hz	600	FDI	–
Iezzi et al. (2010) (2)	10	6 M: 4F	31.9 ± 6.37	80% aMT, 50 Hz/5 Hz	600	FDI	–
Iezzi et al. (2011)	10	6 M: 4F	32 ± 5.03	80% aMT, 50 Hz/5 Hz	600	FDI	–
Ishikawa et al. (2007)	10	9 M: 1F	42.3 ± 6.9	80% aMT, 50 Hz/5 Hz	600	FDI	–
Jacobs et al. (2014)	14	6 M: 9F	21.3 ± 1.6 (18 – 23)	55% rMT, 30 Hz/6 Hz	600	FDI	–
Kishore et al. (2012a)	10	8 M: 2F	45.6 ± 7.8	80% aMT, 50 Hz/5 Hz	600	FDI	–
Kishore et al. (2012b)	10	8 M: 2F	45.6 ± 7.8	80% aMT, 50 Hz/5 Hz	600	FDI	–
Koch et al. (2012)	14	9 M: 5F	–	80% aMT, 50 Hz/5 Hz	600	FDI	–
Koch et al. (2014)	10	6 M: 4F	68.3 ± 5.6	80% aMT, 50 Hz/5 Hz	600	FDI	–
Mastroeni et al. (2013) (1)	17	29M	26.0 ± 3.2	80% aMT, 50 Hz/5 Hz	600	FDI	Val/Val
Mastroeni et al. (2013) (2)	12	29 M 4 M: 5F	26.0 ± 3.2 28.3 ± 11.1	80% aMT, 50 Hz/5 Hz	600	FDI	Val/Met
Mastroeni et al. (2013) (3)	17	29M	26.0 ± 3.2	80% aMT, 50 Hz/5 Hz	1200 (600 – 30 min – 600)	FDI	Val/Val
Mastroeni et al. (2013) (4)	12			80% aMT, 50 Hz/5 Hz	1200 (600 – 30 min – 600)	FDI	Val/Met
McAllister et al. (2009)	9	4 M: 5F	28.3 ± 11.1	70% aMT, 50 Hz/5 Hz	600	FDI	–
McAllister et al. (2011)	23	10 M: 13F	27.9 ± 8.3	80% aMT, 50 Hz/5 Hz	600	FDI	–
McAllister et al. (2013)	16	7 M: 9F	(19 – 44)	80% aMT, 50 Hz/5 Hz	600	FDI	–
McDonnell et al. (2013)	25	9 M: 16F	27 ± 8.2 (18 – 60)	80% aMT, 50 Hz/5 Hz	600	FDI	–
Monte-Silva et al. (2011)	12	6 M: 6F	25.75 ± 5.11	80% aMT, 50 Hz/5 Hz (with placebo)	600	FDI	–
Mori et al. (2012)	77	31 M: 46F	38.3 ± 10.2	80% aMT, 50 Hz/5 Hz	600	FDI	–
Mori et al. (2013)	13	8 M: 5F	35.5 ± 9.2	80% aMT, 50 Hz/5 Hz	600	FDI	–
Munneke et al. (2013)	10	–	49.0 ± 3.6	70% rMT, 50 Hz/5 Hz	600	APB	–
Murakami et al. (2008)	6	13 M: 15F	27.1 ± 4.8	80% aMT, 50 Hz/5 Hz	600	FDI	–
Murakami et al. (2012) (1)	9	7 M: 2F	29.2 ± 6.9	80% aMT, 50 Hz/4.2 Hz	600	FDI	–
Murakami et al. (2012) (2)	9	7 M: 2F	29.2 ± 6.9	80% aMT, 50 Hz/4.2 Hz	1200 (600 – 15 min – 600)	FDI	–
Murakami et al. (2012) (3)	8	5 M: 3F	27.4 ± 4.7	70, 80% aMT, 50 Hz/4.2 Hz	600	FDI	–
Oberman et al. (2010)	2*	2 M: 3F	38.6 ± 13.8 (22 – 54)	80% aMT, 50 Hz/5 Hz	600	FDI	–
Oberman et al. (2012)	20	16 M: 4F	34.9 ± 16.2	80% aMT, 50 Hz/5 Hz	600	FDI	–
Opie et al. (2013)	11	9 M: 2F	43 ± 10.3	80% aMT, 50 Hz/5 Hz	600	FDI	–
Orth et al. (2010)	14	6 M: 9F	42.4 (28 – 62)	80% aMT, 50 Hz/5 Hz	300	FDI	–
Stefan et al. (2008)	14*	10 M: 8F	25.7 ± 5.6 (20 – 40)	70% rMT, 50 Hz/5 Hz	300	APB	–
Suppa et al. (2008) (1)	15	11 M: 7F	31 ± 5 (26 – 45)	80% aMT, 50 Hz/5 Hz	600	FDI	–
Suppa et al. (2008) (2)	5*			80% aMT, 50 Hz/5 Hz	600	FDI	–
Suppa et al. (2011a)	12	7 M: 5F	30 ± 4.9 (25 – 40)	80% aMT, 50 Hz/5 Hz	600	FDI	–
Suppa et al. (2014a)	20	14 M: 6F	32.8 ± 11.2	80% aMT, 50 Hz/5 Hz	600	FDI	–
Suppa et al. (2014b)	20	10 M: 10F	58.6 ± 11.5 (36 – 81)	80% aMT, 50 Hz/5 Hz	600	FDI	–
Talelli et al. (2007) (1)	10	9 M: 9F	29.6 ± 3.9	80% aMT, 50 Hz/5 Hz	300	FDI	–
Talelli et al. (2007) (2)	10			100% aMT, 50 Hz/5 Hz	300	FDI	–

Table 5 (*Continued*)

Studies (no. of experiments)	Sample size (n)	Gender ratio	Mean age ± SD (age range)	cTBS parameters (variable)	cTBS pulse number (interval setting)	Target Muscle	Poly-morphism
Todd et al. (2009)	20	8 M: 12F	25 ± 8	80% aMT, 50 Hz/5 Hz	600	FDI	–
Tsang et al. (2014)	18	7 M: 11F	21 ± 2.0 (19 – 25)	70% rMT, 30 Hz/6 Hz	600	FDI	–
Vallence et al. (2013)	18	9 M: 9F	23.3 ± 2.7	80% aMT, 50 Hz/5 Hz	600	APB	–
Vernet et al. (2013)	10	6 M: 4F	21 ± 2 (18 – 24)	80% aMT, 50 Hz/4.17 Hz	600	APB	–
Vernet et al. (2014)	10	5 M: 5F	33 ± 18 (21 – 67)	80% aMT, 50 Hz/4.17 Hz	600	FDI	–
Wu et al. (2012)	9*	8 M: 10F	33 ± 9.0	90% rMT, 30 Hz/5 Hz	600	FDI	–
Zafar et al. (2008)	9	4 M: 5F	21.3 (21 – 26)	80% aMT, 50 Hz/5 Hz	600	ADM	–

aMT/rMT – active/resting motor threshold; APB – abductor pollicis brevis; ADM – abductor digiti minimi; cTBS – continuous theta burst stimulation; FCR – flexor carpi radialis; FDI – first dorsal interosseous; tDCS – transcranial direct current stimulation * indicates numbers that are subset of total recruited subjects, + indicates age used for age-matched group

Table 6
SICI – cTBS.

Studies (no. of experiments)	Sample size (n)	Gender ratio	Mean age ± SD (age range)	cTBS parameters (variable)	SICI ISI	Target muscle
Bradnam et al. (2010)	9	2 M:7F	26 ± 2.5 (21 – 45)	70% aMT, 50 Hz/5 Hz, 600 pulses	3 ms	BB
Brownjohn et al. (2014)	9*	9 M: 1F	26.9 ± 4.7 (22- 37)	80% aMT, 50 Hz/5 Hz, 600 pulses	3 ms	FDI
Di Lazzaro et al. (2011)	10	–	26.6 ± 4.1	80% aMT, 50 Hz/5 Hz, 600 pulses	2 ms	FDI
Doeltgen and Ridding (2011a) (1)	16	8 M: 8F	25.2 ± 3.5	60, 65, 70% rTM, 50 Hz/5 Hz, 300 pulses	2 & 3 ms	FDI
Doeltgen and Ridding (2011a) (2)	11*	8 M: 8F	25.2 ± 3.5	60 rTM, 50 Hz/5 Hz, 300 pulses	2 & 3 ms	FDI
Doeltgen and Ridding (2011b)	14	4 M: 10F	24.5 ± 3.1	80% aMT, 50 Hz/5 Hz, 600 pulses	2 & 3 ms	FDI
Goldsworthy et al. (2013)	14	7 M: 7F	23.8 ± 4.7	70% rMT, 50 Hz/5 Hz, 600 pulses (with sham TBS)	2 ms	FDI
Hasan et al. (2012)	9	7 M: 2F	30.3 ± 1.5	80% aMT, 50 Hz/5 Hz, 600 pulses (with sham cathodal tDCS)	2 & 3 ms	FDI
Huang et al. (2005)	7*	–	33.6 ± 7.8 (23- 52)	80% aMT, 50 Hz/5 Hz, 600 pulses	2 ms	FDI
Huang et al. (2010b)	6	2 M: 4F	30.3 ± 3.1	80% aMT, 50 Hz/5 Hz, 150 pulses	2 & 3 ms	FDI
Jacobs et al. (2014)	14	5 M: 9F	21.3 ± 1.6 (18 – 23)	55% rMT, 30 Hz/6 Hz, 600 pulses	2 ms	FDI
McAllister et al. (2009)	9	4 M: 5F	28.3 ± 11.1	70% aMT, 50 Hz/5 Hz, 600 pulses	3 ms	FDI
Munneke et al. (2013)	10	–	49.0 ± 3.6	70% rMT, 50 Hz/5 Hz, 600 pulses	2 & 3 ms	APB
Murakami et al. (2008)	6*	13 M: 15F	27.1 ± 4.8	80% aMT, 50 Hz/5 Hz, 600 pulses	2 ms	FDI
Murakami et al. (2012) (1)	9	7 M: 2F	29.2 ± 6.9	80% aMT, 50 Hz/4.2 Hz, 600 pulses	2 ms	FDI
Murakami et al. (2012) (2)	8	5 M: 3F	27.4 ± 4.7	70, 80% aMT, 50 Hz/4.2 Hz, 600 pulses	2 ms	FDI
Suppa et al. (2008)	5*	11 M: 7F	31 ± 5 (26 – 45)	80% aMT, 50 Hz/5 Hz, 600 pulses	3 ms	FDI
Talelli et al. (2007)	8*	9 M: 9F	29.6 ± 3.9	100% aMT, 50 Hz/5 Hz, 300 pulses	2 ms	FDI

aMT/rMT – active/resting motor threshold; APB – abductor pollicis brevis; BB – biceps brachii; cTBS – continuous theta burst stimulation; FDI – first dorsal interosseous; ISI – interstimulus interval; SICI – short interval intracortical inhibition * indicates numbers that are subset of total recruited subjects

post). A total of 9 datasets were included in the analysis, with 78 subjects.

No significant differences were found in ICF at both early (SMD = 0.31, 95% CI: −0.57; 1.19, $P = 0.19$) (see Supplementary Fig. 3A) and mid time points (SMD = −0.19, 95% CI: −0.6; 0.22, $P = 0.37$) (Supplementary Fig. 3B). The test of heterogeneity was significant for ICF measured at the early time point after cTBS ($Q = 21.69$, $p = 0.0006$, $I^2 = 76.95\%$), but not for the mid time point ($Q = 5.56$, $p = 0.35$, $I^2 = 9.99\%$).

4. Discussion

The primary aim of this study was to comprehensively explore the effects of intermittent and continuous TBS paradigms on corticospinal excitability induced by single pulse TMS in

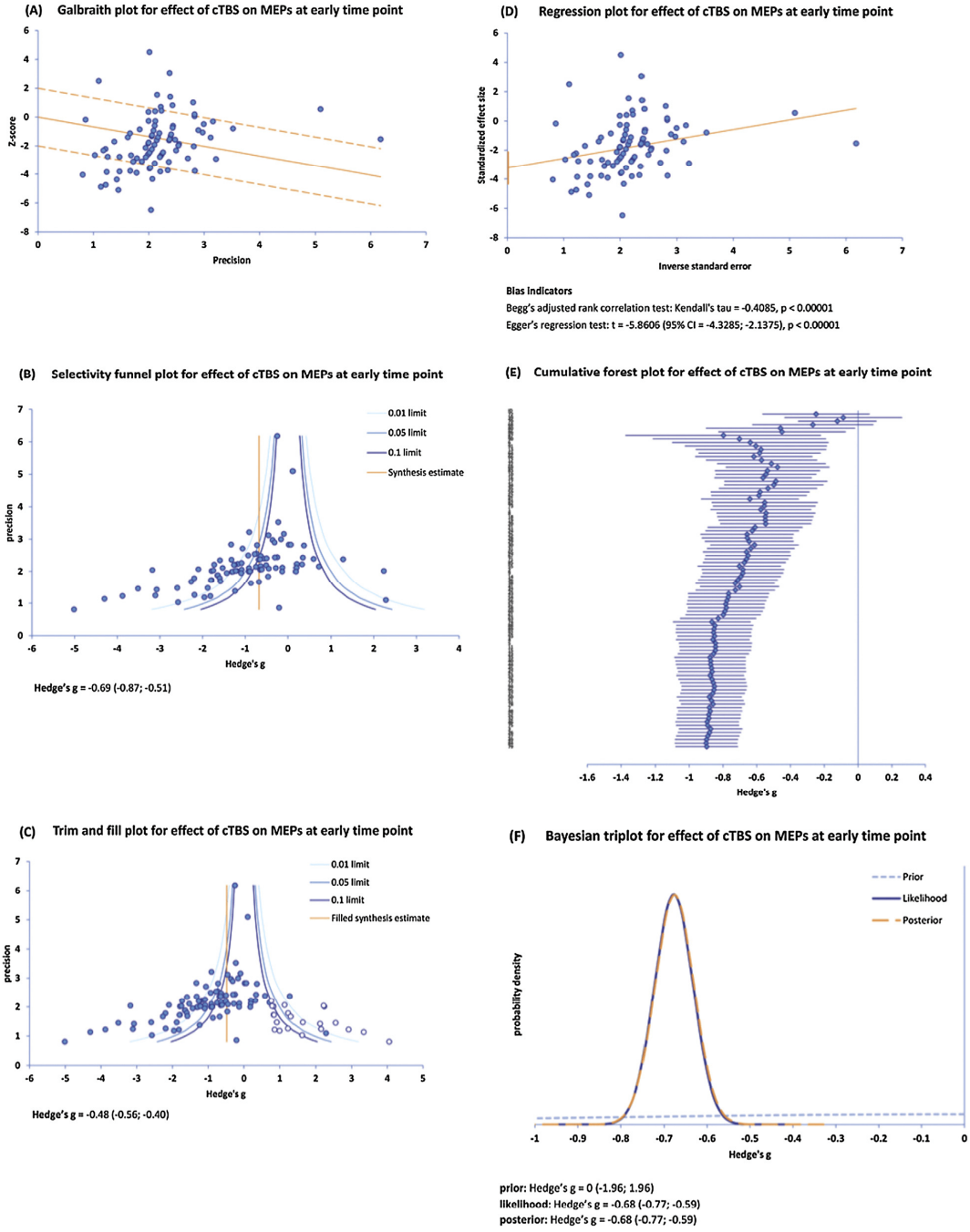

Fig. 7. Series of tests for heterogeneity and publication bias for all studies for MEPs amplitude after cTBS measured post 0–5 min; (A) Galbraith plot, (B) Selectivity funnel plot, (C) Trim and fill plot, (D) Regression plot, (E) Cumulative forest plot and (F) Bayesian triplot.

healthy individuals. Overall, iTBS was found to increase corticospinal excitability, but had no effect on SICI or ICF, while cTBS decreased corticospinal excitability, as well as SICI, without any effect on ICF. The present study also examined specific factors potentially affecting the outcome of stimulation, including stimulation frequency, number of pulses and BDNF polymorphism. Assessments for any potential publication bias were also performed.

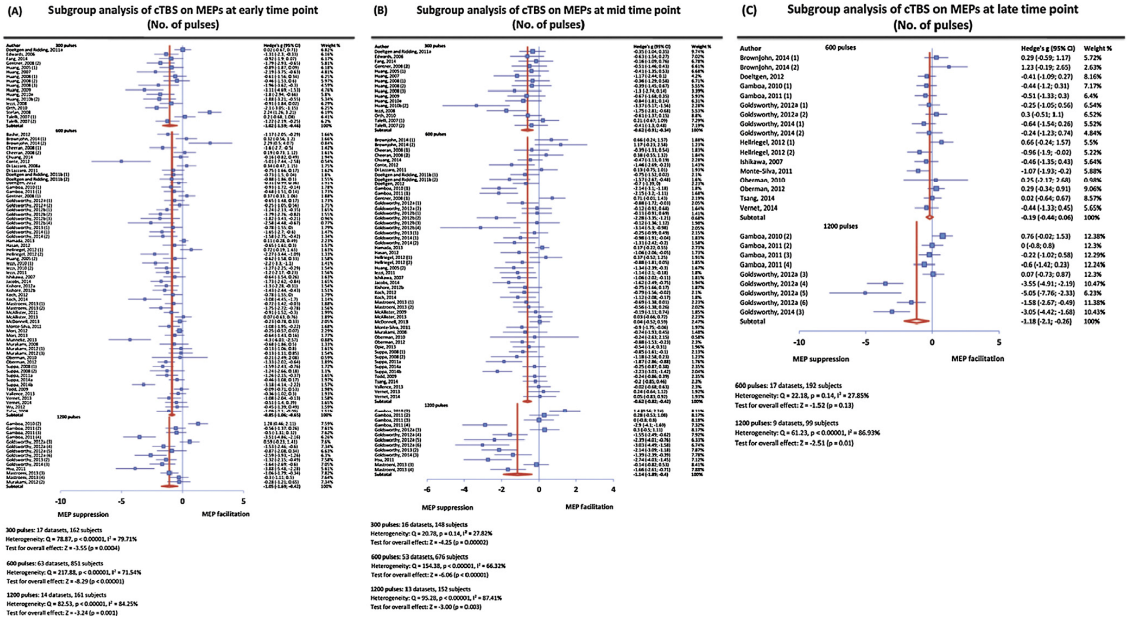

Fig. 8. Forest plot of the Hedge's adjusted g analysis for subgroup studies (no. of pulses) of MEPs amplitude after cTBS measured post 0–5 min (A), 20–30 min (B) and 50–60 min (C).

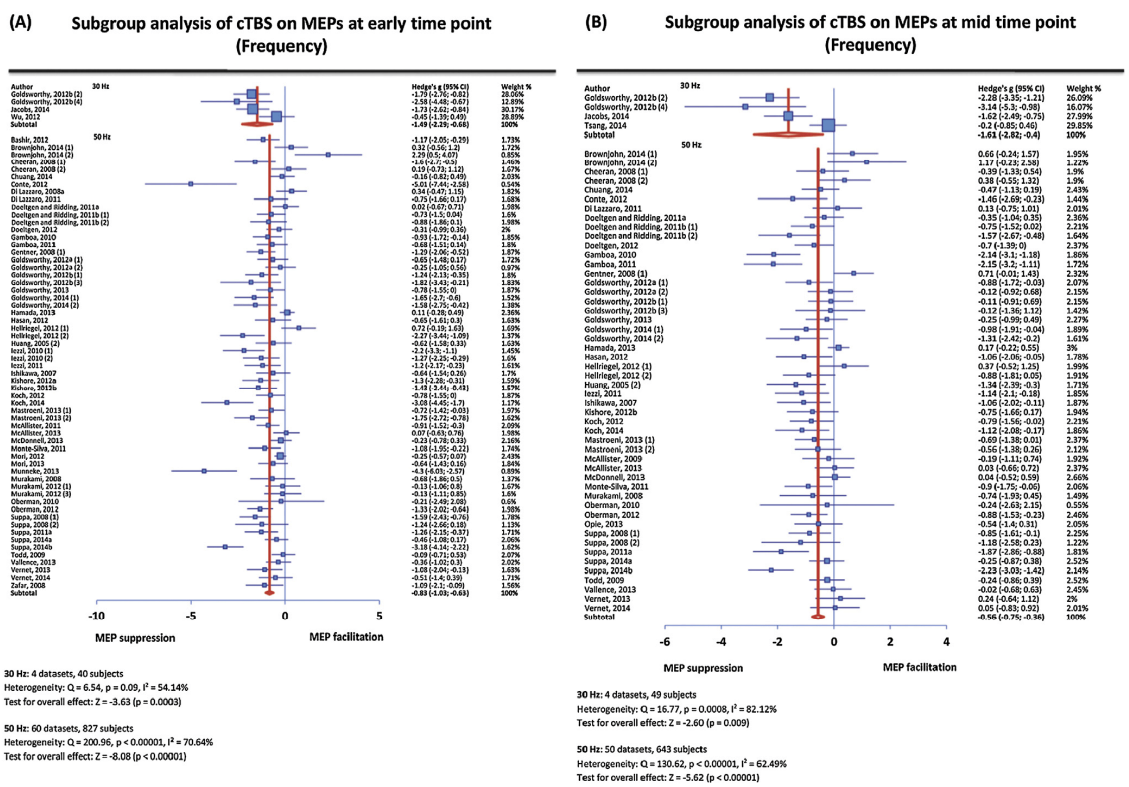

Fig. 9. Forest plot of the Hedge's adjusted g analysis for subgroup studies (frequency of stimulation) of MEPs amplitude after cTBS measured post 0–5 min (A) and 20–30 min (B).

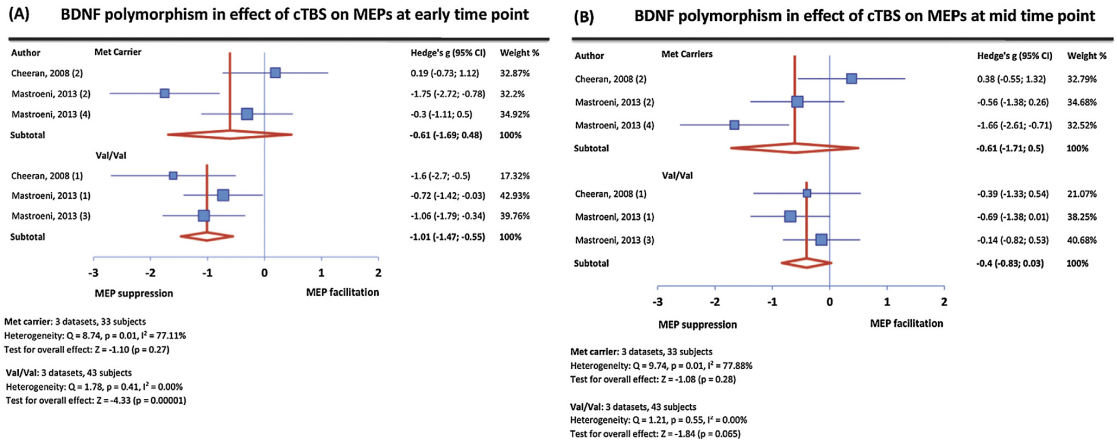

Fig. 10. Forest plot of the Hedge's adjusted g analysis for influence of BDNF polymorphism on MEPs amplitude after cTBS measured post 0–5 min (A) and 20–30 min (B).

Table 7
ICF – cTBS.

Studies (no. of experiments)	Sample size (n)	Gender ratio	Mean age ± SD (age range)	cTBS parameters (variable)	ICF ISI	Target muscle
Di Lazzaro et al. (2011)	10	–	26.6 ± 4.1	80% aMT, 50 Hz/5 Hz, 600 pulses	15 ms	FDI
Hasan et al. (2012)	9	7 M: 2F	30.3 ± 1.5	80% aMT, 50 Hz/5 Hz, 600 pulses (with sham tDCS)	10 & 12 ms	FDI
Huang et al. (2005)	7*	–	33.6 ± 7.8 (23–52)	80% aMT, 50 Hz/5 Hz, 600 pulses	10 ms	FDI
Huang et al. (2010b)	6	2 M: 4F	30.3 ± 3.1	80% aMT, 50 Hz/5 Hz, 150 pulses	10 & 12 ms	FDI
Jacobs et al. (2014)	14	6 M: 9F	21.3 ± 1.6 (18–23)	55% rMT, 30 Hz/6 Hz, 600 pulses	10 ms	FDI
McAllister et al. (2009)	9	4 M: 5F	28.3 ± 11.1	70% aMT, 50 Hz/5 Hz, 600 pulses	10 ms	FDI
Munneke et al. (2013)	10	–	49.0 ± 3.6	70% rMT, 50 Hz/5 Hz, 600 pulses	10 & 12 ms	APB
Suppa et al. (2008)	5*	11 M: 7F	31 ± 5 (26–45)	80% aMT, 50 Hz/5 Hz, 600 pulses	10 ms	FDI
Talelli et al. (2007)	8*	9 M: 9F	29.6 ± 3.9	100% aMT, 50 Hz/5 Hz, 300 pulses	10 ms	FDI

aMT/rMT – active/resting motor threshold; APB – abductor pollicis brevis; cTBS – continuous theta burst stimulation; FDI – first dorsal interosseous; ISI – interstimulus interval; ICF – intracortical facilitation * indicates numbers that are subset of total recruited subjects

4.1. TBS and corticospinal excitability

The results of this meta-analysis support our hypothesis that both intermittent and continuous TBS paradigms can effectively influence corticospinal excitability in healthy individuals, increasing it with iTBS and decreasing it with cTBS. Interestingly, the greatest effect sizes were most often observed at mid time points (20–30 min post-stimulation; Fig. 2B) for iTBS, while the effects of cTBS were greatest at early time points (≤5 min post stimulation; Fig. 6A). Prolonged effects (i.e., >30 min) remained significant only for cTBS (Fig. 6C) and when taken together with the finding that overall iTBS effect sizes were smaller than cTBS, suggest that iTBS may not be as effective in modulating cortical excitability as cTBS. On the surface, this finding seems contradictory to a previously published quantitative analysis on TBS (Wischnewski and Schutter, 2015), which found that the potentiating effect of iTBS was greater than the depressing effect of cTBS. However, effect sizes are affected by standard deviation values, such that larger values decrease effect size and because changes produced with iTBS were more variable, our data showed greater effect sizes with cTBS. Other forms of brain stimulation, such as rTMS (Maeda et al., 2000a), PAS (Delvendahl et al., 2012; Huber et al., 2008) and tDCS (Horvath et al., 2015; Nitsche and Paulus, 2000), have also shown greater potentiating effects than depressing effects and have also displayed similar trends with regards to standard deviations. However, currently, there is no meta-analytic study investigating corticospinal excitability for these techniques to allow for direct comparison of effect sizes.

4.1.1. Publication bias

The presence of publication bias can influence the results of a meta-analysis. Therefore, several methods were used to test for publication bias in this study. The results showed that the studies with large sample sizes failed to align with the findings of this meta-analysis and a series of tests were suggestive of a degree of publication bias. However, some caution should be taken when interpreting these results. A number of methods have been established to test for publication bias, but often limitations follow, especially when the studies are highly heterogeneous (Terrin et al., 2003). In addition, potential confounding variables, such as age and gender, were not identified for more precise analyses.

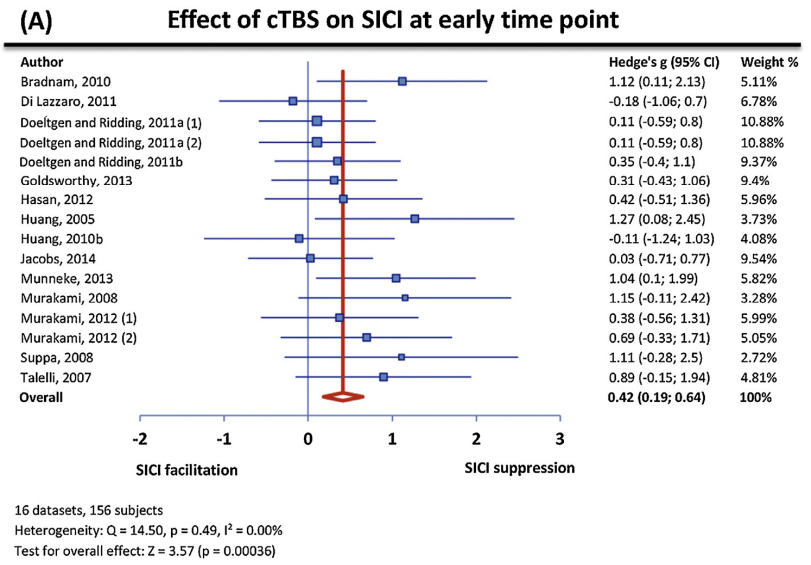

Fig. 11. Forest plot of the Hedge's adjusted g analysis for SICI after cTBS measured post 0–5 min (A) and 20–30 min (B).

4.1.2. TBS and corticospinal excitability based on stimulation parameters and BDNF polymorphism

Both iTBS and cTBS paradigms displayed similar effect sizes across different subgroups (300 pulses and/or 600 pulses and 1200 pulses) at the early time point, with the exception of the 600 pulse cTBS approach, which produced a less robust effect (Fig. 8A). The majority of the studies used 600 pulses of stimulation and differences in the number of studies in each subgroup may have affected the results. However, the differences between subgroups became more evident from mid time point onward (Figs. 4 and 8B and). 1200 pulses of cTBS produced greater effects compared to 300 pulses and 600 pulses. However, it is intriguing that 300 pulses and 600 pulses of cTBS yielded very similar effect sizes up to the mid time point. It is somewhat difficult to ascertain whether 300 pulses and 600 pulses of cTBS had a similar effect over time, given that there were no data at the late time point for 300 pulses. A sustained and large effect size with 1200 pulses at late time point for cTBS is indicative of a dose-dependent effect of stimulation. Dose-dependency has also been described in the use of TBS for treatment of depression (Chung et al., 2015), visual neglect (Nyffeler et al., 2009) and saccade triggering (Nyffeler et al., 2006). 1200 pulses of iTBS at the mid time point produced a larger effect than 600 pulses of iTBS, which was more marginal than the differences observed with cTBS. However, we found an unexpected outcome with 1200 pulses of iTBS at the late time point, which was non-significant but leaning toward MEP suppression. Varying intervals between each block of

TBS (600 pulses) were combined in this analysis (0, 2, 5 and 20 min), which may have affected this outcome, suggesting that the optimal interval for iTBS to produce longer-lasting effect has not yet been established.

Supporting our hypothesis, 30 Hz TBS produced a larger change in cortical excitability than 50 Hz TBS. Specifically, while 50 Hz TBS demonstrated less of an effect over time, 30 Hz TBS showed persistent, and even greater effects over time. However, the subgroup analysis was largely limited due to only a small number of studies available in one group for comparison, which could have potentially skewed the result. Nonetheless, this finding highlights a potential for improvement in TBS outcomes with slower (30 Hz) stimulation frequencies. Currently, there is only one study that directly compared the effects of 30 Hz cTBS with 50 Hz cTBS in M1, demonstrating a superior neuroplastic change at 30 Hz (Goldsworthy et al., 2012b), which is consistent with our finding. It must also be noted that the studies included in the present meta-analysis used different inter-burst frequency (5 Hz & 6 Hz) which may also be one of the factors affecting the outcome. More studies with different frequency settings would allow for more systematic comparisons.

BDNF polymorphisms have been shown to modulate hippocampal plasticity in cell models and in animals (Egan et al., 2003). In particular, Val66Met is commonly associated with decreased activity-dependent BDNF release in the human brain (McHughen et al., 2010). Different stimulation protocols such as PAS and tDCS have demonstrated the impact of BDNF polymorphism on stimulation outcomes, albeit with mixed results. Anodal and cathodal tDCS have shown more effective plasticity-inducing effects with Met carriers (Antal et al., 2010), whereas PAS was more effective with Val/Val individuals (Cirillo et al., 2012). However, no influence of BDNF polymorphism has been described with QPS (Nakamura et al., 2011) and 5 Hz rTMS (Li Voti et al., 2011). In line with the PAS study, the results of the present meta-analysis indicate that the effects of TBS were also influenced by the BDNF polymorphism, with greater effect sizes seen in Val/Val individuals, particularly for iTBS. Met carriers showed more variability in response compared to Val/Val subgroups, suggesting that the BDNF polymorphism, the Met-containing genotype in particular, may be one factor contributing to variability in response to TBS.

4.2. TBS and SICI/ICF

Measuring SICI and ICF is a common method for exploring intracortical excitability and facilitatory circuits. However, a significant change in SICI was seen only with cTBS at the early time point (Fig. 11A) and not with iTBS (Supplementary Fig. 1). Neither paradigm influenced ICF, which is consistent with findings from tDCS research (Horvath et al., 2015). This suggests that TBS does not influence the cortical pathways assessed with SICI and ICF, with the exception of cTBS activating the SICI circuit, reducing the excitability of its neuronal connections. It has been shown that TBS effects on SICI are intensity-dependent (McAllister et al., 2009). In addition, the intensity of the test stimulus used for SICI measurement influences the amount of SICI, lowering SICI with low test MEP amplitude (Roshan et al., 2003). It should also be noted that the test pulse intensity after the intervention in the paired-pulse paradigms were often not re-adjusted in these experiments. Furthermore, the lower intensites used in TBS paradigms (typically 80% of active motor threshold (Huang et al., 2005)) may not be sufficient to affect ICF as higher stimulation intensities are required to recruit ICF pathways (Ziemann et al., 1996). Different parameters for measuring ICF and SICI (varying intensities and ISI) were combined in this analysis, and together with the varying TBS parameters used (intensity, number of pulses and frequency) may also have resulted in a non-significant outcome.

4.3. Limitations of the study

Several limitations should be considered when interpreting the results of this study. First, all included studies of the effect of TBS on MEP amplitudes were pre-post study designs and sham studies were not included. For subgroup analyses, the number of studies included in each subgroup varied, some more than others, which may have affected overall result and statistical significance. In addition, certain methodological differences between studies were not discussed, such as differences in intensity of stimulation or interstimulus intervals. Factors that may affect the outcome of the TBS effects, namely gender, age, TBS intensity and intensity of single-pulse TMS for MEPs measurement, were not studied as not enough data was available for analyses. Investigation of homeostatic metaplasticity and depotentiation/de-depression was beyond the scope of this meta-analysis as more studies were required to constitute a representative sample for such statistical analysis. Furthermore, data collected between the three designated time points were not included in the analysis. Lastly, the literature search was limited to peer-reviewed English language articles, which may have decreased the number of pooled studies.

5. Conclusions and future directions

Studies of plasticity change using TBS suggest that it is one of the most powerful neuromodulatory NIBS techniques currently available. This systematic review and meta-analysis has shown that both iTBS and cTBS paradigms can produce statistically significant and large effects on corticospinal excitability induced by single pulse TMS in healthy individuals. The results also highlight the factors that may affect the outcome of after-effects of TBS, such as the number of pulses, frequency of stimulation and BDNF polymorphism. These findings could help guide future research aimed at further exploring variables affecting TBS efficacy. Inter- and intra-individual variability has been described in response to TBS, and this is also an important area for future research. Furthermore, in addition to the differences in homosynaptic plasticity (Ridding and Ziemann, 2010), a recent study has shown a strong correlation between the after-effects of TBS and the type of interneuron networks being recruited (Hamada et al., 2013). Optimizing the conditions for late I-wave recruitment might also improve efficacy of TBS paradigms and warrants further investigation. Developing more robust means of probing TBS induced changes in corticospinal excitability may be necessary. Consistent cTBS-induced MEP reductions were observed at higher stimulus intensities (>150% rMT), compared to conventional intensities of 110–120 aMT/rMT (Goldsworthy et al., 2015), suggesting a more tailored way of probing changes in cortical excitability is required for different neuromodulatory paradigms. Combining TMS with neuroimaging techniques such as fMRI and EEG may also provide additional information on the impact of TBS induced changes in both motor and non-motor regions.

Disclosures and conflict of interest

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2016.01.008.

References

Antal, A., Chaieb, L., Moliadze, V., Monte-Silva, K., Poreisz, C., Thirugnanasambandam, N., Nitsche, M.A., Shoukier, M., Ludwig, H., Paulus, W., 2010. Brain-derived neurotrophic factor (BDNF) gene polymorphisms shape cortical plasticity in humans. Brain Stimul. 3, 230–237.

Bashir, S., Yoo, W.K., Mizrahi, I., Theoret, H., Pascual-Leone, A., 2012. Changes in cortical plasticity after mild traumatic brain injury. Restor. Neurol. Neurosci. 30, 277–282.

Bax, L., 2010. MIX 2.0. Professional software for meta-analysis in Excel (Version 2.0.1.2). BiostatXL. Retrieved from http://www.meta-analysis-made-easy.com.

Begg, C.B., Mazumdar, M., 1994. Operating characteristics of a rank correlation test for publication bias. Biometrics 50, 1088–1101.

Belvisi, D., Suppa, A., Marsili, L., Di Stasio, F., Parvez, A.K., Agostino, R., Fabbrini, G., Berardelli, A., 2013. Abnormal experimentally- and behaviorally-induced LTP-like plasticity in focal hand dystonia. Exp. Neurol. 240, 64–74.

Borenstein, M., Hedges, L.V., Higgins, J.P., Rothstein, H.R., 2009. Introduction to Meta-analysis. John Wiley & Sons Ltd, Chichester.

Borenstein, M., Hedges, L.V., Higgins, J.P., Rothstein, H.R., 2010. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res. Synth. Methods 1, 97–111.

Bradnam, L.V., Stinear, C.M., Byblow, W.D., 2010. Theta burst stimulation of human primary motor cortex degrades selective muscle activation in the ipsilateral arm. J. Neurophysiol. 104, 2594–2602.

Brownjohn, P.W., Reynolds, J.N.J., Matheson, N., Fox, J., Shemmell, J.B.H., 2014. The effects of individualized theta burst stimulation on the excitability of the human motor system. Brain Stimul. 7, 260–268.

Cardenas-Morales, L., Volz, L.J., Michely, J., Rehme, A.K., Pool, E.M., Nettekoven, C., Eickhoff, S.B., Fink, G.R., Grefkes, C., 2014. Network connectivity and individual responses to brain stimulation in the human motor system. Cereb. Cortex 24, 1697–1707.

Cheeran, B., Talelli, P., Mori, F., Koch, G., Suppa, A., Edwards, M., Houlden, H., Bhatia, K., Greenwood, R., Rothwell, J.C., 2008. A common polymorphism in the brain-derived neurotrophic factor gene (BDNF) modulates human cortical plasticity and the response to rTMS. J. Physiol. 586, 5717–5725.

Chuang, W.L., Huang, Y.Z., Lu, C.S., Chen, R.S., 2014. Reduced cortical plasticity and GABAergic modulation in essential tremor. Mov. Disord. 29, 501–507.

Chung, S.W., Hoy, K.E., Fitzgerald, P.B., 2015. Theta-burst stimulation: a new form of TMS treatment for depression? Depress Anxiety 32, 182–192.

Cirillo, J., Hughes, J., Ridding, M., Thomas, P.Q., Semmler, J.G., 2012. Differential modulation of motor cortex excitability in BDNF Met allele carriers following experimentally induced and use-dependent plasticity. Eur. J. Neurosci. 36, 2640–2649.

Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences, 2nd ed. Lawrence Erlbaum Publishers, New Jersey.

Conte, A., Belvisi, D., Bologna, M., Ottaviani, D., Fabbrini, G., Colosimo, C., Williams, D.R., Berardelli, A., 2012. Abnormal cortical synaptic plasticity in primary motor area in progressive supranuclear palsy. Cereb. Cortex 22, 693–700.

Conte, A., Gilio, F., Iezzi, E., Frasca, V., Inghilleri, M., Berardelli, A., 2007. Attention influences the excitability of cortical motor areas in healthy humans. Exp. Brain Res. 182, 109–117.

Deeks, J.J., Macaskill, P., Irwig, L., 2005. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. J. Clin. Epidemiol. 58, 882–893.

Delvendahl, I., Jung, N.H., Kuhnke, N.G., Ziemann, U., Mall, V., 2012. Plasticity of motor threshold and motor-evoked potential amplitude—a model of intrinsic and synaptic plasticity in human motor cortex? Brain Stimul. 5, 586–593.

Di Lazzaro, V., Dileone, M., Pilato, F., Capone, F., Musumeci, G., Ranieri, F., Ricci, V., Bria, P., Iorio, R.D., de Waure, C., Pasqualetti, P., Profice, P., 2011. Modulation of motor cortex neuronal networks by rTMS: comparison of local and remote effects of six different protocols of stimulation. J. Neurophysiol. 105, 2150–2156.

Di Lazzaro, V., Pilato, F., Dileone, M., Profice, P., Capone, F., Ranieri, F., Musumeci, G., Cianfoni, A., Pasqualetti, P., Tonali, P.A., 2008a. Modulating cortical excitability in acute stroke: a repetitive TMS study. Clin. Neurophysiol. 119, 715–723.

Di Lazzaro, V., Pilato, F., Dileone, M., Profice, P., Oliviero, A., Mazzone, P., Insola, A., Ranieri, F., Meglio, M., Tonali, P.A., Rothwell, J.C., 2008b. The physiological basis of the effects of intermittent theta burst stimulation of the human motor cortex. J. Physiol. 586, 3871–3879.

Di Lazzaro, V., Pilato, F., Dileone, M., Ranieri, F., Ricci, V., Profice, P., Bria, P., Tonali, P.A., Ziemann, U., 2006. GABAA receptor subtype specific enhancement of inhibition in human motor cortex. J. Physiol. 575, 721–726.

Doeltgen, S.H., McAllister, S.M., Ridding, M.C., 2012. Simultaneous application of slow-oscillation transcranial direct current stimulation and theta burst stimulation prolongs continuous theta burst stimulation-induced suppression of corticomotor excitability in humans. Eur. J. Neurosci. 36, 2661–2668.

Doeltgen, S.H., Ridding, M.C., 2011a. Low-intensity, short-interval theta burst stimulation modulates excitatory but not inhibitory motor networks. Clin. Neurophysiol. 122, 1411–1416.

Doeltgen, S.H., Ridding, M.C., 2011b. Modulation of cortical motor networks following primed theta burst transcranial magnetic stimulation. Exp. Brain Res. 215, 199–206.

Duval, S., Tweedie, R., 2000. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 56, 455–463.

Edwards, M.J., Huang, Y.Z., Mir, P., Rothwell, J.C., Bhatia, K.P., 2006. Abnormalities in motor cortical plasticity differentiate manifesting and nonmanifesting DYT1 carriers. Mov. Disord. 21, 2181–2186.

Egan, M.F., Kojima, M., Callicott, J.H., Goldberg, T.E., Kolachana, B.S., Bertolino, A., Zaitsev, E., Gold, B., Goldman, D., Dean, M., Lu, B., Weinberger, D.R., 2003. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 112, 257–269.

Egger, M., Davey Smith, G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ 315, 629–634.

Fang, J.-H., Huang, Y.-Z., Hwang, I.-S., Chen, J.-J.J., 2014. Selective modulation of motor cortical plasticity during voluntary contraction of the antagonist muscle. Eur. J. Neurosci. 39, 2083–2088.

Gamboa, O.L., Antal, A., Laczo, B., Moliadze, V., Nitsche, M.A., Paulus, W., 2011. Impact of repetitive theta burst stimulation on motor cortex excitability. Brain Stimul. 4, 145–151.

Gamboa, O.L., Antal, A., Moliadze, V., Paulus, W., 2010. Simply longer is not better: reversal of theta burst after-effect with prolonged stimulation. Exp. Brain Res. 204, 181–187.

Gentner, R., Wankerl, K., Reinsberger, C., Zeller, D., Classen, J., 2008. Depression of human corticospinal excitability induced by magnetic theta-burst stimulation: evidence of rapid polarity-reversing metaplasticity. Cereb. Cortex 18, 2046–2053.

Goldsworthy, M.R., Müller-Dahlhaus, F., Ridding, M.C., Ziemann, U., 2014. Resistant against de-depression: LTD-like plasticity in the human motor cortex induced by spaced cTBS. Cereb. Cortex (New York, N.Y.: 1991).

Goldsworthy, M.R., Pitcher, J.B., Ridding, M.C., 2012a. The application of spaced theta burst protocols induces long-lasting neuroplastic changes in the human motor cortex. Eur. J. Neurosci. 35, 125–134.

Goldsworthy, M.R., Pitcher, J.B., Ridding, M.C., 2012b. A comparison of two different continuous theta burst stimulation paradigms applied to the human primary motor cortex. Clin. Neurophysiol. 123, 2256–2263.

Goldsworthy, M.R., Pitcher, J.B., Ridding, M.C., 2013. Neuroplastic modulation of inhibitory motor cortical networks by spaced theta burst stimulation protocols. Brain Stimul. 6, 340–345.

Goldsworthy, M.R., Vallence, A.M., Hodyl, N.A., Semmler, J.G., Pitcher, J.B., Ridding, M.C., 2015. Probing changes in corticospinal excitability following theta burst stimulation of the human primary motor cortex. Clin. Neurophysiol.

Guan, M., Vandekerckhove, J., 2015. A Bayesian approach to mitigation of publication bias. Psychon. Bull. Rev.

Hamada, M., Murase, N., Hasan, A., Balaratnam, M., Rothwell, J.C., 2013. The role of interneuron networks in driving human motor cortical plasticity. Cereb. Cortex 23, 1593–1605.

Hasan, A., Hamada, M., Nitsche, M.A., Ruge, D., Galea, J.M., Wobrock, T., Rothwell, J.C., 2012. Direct-current-dependent shift of theta-burst-induced plasticity in the human motor cortex. Exp. Brain Res. 217, 15–23.

Hedges, L.V., Olkin, I., 1985. Statistical Methods for Meta-Analysis. Academic Press, Orlando, FL.

Hellriegel, H., Schulz, E.M., Siebner, H.R., Deuschl, G., Raethjen, J.H., 2012. Continuous theta-burst stimulation of the primary motor cortex in essential tremor. Clin. Neurophysiol. 123, 1010–1015.

Higgins, J., Green, S., 2008. Cochrane Handbook for Systematic Reviews of Interventions: The Cochrane Collaboration. Wiley.

Higgins, J.P., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. BMJ 327, 557–560.

Hinder, M.R., Goss, E.L., Fujiyama, H., Canty, A.J., Garry, M.I., Rodger, J., Summers, J.J., 2014. Inter- and Intra-individual variability following intermittent theta burst stimulation: implications for rehabilitation and recovery. Brain Stimul. 7, 365–371.

Horvath, J.C., Forte, J.D., Carter, O., 2015. Evidence that transcranial direct current stimulation (tDCS) generates little-to-no reliable neurophysiologic effect beyond MEP amplitude modulation in healthy human subjects: A systematic review. Neuropsychologia 66, 213–236.

Hsu, Y.F., Liao, K.K., Lee, P.L., Tsai, Y.A., Yeh, C.L., Lai, K.L., Huang, Y.Z., Lin, Y.Y., Lee, I.H., 2011. Intermittent theta burst stimulation over primary motor cortex enhances movement-related beta synchronisation. Clin. Neurophysiol. 122, 2260–2267.

Huang, Y.-Z., Rothwell, J.C., Lu, C.-S., Wang, J., Chen, R.-S., 2010a. Restoration of motor inhibition through an abnormal premotor-motor connection in dystonia. Mov.Disord. 25, 696–703.

Huang, Y., Rothwell, J.C., Lu, C.S., Chuang, W.L., Lin, W.Y., Chen, R.S., 2010b. Reversal of plasticity-like effects in the human motor cortex. J. Physiol. 588, 3683–3693.

Huang, Y.Z., Chen, R.S., Rothwell, J.C., Wen, H.Y., 2007. The after-effect of human theta burst stimulation is NMDA receptor dependent. Clin. Neurophysiol. 118, 1028–1032.

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, 201–206.

Huang, Y.Z., Rothwell, J.C., Edwards, M.J., Chen, R.S., 2008. Effect of physiological activity on an NMDA-dependent form of cortical plasticity in human. Cereb. Cortex 18, 563–570.
Huang, Y.Z., Rothwell, J.C., Lu, C.S., Wang, J., Weng, Y.H., Lai, S.C., Chuang, W.L., Hung, J., Chen, R.S., 2009. The effect of continuous theta burst stimulation over premotor cortex on circuits in primary motor cortex and spinal cord. Clin. Neurophysiol. 120, 796–801.
Huber, R., Maatta, S., Esser, S.K., Sarasso, S., Ferrarelli, F., Watson, A., Ferreri, F., Peterson, M.J., Tononi, G., 2008. Measures of cortical plasticity after transcranial paired associative stimulation predict changes in electroencephalogram slow-wave activity during subsequent sleep. J. Neurosci. 28, 7911–7918.
Huwaldt, J.A., 2010. Plot Digitizer, open source software available at http://plotdigitizer.sourceforge.net/.
Iezzi, E., Conte, A., Suppa, A., Agostino, R., Dinapoli, L., Scontrini, A., Berardelli, A., 2008. Phasic voluntary movements reverse the aftereffects of subsequent theta-burst stimulation in humans. J. Neurophysiol. 100, 2070–2076.
Iezzi, E., Suppa, A., Conte, A., Agostino, R., Nardella, A., Berardelli, A., 2010. Theta-burst stimulation over primary motor cortex degrades early motor learning. Eur. J. Neurosci. 31, 585–592.
Iezzi, E., Suppa, A., Conte, A., Li Voti, P., Bologna, M., Berardelli, A., 2011. Short-term and long-term plasticity interaction in human primary motor cortex. Eur. J. Neurosci. 33, 1908–1915.
Ishikawa, S., Matsunaga, K., Nakanishi, R., Kawahira, K., Murayama, N., Tsuji, S., Huang, Y.Z., Rothwell, J.C., 2007. Effect of theta burst stimulation over the human sensorimotor cortex on motor and somatosensory evoked potentials. Clin. Neurophysiol. 118, 1033–1043.
Jacobs, M.F., Tsang, P., Lee, K.G., Asmussen, M.J., Zapallow, C.M., Nelson, A.J., 2014. 30 Hz theta-burst stimulation over primary somatosensory cortex modulates corticospinal output to the hand. Brain Stimul. 7, 269–274.
Kishore, A., Joseph, T., Velayudhan, B., Popa, T., Meunier, S., 2012a. Early, severe and bilateral loss of LTP and LTD-like plasticity in motor cortex (M1) in de novo Parkinson's disease. Clin. Neurophysiol. 123, 822–828.
Kishore, A., Popa, T., Velayudhan, B., Joseph, T., Balachandran, A., Meunier, S., 2012b. Acute dopamine boost has a negative effect on plasticity of the primary motor cortex in advanced Parkinson's disease. Brain 135, 2074–2088.
Klein, J.A., Chan, S., Pringle, E., Schallert, K., Procaccio, V., Jimenez, R., Cramer, S.C., 2006. BDNF val66met polymorphism is associated with modified experience-dependent plasticity in human motor cortex. Nat. Neurosci. 9, 735–737.
Kobayashi, M., Pascual-Leone, A., 2003. Transcranial magnetic stimulation in neurology. Lancet Neurol. 2, 145–156.
Koch, G., Di Lorenzo, F., Bonni, S., Giacobbe, V., Bozzali, M., Caltagirone, C., Martorana, A., 2014. Dopaminergic modulation of cortical plasticity in Alzheimer's disease patients. Neuropsychopharmacology.
Koch, G., Lorenzo, F., Bonnì, S., Ponzo, V., Caltagirone, C., Martorana, A., 2012. Impaired LTP-but not LTD-like cortical plasticity in Alzheimer's disease patients. J. Alzheimer's Dis. 31, 593–599.
Lee, M., Kim, S.E., Kim, W.S., Lee, J., Yoo, H.K., Park, K.D., Choi, K.G., Jeong, S.Y., Kim, B.G., Lee, H.W., 2013. Interaction of motor training and intermittent theta burst stimulation in modulating motor cortical plasticity: influence of BDNF Val66Met polymorphism. PLoS One 8, e57690.
Li Voti, P., Conte, A., Suppa, A., Iezzi, E., Bologna, M., Aniello, M.S., Defazio, G., Rothwell, J.C., Berardelli, A., 2011. Correlation between cortical plasticity, motor learning and BDNF genotype in healthy subjects. Exp. Brain Res. 212, 91–99.
Liepert, J., Schwenkreis, P., Tegenthoff, M., Malin, J.P., 1997. The glutamate antagonist riluzole suppresses intracortical facilitation. J. Neural Transm. 104, 1207–1214.
López-Alonso, V., Cheeran, B., Río-Rodríguez, D., Fernández-Del-Olmo, M., 2014. Inter-individual variability in response to non-invasive brain stimulation paradigms. Brain Stimul. 7, 372–380.
Lu, B., 2003. BDNF and activity-dependent synaptic modulation. Learn. Mem. 10, 86–98.
Maeda, F., Keenan, J.P., Tormos, J.M., Topka, H., Pascual-Leone, A., 2000a. Interindividual variability of the modulatory effects of repetitive transcranial magnetic stimulation on cortical excitability. Exp. Brain Res. 133, 425–430.
Maeda, F., Keenan, J.P., Tormos, J.M., Topka, H., Pascual-Leone, A., 2000b. Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation. Clin. Neurophysiol. 111, 800–805.
Martin, P.G., Gandevia, S.C., Taylor, J.L., 2006. Theta burst stimulation does not reliably depress all regions of the human motor cortex. Clin. Neurophysiol. 117, 2684–2690.
Mastroeni, C., Bergmann, T.O., Rizzo, V., Ritter, C., Klein, C., Pohlmann, I., Brueggemann, N., Quartarone, A., Siebner, H.R., 2013. Brain-derived neurotrophic factor—a major player in stimulation-induced homeostatic metaplasticity of human motor cortex? PLoS One, 8.
McAllister, C.J., Ronnqvist, K.C., Stanford, I.M., Woodhall, G.L., Furlong, P.L., Hall, S.D., 2013. Oscillatory beta activity mediates neuroplastic effects of motor cortex stimulation in humans. J. Neurosci. 33, 7919–7927.
McAllister, S.M., Rothwell, J.C., Ridding, M.C., 2009. Selective modulation of intracortical inhibition by low-intensity theta burst stimulation. Clin. Neurophysiol. 120, 820–826.
McAllister, S.M., Rothwell, J.C., Ridding, M.C., 2011. Cortical oscillatory activity and the induction of plasticity in the human motor cortex. Eur. J. Neurosci. 33, 1916–1924.
McDonnell, M.N., Buckley, J.D., Opie, G.M., Ridding, M.C., Semmler, J.G., 2013. 2013 A single bout of aerobic exercise promotes motor cortical neuroplasticity. J. Appl. Physiol. (Bethesda, Md.: 1985) 114, 1174–1182.
McHughen, S.A., Rodriguez, P.F., Kleim, J.A., Kleim, E.D., Marchal Crespo, L., Procaccio, V., Cramer, S.C., 2010. BDNF val66met polymorphism influences motor system function in the human brain. Cereb. Cortex 20, 1254–1262.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., Group, P., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 339, b2535.
Moliadze, V., Fritzsche, G., Antal, A., 2014. Comparing the efficacy of excitatory transcranial stimulation methods measuring motor evoked potentials. 2014, 837141.
Monte-Silva, K., Ruge, D., Teo, J.T., Paulus, W., Rothwell, J.C., Nitsche, M.A., 2011. D2 receptor block abolishes theta burst stimulation-induced neuroplasticity in the human motor cortex. Neuropsychopharmacology 36, 2097–2102.
Mori, F., Ribolsi, M., Kusayanagi, H., Monteleone, F., Mantovani, V., Buttari, F., Marasco, E., Bernardi, G., Maccarrone, M., Centonze, D., 2012. TRPV1 channels regulate cortical excitability in humans. J. Neurosci. 32, 873–879.
Mori, F., Rossi, S., Piccinin, S., Motta, C., Mango, D., Kusayanagi, H., Bergami, A., Studer, V., Nicoletti, C.G., Buttari, F., Barbieri, F., Mercuri, N.B., Martino, G., Furlan, R., Nisticò, R., Centonze, D., 2013. Synaptic plasticity and PDGF signaling defects underlie clinical progression in multiple sclerosis. J. Neurosci. 33, 19112–19119.
Muller-Dahlhaus, J.F., Orekhov, Y., Liu, Y., Ziemann, U., 2008. Interindividual variability and age-dependency of motor cortical plasticity induced by paired associative stimulation. Exp. Brain Res. 187, 467–475.
Munneke, M.A.M., Rongen, J.J., Overeem, S., Schelhaas, H.J., Zwarts, M.J., Stegeman, D.F., 2013. Cumulative effect of 5 daily sessions of θ burst stimulation on corticospinal excitability in amyotrophic lateral sclerosis. Muscle Nerve 48, 733–738.
Murakami, T., Muller-Dahlhaus, F., Lu, M.K., Ziemann, U., 2012. Homeostatic metaplasticity of corticospinal excitatory and intracortical inhibitory neural circuits in human motor cortex. J. Physiol. 590, 5765–5781.
Murakami, T., Sakuma, K., Nomura, T., Nakashima, K., Hashimoto, I., 2008. High-frequency oscillations change in parallel with short-interval intracortical inhibition after theta burst magnetic stimulation. Clin. Neurophysiol. 119, 301–308.
Nakamura, K., Enomoto, H., Hanajima, R., Hamada, M., Shimizu, E., Kawamura, Y., Sasaki, T., Matsuzawa, D., Sutoh, C., Shirota, Y., Terao, Y., Ugawa, Y., 2011. Quadri-pulse stimulation (QPS) induced LTP/LTD was not affected by Val66Met polymorphism in the brain-derived neurotrophic factor (BDNF) gene. Neurosci. Lett. 487, 264–267.
Nettekoven, C., Volz, L.J., Kutscha, M., Pool, E.M., Rehme, A.K., Eickhoff, S.B., Fink, G.R., Grefkes, C., 2014. Dose-dependent effects of theta burst rTMS on cortical excitability and resting-state connectivity of the human motor system. J. Neurosci. 34, 6849–6859.
Nitsche, M.A., Paulus, W., 2000. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J. Physiol. 527 (Pt 3), 633–639.
Nyffeler, T., Cazzoli, D., Hess, C.W., Muri, R.M., 2009. One session of repeated parietal theta burst stimulation trains induces long-lasting improvement of visual neglect. Stroke 40, 2791–2796.
Nyffeler, T., Wurtz, P., Luscher, H.R., Hess, C.W., Senn, W., Pflugshaupt, T., von Wartburg, R., Luthi, M., Muri, R.M., 2006. Extending lifetime of plastic changes in the human brain. Eur. J. Neurosci. 24, 2961–2966.
Oberman, L., Eldaief, M., Fecteau, S., Ifert-Miller, F., Tormos, J.M., Pascual-Leone, A., 2012. Abnormal modulation of corticospinal excitability in adults with Asperger's syndrome. Eur. J. Neurosci. 36, 2782–2788.
Oberman, L., Ifert-Miller, F., Najib, U., Bashir, S., Woollacott, I., Gonzalez-Heydrich, J., Picker, J., Rotenberg, A., Pascual-Leone, A., 2010. Transcranial magnetic stimulation provides means to assess cortical plasticity and excitability in humans with fragile x syndrome and autism spectrum disorder. Front. Synaptic Neurosci. 2, 26.
Opie, G.M., Catcheside, P.G., Usmani, Z.A., Ridding, M.C., Semmler, J.G., 2013. Motor cortex plasticity induced by theta burst stimulation is impaired in patients with obstructive sleep apnoea. Eur. J. Neurosci. 37, 1844–1852.
Orth, M., Schippling, S., Schneider, S.A., Bhatia, K.P., Talelli, P., Tabrizi, S.J., Rothwell, J.C., 2010. Abnormal motor cortex plasticity in premanifest and very early manifest Huntington disease. J. Neurol. Neurosurg. Psychiatry 81, 267–270.
Peters, J.L., Sutton, A.J., Jones, D.R., Abrams, K.R., Rushton, L., 2007. Performance of the trim and fill method in the presence of publication bias and between-study heterogeneity. Stat. Med. 26, 4544–4562.
Pichiorri, F., Vicenzini, E., Gilio, F., Giacomelli, E., Frasca, V., Cambieri, C., Ceccanti, M., Di Piero, V., Inghilleri, M., 2012. Effects of intermittent theta burst stimulation on cerebral blood flow and cerebral vasomotor reactivity. J. Ultrasound Med. 31, 1159–1167.
Player, M.J., Taylor, J.L., Alonzo, A., Loo, C.K., 2012. Paired associative stimulation increases motor cortex excitability more effectively than theta-burst stimulation. Clin. Neurophysiol. 123, 2220–2226.
Popa, T., Velayudhan, B., Hubsch, C., Pradeep, S., Roze, E., Vidailhet, M., Meunier, S., Kishore, A., 2013. Cerebellar processing of sensory inputs primes motor cortex plasticity. Cereb. Cortex 23, 305–314.
Ridding, M.C., Ziemann, U., 2010. Determinants of the induction of cortical plasticity by non-invasive brain stimulation in healthy subjects. J. Physiol. 588, 2291–2304.

Roshan, L., Paradiso, G.O., Chen, R., 2003. Two phases of short-interval intracortical inhibition. Exp. Brain Res. 151, 330–337.
Sale, M.V., Ridding, M.C., Nordstrom, M.A., 2008. Cortisol inhibits neuroplasticity induction in human motor cortex. J. Neurosci. 28, 8285–8293.
Stefan, K., Gentner, R., Zeller, D., Dang, S., Classen, J., 2008. Theta-burst stimulation: remote physiological and local behavioral after-effects. Neuroimage 40, 265–274.
Sterne, J.A., Egger, M., Smith, G.D., 2001. Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis. BMJ 323, 101–105.
Sterne, J.A., Gavaghan, D., Egger, M., 2000. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. J. Clin. Epidemiol. 53, 1119–1129.
Suppa, A., Belvisi, D., Bologna, M., Marsili, L., Berardelli, I., Moretti, G., Pasquini, M., Fabbrini, G., Berardelli, A., 2011a. Abnormal cortical and brain stem plasticity in Gilles de la Tourette syndrome. Mov. Disord. 26, 1703–1710.
Suppa, A., Marsili, L., Belvisi, D., Conte, A., Iezzi, E., Modugno, N., Fabbrini, G., Berardelli, A., 2011b. Lack of LTP-like plasticity in primary motor cortex in Parkinson's disease. Exp. Neurol. 227, 296–301.
Suppa, A., Marsili, L., Di Stasio, F., Berardelli, I., Roselli, V., Pasquini, M., Cardona, F., Berardelli, A., 2014a. Cortical and brainstem plasticity in Tourette syndrome and obsessive-compulsive disorder. Mov. Disord.
Suppa, A., Marsili, L., Di Stasio, F., Latorre, A., Parvez, A., Colosimo, C., Berardelli, A., 2014b. Primary motor cortex long-term plasticity in multiple system atrophy. Mov. Disord. 29, 97–104.
Suppa, A., Ortu, E., Zafar, N., Deriu, F., Paulus, W., Berardelli, A., Rothwell, J.C., 2008. Theta burst stimulation induces after-effects on contralateral primary motor cortex excitability in humans. J. Physiol. 586, 4489–4500.
Swayne, O.B.C., Teo, J.T.H., Greenwood, R.J., Rothwell, J.C., 2009. The facilitatory effects of intermittent theta burst stimulation on corticospinal excitability are enhanced by nicotine. Clin. Neurophysiol. 120, 1610–1615.
Talelli, P., Cheeran, B.J., Teo, J.T., Rothwell, J.C., 2007. Pattern-specific role of the current orientation used to deliver theta burst stimulation. Clin. Neurophysiol. 118, 1815–1823.
Tecchio, F., Zappasodi, F., Pasqualetti, P., De Gennaro, L., Pellicciari, M.C., Ercolani, M., Squitti, R., Rossini, P.M., 2008. Age dependence of primary motor cortex plasticity induced by paired associative stimulation. Clin. Neurophysiol. 119, 675–682.
Teo, J.T.H., Swayne, O.B., Rothwell, J.C., 2007. Further evidence for NMDA-dependence of the after-effects of human theta burst stimulation. Clin. Neurophysiol. 118, 1649–1651.
Terrin, N., Schmid, C.H., Lau, J., Olkin, I., 2003. Adjusting for publication bias in the presence of heterogeneity. Stat. Med. 22, 2113–2126.
Todd, G., Flavel, S.C., Ridding, M.C., 2009. Priming theta-burst repetitive transcranial magnetic stimulation with low- and high-frequency stimulation. Exp. Brain Res. 195, 307–315.
Todd, G., Kimber, T.E., Ridding, M.C., Semmler, J.G., 2010. Reduced motor cortex plasticity following inhibitory rTMS in older adults. Clin. Neurophysiol. 121, 441–447.
Tsang, P., Jacobs, M.F., Lee, K.G.H., Asmussen, M.J., Zapallow, C.M., Nelson, A.J., 2014. Continuous theta-burst stimulation over primary somatosensory cortex modulates short-latency afferent inhibition. Clin. Neurophysiol.
Vallence, A.-M., Kurylowicz, L., Ridding, M.C., 2013. A comparison of neuroplastic responses to non-invasive brain stimulation protocols and motor learning in healthy adults. Neurosci. Lett. 549, 151–156.
Verdon, C.M., Saba, G., Januel, D., 2004. Transcranial magnetic stimulation in cognition and neuropsychology. L'Encephale 30, 363–368.
Vernet, M., Bashir, S., Yoo, W.-K., Perez, J.M., Najib, U., Pascual-Leone, A., 2013. Insights on the neural basis of motor plasticity induced by theta burst stimulation from TMS-EEG. Eur. J. Neurosci. 37, 598–606.
Vernet, M., Bashir, S., Yoo, W.K., Oberman, L., Mizrahi, I., Ifert-Miller, F., Beck, C.J., Pascual-Leone, A., 2014. Reproducibility of the effects of theta burst stimulation on motor cortical plasticity in healthy participants. Clin. Neurophysiol. 125, 320–326.
Wischnewski, M., Schutter, D.J., 2015. Efficacy and time course of theta burst stimulation in healthy humans. Brain Stimul. 8, 685–692.
Wu, S.W., Gilbert, D.L., 2012. Altered neurophysiologic response to intermittent theta burst stimulation in Tourette syndrome. Brain Stimul. 5, 315–319.
Wu, S.W., Shahana, N., Huddleston, D.A., Gilbert, D.L., 2012. Effects of 30 Hz theta burst transcranial magnetic stimulation on the primary motor cortex. J. Neurosci. Methods 208, 161–164.
Young-Bernier, M., Tanguay, A.N., Davidson, P.S.R., Tremblay, F., 2014. Short-latency afferent inhibition is a poor predictor of individual susceptibility to rTMS-induced plasticity in the motor cortex of young and older adults. Front. Aging Neurosci. 6.
Zafar, N., Paulus, W., Sommer, M., 2008. Comparative assessment of best conventional with best theta burst repetitive transcranial magnetic stimulation protocols on human motor cortex excitability. Clin. Neurophysiol. 119, 1393–1399.
Zamir, O., Gunraj, C., Ni, Z., Mazzella, F., Chen, R., 2012. Effects of theta burst stimulation on motor cortex excitability in Parkinson's disease. Clin. Neurophysiol. 123, 815–821.
Ziemann, U., Rothwell, J.C., Ridding, M.C., 1996. Interaction between intracortical inhibition and facilitation in human motor cortex. J. Physiol. 496 (Pt 3), 873–881.

CHAPTER EIGHT

Effects of TBS in the prefrontal cortex

Chung SW, Lewis BP, Rogasch NC, Saeki T, Thomson RH, Hoy KE, Bailey NW, Fitzgerald PB. 2017. Demonstration of short-term plasticity in the dorsolateral prefrontal cortex with theta burst stimulation: A TMS-EEG study. *Clinical Neurophysiology.* 128(7):1117-26.

Preamble to empirical paper

In Chapter 7, it was demonstrated that TBS has overall effects in changing corticospinal excitability, with iTBS increasing and cTBS decreasing the size of MEPs. Despite overestimated effect sizes in the literature, TBS does indeed have a modulatory capacity in the motor cortex. In addition, changes in stimulation parameters such as frequency of stimulation and repeated applications can result in more robust changes in MEPs.

In the prefrontal cortex, the physiological measure such as MEPs is not available. The methods for directly assessing plastic changes following TBS in the prefrontal cortex has not been established, and therefore it was necessary to first investigate whether TMS-EEG could be utilised to measure TBS-induced changes prior to investing the effect of different stimulation parameters in this cortical region. A limited number of studies have investigated TBS-induced changes using TMS-EEG (Casula et al., 2016b; Harrington and Hammond-Tooke, 2015; Vernet et al., 2013), however, none in the prefrontal region. Furthermore, these studies demonstrated inconsistent results partly due to differences in stimulation parameter and analysis method. The following chapter provides a detailed examination of cortical

reactivity and cortical inhibition following iTBS and cTBS over the left prefrontal cortex. Importantly, the evidence is provided on the utility of TMS-EEG as a tracking tool for modulatory changes following prefrontal TBS. This study also demonstrates polarity-specific changes of TBS in a similar manner observed in the motor cortex (Huang et al., 2005), establishing the indices of measurement for protocol optimisation.

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Demonstration of short-term plasticity in the dorsolateral prefrontal cortex with theta burst stimulation: A TMS-EEG study

Sung Wook Chung [a,*], Benjamin P. Lewis [a], Nigel C. Rogasch [b], Takashi Saeki [a], Richard H. Thomson [a], Kate E. Hoy [a], Neil W. Bailey [b], Paul B. Fitzgerald [a]

[a] Monash Alfred Psychiatry Research Centre, Monash University, Central Clinical School and The Alfred, Melbourne, Australia
[b] Brain and Mental Health Laboratory, School of Psychological Sciences and Monash Biomedical Imaging, Monash Institute of Cognitive and Clinical Neuroscience, Monash University, Melbourne, Australia

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HIGHLIGHTS

- Effects of intermittent theta burst stimulation (iTBS) and continuous theta burst stimulation (cTBS) were studied in the dorsolateral prefrontal cortex (DLPFC) using TMS-EEG.
- iTBS increased N120 amplitude, theta power and long-interval intracortical inhibition of theta oscillations.
- cTBS decreased theta power alone.

ABSTRACT

Objectives: To examine the effects of intermittent TBS (iTBS) and continuous TBS (cTBS) on cortical reactivity in the dorsolateral prefrontal cortex.
Methods: 10 healthy participants were stimulated with either iTBS, cTBS or sham at F3 electrode. Single- and paired-pulse TMS and concurrent electroencephalography (EEG) were used to assess change in cortical reactivity and long-interval intracortical inhibition (LICI) via TMS-evoked potentials (TEPs) and TMS-evoked oscillations.
Results: Significant increases in N120 amplitudes ($p < 0.01$) were observed following iTBS over prefrontal cortex. Changes in TMS-evoked theta oscillations and LICI of theta oscillations were also observed following iTBS (increase) and cTBS (decrease). Change in LICI of theta oscillations correlated with change in N120 amplitude following TBS ($r = -0.670$, $p = 0.001$).
Conclusions: This study provides preliminary evidence that TBS produces direct changes in cortical reactivity in the prefrontal cortex. Combining TBS with TMS-EEG may be a useful approach to optimise stimulation paradigms prior to the conduct of clinical trials.
Significance: TBS is able to modulate cortical reactivity and cortical inhibition in the prefrontal cortex.

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation method capable of modulating the excitability of cortical circuits for extended periods of time and has been utilized in both research and clinical applications (Machado et al., 2013). A variety of rTMS methods have been shown to modulate cortical functioning, including high (>5 Hz) and low (~1 Hz) frequency forms of rTMS, which have demonstrated lasting, but divergent effects on cortical excitability (Grossheinrich et al., 2009; Cardenas-Morales et al., 2010; Guse et al., 2010; Esslinger et al., 2014). A more recently developed method of delivering rTMS involves the application of magnetic stimulation in specific frequency patterns, which are thought have greater efficacy in modulating cortical activity. Theta burst stimulation (TBS) involves the application of a burst of three pulses at 50 Hz repeated at 5 Hz. Continuous TBS (cTBS) employs a continuous series of bursts for a total of 40 seconds (600 pulses), and has been shown to decrease cortical excitability in the motor cortex measured using motor evoked potentials (MEPs). On the other

* Corresponding author at: Monash Alfred Psychiatry Research Centre, Level 4, 607 St Kilda Road, Melbourne, Victoria 3004, Australia. Fax: +61 3 9076 8545.
E-mail address: sung.chung@monash.edu (S.W. Chung).

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hand, intermittent TBS (iTBS) involves the application of a 2-second train of TBS repeated every 10 seconds for a total of 192 seconds, and has been shown to increase MEP amplitude (Huang et al., 2005). TBS was originally developed based on the observations of natural firing patterns within the hippocampus, and the application of higher-frequency bursts (gamma) nested within lower-frequency rhythms (theta) resulted in reliable and robust long-term potentiation (LTP) (Larson et al., 1986). Rhythmic synchronization, in particular, coupling of theta and gamma frequencies has been shown to play a key role in the communication between neuronal networks, as well as in synaptic plasticity to promote learning and memory (Fell and Axmacher, 2011; Machado et al., 2013; Colgin, 2015; Lega et al., 2016). As such, this phase-locked firing pattern of stimulation appears to have effects on cortical excitability that are the equivalent, if not greater than those produced with traditional rTMS methods, and there is some evidence of longer-lasting aftereffect duration (Nyffeler et al., 2006; Yang et al., 2015).

The vast majority of TBS studies have demonstrated reliable corticospinal excitability change following motor cortex stimulation (Wischnewski and Schutter, 2015). However, recent studies with larger sample sizes have shown no group-level effect of TBS (Hamada et al., 2013; Hinder et al., 2014), and a meta-analysis has revealed publication bias (Chung et al., 2016), suggesting a degree of inter-individual variability. Furthermore, little is known about the effects of TBS on cortical excitability/inhibition outside the motor cortex.

This is important as there is increasing interest in the use of TBS as a therapeutic tool for disorders such as depression (Li et al., 2014; Plewnia et al., 2014; Bakker et al., 2015; Chistyakov et al., 2015; Chung et al., 2015a; Cheng et al., 2016) and schizophrenia (Demirtas-Tatlidede et al., 2010; Brunelin et al., 2011; Hasan et al., 2015), where dorsolateral prefrontal cortex (DLPFC) is the primary target for treatment. In developing clinical applications using TBS, there is a need to explore the cortical excitability effects of TBS in non-motor cortical regions. Establishing that changes in cortical excitability due to TBS can be detected with TMS-EEG will also allow the use of these approaches in preclinical studies investigating the optimal methods to induce changes in cortical activity.

Measuring TMS-evoked activity with EEG can be used to assess changes in cortical properties before and after an intervention (for review, see (Chung et al., 2015b)), and allows investigation beyond motor cortex. A number of studies have previously described TMS-evoked potentials (TEPs) found at latencies of 40, 60, 100 and 200 ms post a single stimulus and attempted to understand how these TEPs relate to aspects of cortical function (Rogasch et al., 2013a; Bortoletto et al., 2015; Gosseries et al., 2015). For example, TEPs at latencies of ~100 ms (N120) has been associated with cortical inhibitory processes (Bikmullina et al., 2009; Rogasch et al., 2013a; Premoli et al., 2014). However, the origin of other TEP components is still largely unknown.

The aim of this study was to examine the effects of iTBS and cTBS on cortical reactivity in the dorsolateral prefrontal cortex (DLPFC), a brain region relevant to the treatment of a number of neuropsychiatric disorders including depression, schizophrenia and movement disorders (Spronk et al., 2008; Cardenas-Morales et al., 2010; Leonard et al., 2013). Healthy subjects were stimulated in three separate sessions with either iTBS, cTBS or sham stimulation with the EEG responses to single and paired TMS pulses used to assess cortical reactivity and inhibition respectively, pre-and post-TBS. We hypothesized that iTBS and cTBS protocol would increase and decrease cortical reactivity respectively with respect to sham condition. In addition, we hypothesised that TBS-induced changes would be observed in the theta and gamma band oscillations, as these frequencies are targeted by TBS.

2. Materials and methods

2.1. Participants

10 right-handed participants (mean age 31.3 ± 9.3 years, range 21–51, 4 female) completed all 3 testing sessions. A number of state-dependent factors including the effect of medications, and substances such as alcohol and caffeine, can affect a participant's response to TBS (Silvanto and Pascual-Leone, 2008). Participants were asked to refrain from the consumption of alcohol and caffeine prior to the experiment and participants taking psychotropic medications were excluded from the study.

Four participants had partaken in previous TMS experiments but none in the month prior to participation. All participants gave informed consent prior to the experiment and were screened with the Mini International Neuropsychiatric Interview (MINI) in order to exclude psychopathology (Sheehan et al., 1998). The Alfred Hospital and Monash University Human Research and ethics committee approved the experiment.

2.2. Procedure

This study consisted of the recording of EEG responses to 50 single and paired TMS pulses both before and after one type of TBS at each session. Each participant attended for three sessions with at least one week apart, and the sessions were pseudorandomized and counterbalanced in administering either cTBS, iTBS or sham stimulation. Participants were required to keep their eyes open throughout the experiment and interaction with participants was limited during testing.

2.2.1. TMS

TMS was targeted to the left DLPFC throughout the experiment utilising the 10/20 method of electrode placement. It has been shown that DLPFC is approximately at the midpoint between the F3 and AF3 electrode position in 10/20 system, but slightly closer to F3 (Fitzgerald et al., 2009), and therefore the centre of the coil was placed at F3 electrode. In addition, the coil was positioned at 45 degrees to the midline as it has shown to produce the strongest stimulation in the DLPFC (Thomson et al., 2013). A Magstim 200 stimulator with a figure of eight coil (Magstim Ltd, Withland, Wales, UK) was used for single and paired pulse stimulation pre- and post-TBS using monophasic pulses (posterior-anterior current direction in the underlying cortex). TBS was delivered with a single MagVenture B-65 fluid-cooled coil (MagVenture, Copenhagen, Denmark) using biphasic pulses (antero-posterior to postero-anterior current direction in the underlying cortex). Stimulus intensity was set relative to resting motor threshold (rMT) obtained from the left motor cortex, which was identified via Ag/AgCl EMG electrodes attached to the first dorsal interosseous (FDI) muscle. The rMT was used to calibrate and normalise TMS coil output energy for inter- and intra-individual physiological variability, and was measured at the beginning of each session separately for each TMS machine. The EEG cap was mounted, and the rMT was determined as the minimum intensity required to evoke at least 3 out of 6 MEPs >0.05 mV in amplitude (Conforto et al., 2004).

Participants received 50 single (5 s interval ±10% jitter) and 50 paired pulses (100 ms interval) over the DLPFC at 120% rMT before and after TBS. The supra-threshold intensity was chosen to improve the signal to noise ratio (SNR) given the low number of trials. cTBS, iTBS or sham (depending on the session) was delivered at 80% rMT: cTBS – a burst of 3 pulses of stimulation given at 50 Hz repeated every 5 Hz for a total of 40 s, iTBS – a 2 s train of TBS

repeated every 10 s for a total of 192 s. Sham stimulation was applied using the iTBS protocol, with the coil orientated at 90 degrees to the scalp so the magnetic field would be delivered tangentially away from the scalp. Each condition delivered a total of 600 pulses.

2.2.2. EEG recording

EEG responses to TMS pulses were recorded with a 64-channel TMS-compatible EEG cap and a TMS-compatible EEG amplifier (SynAmps2, EDIT Compumedics Neuroscan, Texas, USA). Recordings were obtained from 39 electrodes positioned around the scalp (AF3, AF4, F7, F5, F3, F1, Fz, F2, F4, F6, F8, FC5, FC3, FC1, FCz, FC2, FC4, FC6, T7, C5, C3, C1, Cz, C2, C4, C6, T8, P7, P5, P3, P1, Pz, P2, P4, P6, P8, O1, Oz, O2). To monitor eye blinks, electrooculography (EOG) recordings were obtained from 4 Ag/AgCl electrodes, two positioned above and below the left eye and two positioned lateral to the outer canthus of both eyes.

Electrodes were online referenced to CPz and grounded to POz. Signals were amplified (1000×), low-pass filtered (2000 Hz) and recorded on a computer for offline analysis. The high acquisition rate (10,000 Hz), large operating range (±200 mV) and DC coupling of the EEG amplifier allows recording of the TMS artefact without amplifier saturation. Electrode impedance levels were kept at <5 kΩ throughout the experiment.

The loud auditory click produced by the TMS coil often produces an auditory EEG response. This was in part controlled by the application of white noise through earphones during TMS/TBS of the experiment.

2.3. EEG data preprocessing

TMS-EEG data were analysed offline using EEGLAB (Delorme and Makeig, 2004), FieldTrip (Oostenveld et al., 2011) and custom scripts on the Matlab platform (R2015b, The MathWorks, USA). Data were epoched around the test TMS pulse (−1000 to 1000 ms), baseline corrected with respect to the TMS-free data (−500 to −110 ms), and data between −5 and 10 ms (around the large signal from the TMS pulse) were removed and linearly interpolated. This baseline period was chosen so that the baseline period is equivalent between single and paired conditions. Both pre- and post-TMS epoched data for each condition were concatenated and analysed concurrently so that rejected components were removed in both sets of data to avoid bias. Data were downsampled to 1000 Hz and visually inspected to remove epochs containing muscle artefact or excessive noise. An average of 5.4 trials was rejected in the cTBS condition, 6.2 trials in the iTBS condition and 2.8 trials in the sham condition across both pre and post conditions. Bad channels (e.g. disconnected) were then removed. An initial round of independent component analysis (ICA) using the symmetric FastICA algorithm with nonlinearity 'tanh' was applied to remove the remainder of the muscle artefact (Korhonen et al., 2011). The remaining tail of TMS-evoked muscle artefact components was identified by the size, topography and properties of the waveform, which have been shown to be consistent with scalp muscle activation (Rogasch et al., 2013b), and was subtracted from the data using the previous artefact rejection method in the DLPFC as a guideline (Rogasch et al., 2014). All data were bandpass filtered (second-order, zero-phase, Butterworth filter, 1–100 Hz & notch at 50 Hz) and epochs were inspected again to remove any anomalous activity in the signal such as excessive muscle activity from jaw-clenching. The data were then submitted to the FastICA algorithm again. Identification and removal of additional artefactual components were based on a previous study (Rogasch et al., 2014), where blink artefacts, decay artefacts and other noise-related artefacts were removed. Removal of auditory evoked potentials described in the aforementioned study was not adopted in the current study as partial noise-masking was applied. Removed channels were interpolated, and data were re-referenced to common average reference. Finally, remaining epochs from each trial within a block were averaged.

2.3.1. TMS-evoked potentials (TEPs)

TEPs were analysed using two different methods. A region of interest (ROI) analysis of the average of 4 electrodes (F3, F1, FC3, FC1) was conducted to access the local effects of TBS. These electrodes were close to the point of stimulation and sat above left prefrontal cortex. The average of these electrodes also adequately represents all of the major peaks (Fig. 1). To ensure the spatial distribution was properly captured, cluster-based statics were used to evaluate global effect of TBS across the scalp. TEPs were compared before and after each type of TBS and compared across different type of TBS. Four peaks (N40, P60, N120 and P200) were chosen based on previous TMS-EEG studies on the DLPFC (Rogasch et al., 2014, 2015). TEP peaks were selected within pre-defined time windows for N40 (30–50 ms), P60 (55–75 ms), N120 (90–140 ms) and P200 (160–240 ms) at the ROI electrodes. The peak amplitude was then calculated as the average signal between ±5 ms of the selected peak latency. The same latency windows were used for global scalp analysis.

For the paired-pulse condition, the single-pulse TMS data was subtracted from the conditioning pulse to account for ongoing effects of the conditioning pulse on the test pulse TEP (Rogasch et al., 2015). For LICI of TEPs, difference between unconditioned (single test pulse) and conditioned (paired test pulse) TEPs were normalised to the value of the overall size of the TEPs (30–240 ms) using the following formula for each peak of interest:

$$\mathrm{LICI}_{\text{negative peak}} = (\mathrm{Single}_{\mathrm{peak}} - \mathrm{Paired}_{\mathrm{peak}})/(\mathrm{Single}_{\mathrm{min}} - \mathrm{Single}_{\mathrm{max}}) \times 100, \text{ where negative peaks are N40 and N120}$$

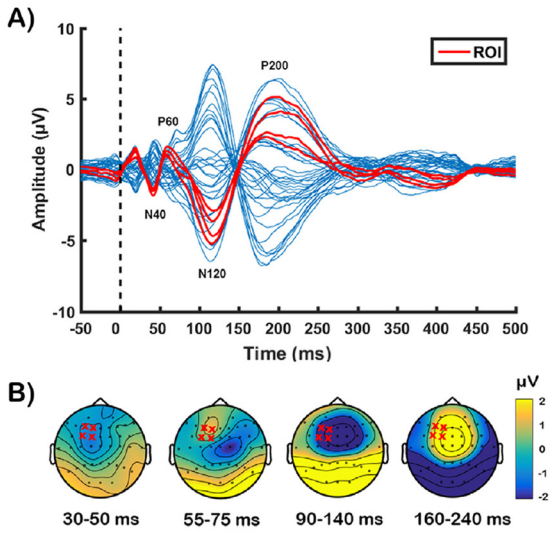

Fig. 1. TMS-evoked potential following single-pulse stimulation over left dorsolateral prefrontal cortex before theta-burst stimulation (averaged across participants). (A) Butterfly plot from all electrodes with major peaks (N40, P60, N120, P200) indicated in text. The red lines indicates the waveform obtained from 4 electrodes (F3, FC3, F1, FC1) around the stimulation site. (B) Voltage distribution for each peak of interest averaged across time indicated below. Red 'x' mark indicates the 4 electrodes chosen. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

$$LICI_{positive\ peak} = (Single_{peak} - Paired_{peak})/(Single_{max} - Single_{min}) \times 100,\ \text{where positive peaks are P60 and P200}$$

Normalisation of the data within a uniform range is necessary to consistently compare differences between single- and paired-pulse responses from peaks of different amplitudes.

2.3.2. TMS-evoked oscillations

TMS-evoked oscillatory power was calculated by converting TEPs into the frequency domain using Morlet wavelet decomposition (3.5 oscillation cycles with steps of 1 Hz between 5 Hz and 70 Hz) on each trial for each electrode. Oscillatory power was then averaged over all trials, maintaining both evoked and induced oscillations. Normalised power was obtained through division of power by a mean baseline value (−650 to −350 ms). ROI analysis of the average of 4 electrodes (F3, F1, FC3, FC1) and global scalp analysis was again used to evaluate the effect of TBS on TMS-evoked oscillations. Oscillations were averaged across frequency bands of interest [theta (5–7 Hz) and gamma (30–70 Hz)] and across time (50–250 ms for theta, 25–125 ms for gamma) based on previous studies of TMS-evoked oscillations over DLPFC (Rogasch et al., 2014, 2015; Hill et al., 2017). Theta and gamma frequencies were chosen for the direct reflection of the stimulation parameters, and the interaction of the two frequencies are implicated in synaptic plasticity (Nyhus and Curran, 2010; Zheng and Zhang, 2015). It is recommended to analyse time-frequency data with regard to all of its possible dimensions (van Ede and Maris, 2016), and therefore, multi-dimensional cluster-based analyses were performed [time (25–500 ms) × frequency (5–70 Hz) × space]. For further subgroup analyses on individual frequency bands, the following bands were used: theta 5–7 Hz, alpha 8–12 Hz, beta 13–29 Hz and gamma 30–70 Hz.

For LICI of TMS-evoked oscillations, the difference between unconditioned and conditioned oscillations in theta, and gamma bands were normalised to the mean power across all frequency band (5–70 Hz) using the following formula:

$$LICI_{freq} = (Single_{freq} - Paired_{freq})/Single_{all} \times 100$$

2.4. Statistical analysis

Statistical analysis was performed in SPSS (Version 22) and Matlab. For the ROI analysis, when data did not meet the requirement for normality (Shapiro-Wilk test), data were winsorised by setting extreme values to the corresponding adjacent 5th or 95th percentile value (Wilcox, 1997). A total of 2.08% of the data were winsorised for single-pulse TEPs and 2.5% of data for LICI of TEPs. A total 1.67% data were winsorised for each TMS-evoked oscillations and LICI of TMS-evoked oscillations. Repeated measures 2 [time (pre and post)] × 3 [stimulation conditions (iTBS, cTBS and Sham)] ANOVAs were performed on ROI analysis of TEP amplitudes and TMS-evoked oscillatory power. Post hoc *t*-tests were conducted with a Bonferroni correction applied to further explore the significant main effects of stimulation.

For global scalp analysis, non-parametric cluster-based permutation statistics were used (Oostenveld et al., 2011). To assess whether each TBS condition altered cortical reactivity over time, differences between pre- and post-TBS measures were compared. To assess whether TBS conditions differentially altered cortical reactivity, relative changes in TEP amplitudes and TMS-evoked oscillatory power following TBS (post–pre) between conditions were compared. Monte Carlo *p*-values were calculated from 5000 randomizations and clusters were defined by two or more neighbouring electrodes with t-statistics at a given time or frequency point exceeding a threshold of $p < 0.05$ (dependent *t*-test).

To assess the relationship between changes in single and paired pulse markers of inhibition, Pearson's correlations were used to compare stimulation-induced change in N120 amplitude with the change in LICI of TEPs and LICI of TMS-evoked oscillations.

3. Results

3.1. Single-Pulse TMS

Single-pulse TMS over DLPFC resulted in a series of negative and positive peaks before and after TBS including N40, P60, N120 and P200 (See Table 1). There was no significant difference in the latency among different TBS conditions (all $p > 0.05$), and in the number of subjects in which peaks were found (iTBS: 10, cTBS: 10, sham: 9.75 ± 0.5). When peaks were not found, data were extracted from the pre-defined latencies (eg. 40 ms for N40). Data were re-analysed excluding one subject for the analyses associated with N40, however, results did not change.

Due to a low number of TMS pulses included in the analyses (~45 pulses), an SNR analysis was performed on the ROI data for each individual. The SNR was estimated by dividing the peak amplitude by the standard deviation of the TEP waveform in the pre-stimulus interval (i.e. −500 to −100 ms), a method used in other ERP studies (Debener et al., 2007; Hu et al., 2010). This calculation would provide how many standard deviations larger the peak is relative to the background, and a value of 3 SDs (99.7% of the baseline distribution) would represent a good SNR. Mean SNR was then averaged across individuals. All the peaks had values above 3 SDs, but qualitatively, it was evident that earlier peaks (N40 and P60) had a lower SNR than later peaks (N120 and P200) (see Table 2).

3.1.1. ROI analysis of the effect of TBS on TEPs

Grand average TEP waveforms are illustrated in Fig. 2. Two-way repeated measures ANOVA yielded a trend in the main effect of time ($F_{1,9} = 4.244$, $p = 0.069$) and a significant interaction ($F_{2,18} = 6.862$, $p = 0.006$) in N120 amplitude. No significant main effect of condition was found ($F_{2,18} = 2.565$, $p = 0.105$). In order to investigate the interaction effect, a series of one-way ANOVA was performed across conditions at each time point (pre- and post-TBS), as well as paired *t*-tests across time for each condition. No significant main effect was observed at pre-TBS ($F_{2,18} = 1.124$, $p = 0.350$), but a significant main effect was found at post-TBS ($F_{2,18} = 5.079$, $p = 0.018$). Post hoc pairwise comparison revealed that N120 amplitude was significantly larger following iTBS compared to sham ($p = 0.015$), however there was no significant differences between iTBS and cTBS ($p = 0.157$), nor between cTBS and sham ($p = 1.000$). Across time within conditions, paired *t*-tests showed significant increase in N120 amplitude following iTBS ($t_{(9)} = -3.297$, $p = 0.009$), but no significant change was observed following cTBS ($t_{(9)} = 0.182$, $p = 0.860$) or sham ($t_{(9)} = -0.777$, $p = 0.457$). No other peaks showed any significant main effects or interaction (all $p > 0.05$).

3.1.2. Global scalp analysis of the effect of TBS on TEPs

Over time, cluster-based statistics across space showed one significant negative cluster ($p = 0.0008$; post signal more negative than pre) at N120, indicating the N120 was more negative following iTBS, and one positive cluster ($p = 0.0098$; post signal more positive than pre) at P200, indicating P200 was more positive following iTBS. Topographical representation revealed a difference in N120 amplitude at the site of stimulation and contralaterally, while the difference in P200 amplitude was close to the stimulation site alone (Fig. 2A). There were no significant differences in other peaks across the scalp (all $p > 0.05$). No significant differences

Table 1
Latencies of each peak before and after each stimulation condition.

	iTBS [mean (SD)]		cTBS [mean (SD)]		Sham [mean (SD)]	
	T0	T1	T0	T1	T0	T1
N40	37.7 (±6.91)	40.5 (±9.24)	41.8 (±8.94)	42.9 (±10.80)	36.4 (±8.42)	39.0 (±7.41)
P60	64.8 (±8.11)	65.5 (±11.18)	63.1 (±8.46)	63.7 (±8.47)	58.1 (±8.12)	60.9 (±6.19)
N120	118.5 (±10.29)	117.3 (±9.23)	115.0 (±6.60)	116.2 (±6.37)	115.2 (±10.48)	113.3 (±8.59)
P200	208.6 (±19.58)	213.5 (±21.21)	197.5 (±24.52)	200.4 (±23.06)	204.5 (±25.27)	202.5 (±29.08)

Table 2
Signal-to-noise ratio of each peak before and after each stimulation condition (mean ± SD).

	iTBS		cTBS		Sham	
	T0	T1	T0	T1	T0	T1
N40	5.59 (±3.63)	5.8 (±4.63)	6.44 (±4.96)	7.21 (±6.48)	6.96 (±6.05)	5.80 (±5.04)
P60	6.60 (±6.12)	5.82 (±7.28)	5.42 (±3.59)	5.01 (±4.10)	5.90 (±6.86)	5.64 (±4.48)
N120	10.21 (±2.67)	12.49 (±3.52)	13.28 (±6.89)	12.92 (±6.82)	10.5 (±5.13)	11.22 (±6.81)
P200	10.07 (±5.74)	10.76 (±6.71)	13.07 (±7.88)	12.09 (±8.17)	10.35 (±6.28)	10.05 (±5.96)

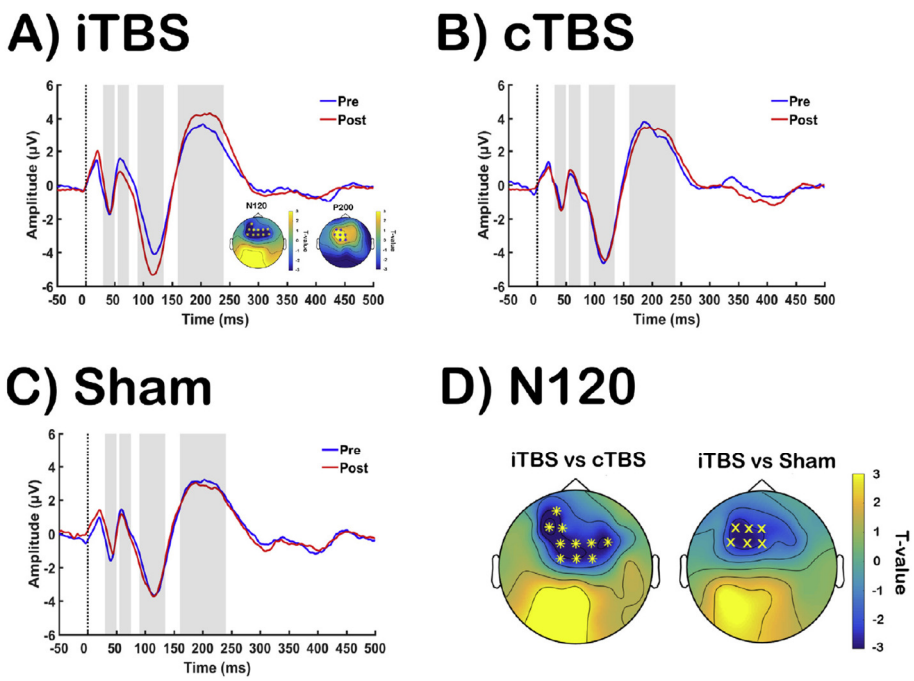

Fig. 2. Assessment of transcranial magnetic stimulation (TMS)-evoked potentials (TEPs) before and after each stimulation condition [A: intermittent theta-burst stimulation (iTBS); B: continuous theta-burst stimulation (cTBS); C: Sham]. Grand average TEP waveforms pre- (blue) and post-TBS (red) for each stimulation conditions, with significant global differences illustrated in topoplots (post more negative (blue) or positive (yellow) than pre). (D) Comparison of different TBS induced N120 amplitude change at global level. Asterisks and 'X's on topoplots indicate significant clusters between comparisons (cluster-based statistics, $^{*}p < 0.01$, $^{X}p < 0.05$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

were observed between pre and post TEPs following cTBS (Fig. 2B) and sham (Fig. 2C) for any peaks (all $p > 0.05$).

In order to evaluate the differences between conditions, TBS-induced changes (post – pre) in TEP amplitude were calculated and compared. One significant negative cluster for the change in N120 (Δ N120) was found between iTBS and cTBS ($p = 0.0002$; iTBS more negative than cTBS), and between iTBS and sham ($p = 0.017$; iTBS more negative than sham). Topographical representation showed the differences were at the site of stimulation for both comparisons, but also contralaterally for the former (Fig. 2D). One positive cluster was observed with each comparison for the change in P200 (Δ P200) [iTBS vs cTBS ($p = 0.009$); iTBS vs sham ($p = 0.005$)], suggesting larger Δ P200 amplitude with iTBS compared to both cTBS and sham. The differences were observed at the stimulation site for cTBS, and frontocentral site for sham.

3.1.3. ROI analysis of the effect of TBS on TMS-evoked oscillations

TBS-induced changes in TMS-evoked oscillations (grand average) at ROI are illustrated in Fig 3 (A: iTBS; B: cTBS; C: Sham). Two-way repeated measures ANOVA yielded no significant effect of time ($F_{1,9} = 0.033$, $p = 0.859$), but a trend in the main effect of condition ($F_{2,18} = 3.211$, $p = 0.064$) and a significant interaction

($F_{2,18}$ = 7.857, p = 0.004) in TMS-evoked theta power. To assess the interaction effect, a series of one-way ANOVA was performed across conditions at each time point (pre- and post-TBS), and paired t-tests were conducted across time for each condition. No significant main effect was observed at pre-TBS ($F_{2,18}$ = 2.529, p = 0.108), but a significant main effect was found at post-TBS ($F_{2,18}$ = 6.876, p = 0.006). Post hoc pairwise comparison revealed that theta power was significantly larger following iTBS compared to sham (p = 0.046), and a trend was seen between iTBS and cTBS (p = 0.069). However, there was no significant difference between cTBS and sham (p = 1.000). Across time within conditions, paired t-tests showed a significant increase in theta power following iTBS ($t_{(9)}$ = 2.416, p = 0.039), a significant decrease in theta power following cTBS ($t_{(9)}$ = 2.377, p = 0.041), but no significant change was observed following sham stimulation ($t_{(9)}$ = 0.007, p = 0.994) (Fig. 3D). No significant main effects or interactions were observed in TMS-evoked gamma power (p > 0.05).

3.1.4. Global analysis of the effects of TBS conditions on TMS-evoked oscillations

To assess the effect of TBS across the scalp in the frequency domain, TMS-evoked oscillations were compared in *a priori* time windows (see dotted boxes in Fig. 3) across space using cluster-based statistics. No significant clusters were found in any frequency band (all p > 0.05) within any stimulation condition across time. In order to evaluate the differences in TMS-evoked oscillations among stimulation conditions, TBS-induced changes (post–pre) were calculated and compared. One significant positive cluster in the change in theta power (Δ theta) was found between iTBS and cTBS (p = 0.008; Δ theta post-iTBS larger than post-cTBS; Fig. 3E) on the contralateral site of stimulation. No other significant cluster was found between other conditions.

To assess possible TBS-related changes in other oscillatory bands and time windows, we also included an exploratory analysis including all dimensions (time × frequency × space), but no significant differences were found (all p > 0.05). When subgroups of data including individual frequency bands were analysed separately [time × individual frequency band (theta, alpha, beta, gamma) × space], only change in theta power showed significant difference between iTBS and cTBS (iTBS > cTBS, 112–314 ms, p = 0.022), in agreement with our *a priori* time window analysis.

3.2. Paired-pulse TMS (LICI)

3.2.1. The effect of TBS on LICI of TEPs

The grand average TEP waveforms of single and paired-pulses are illustrated in Fig. 4. Two-way repeated measures ANOVA at ROI electrodes showed no significant main effects in LICI of TEPs in any peak (all p > 0.05). Globally, no significant cluster was found between pre- and post-TBS, and between conditions in any peak (all p > 0.05).

3.2.2. ROI analysis of the effect of TBS on LICI of TMS-evoked oscillations

Two-way repeated measures ANOVA yielded no significant effect of time ($F_{1,9}$ = 0.010, p = 0.922), but a significant effect of condition ($F_{2,18}$ = 5.421, p = 0.014) and a significant interaction ($F_{2,18}$ = 8.156, p = 0.003) in LICI of theta power. To investigate the interaction effect, a series of one-way ANOVA was performed across conditions at each time point (pre- and post-TBS), and paired t-tests were conducted across time for each condition. No significant main effect was observed at pre-TBS ($F_{2,18}$ = 2.740, p = 0.110), but a significant main effect was found at post-TBS ($F_{2,18}$ = 6.644, p = 0.001). Post hoc pairwise comparison revealed that LICI of theta power was significantly larger following iTBS compared to sham (p = 0.007), and compared to cTBS (p = 0.029). However, no significant differences were observed between cTBS and sham (p = 1.000). Across time within conditions, paired t-tests showed a significant increase in LICI of theta power following iTBS ($t_{(9)}$ = 3.030, p = 0.014), but no significant changes were observed following cTBS ($t_{(9)}$ = −1.652, p = 0.133) or sham

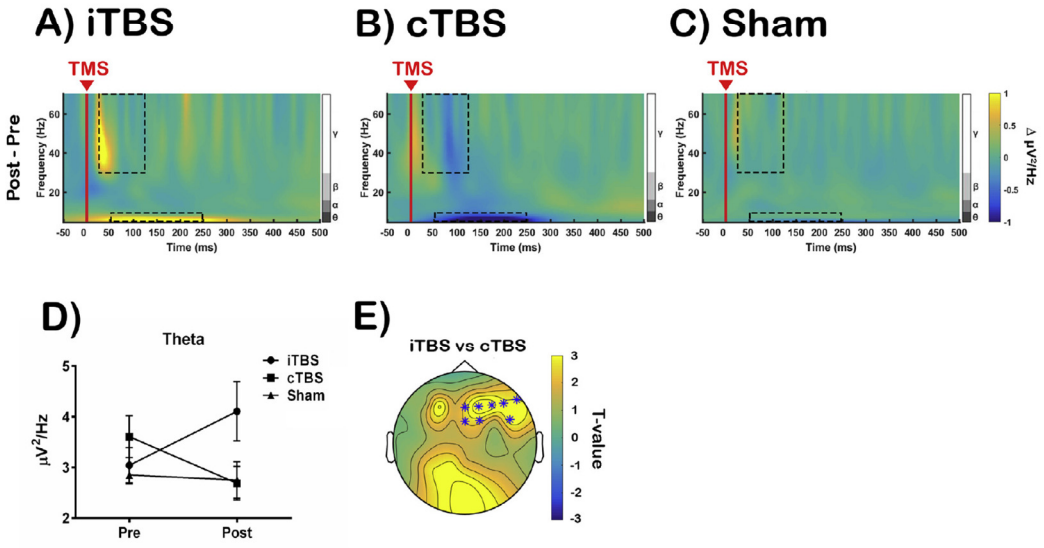

Fig. 3. Comparison of transcranial magnetic stimulation (TMS)-evoked oscillations in TBS-induced changes [A: intermittent theta-burst stimulation (iTBS); B: continuous theta-burst stimulation (cTBS); C: Sham]. Grand average time-frequency plots were obtained from the average of 4 electrodes (F3, FC3, F1, FC1) around the stimulation site. Dotted boxes represent the *a priori* time-frequency windows for gamma and theta bands. (D) TBS-induced theta power change over time among each stimulation condition at the region of interest and (E) comparison of TBS-induced theta power change across the scalp between iTBS and cTBS condition. Asterisks on topoplot indicate significant clusters between Δ theta post-iTBS and post-cTBS (cluster-based statistics, $^{*}p$ < 0.01).

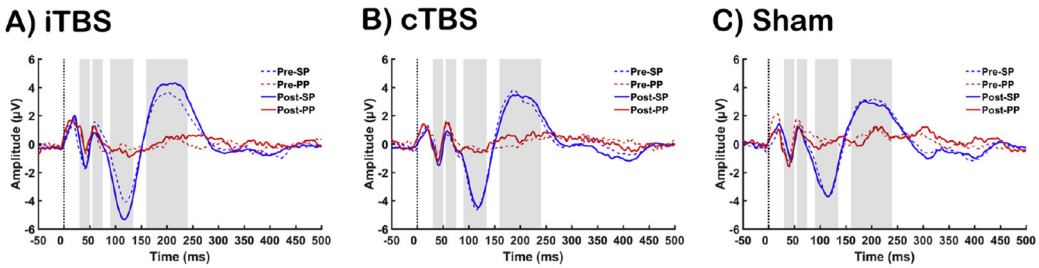

Fig. 4. Assessment of long-interval intracortical inhibition (LICI) before and after each stimulation condition [A: intermittent theta-burst stimulation (iTBS); B: continuous theta-burst stimulation (cTBS); C: Sham], at F3 electrode. Grand average transcranial magnetic stimulation (TMS)-evoked potential (TEP) waveforms illustrate both single-pulse (SP; blue) and paired-pulse (PP; red) before (dotted-line) and after (solid-line) TBS. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

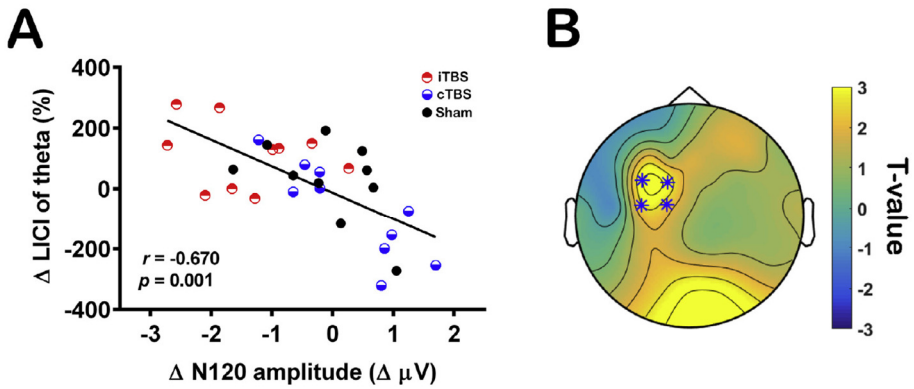

Fig. 5. Theta-burst stimulation (TBS) induced long-interval intracortical inhibition (LICI) of transcranial magnetic stimulation (TMS)-evoked oscillations. (A) Correlation between TBS induced N120 amplitude change and change in LICI of theta frequency. (B) Intermittent TBS (iTBS) induced change in LICI of theta frequency (5–7 Hz; 50–250 ms) across the scalp. Asterisks on topoplot indicate significant clusters between pre- and post-iTBS (cluster-based statistics, $^{*}p < 0.01$).

stimulation ($t_{(9)} = 0.243$, $p = 0.814$). No significant main effect was observed with LICI of gamma power ($p > 0.05$).

To assess whether Δ N120 following TBS was associated with the change in LICI (Δ LICI) of theta frequency band, correlation analysis was performed. Pearson's correlation showed the change in N120 amplitude with TBS significantly correlated with change in LICI strength in the theta band ($r = -0.670$, $p = 0.001$; Fig. 5A), suggesting a larger increase in the negativity of the N120 amplitude corresponds to a larger increase in inhibition of theta frequency oscillations following TBS.

3.2.3. Global analysis of the effect of TBS on LICI of TMS-evoked oscillations

One significant positive cluster was observed in LICI of theta ($p = 0.007$; increase LICI from pre to post-iTBS) but not in gamma band. Topographical representation revealed the difference in LICI of theta at the site of stimulation (Fig. 5B). No significant difference (all $p > 0.05$) was observed with cTBS or sham in any frequency band across the scalp.

Between stimulation conditions, one significant positive cluster in Δ LICI theta was found at the prefrontal region between iTBS and cTBS ($p = 0.013$; Δ LICI theta post-iTBS larger than post-cTBS). No other significant cluster was found between other conditions.

3.3. Control analysis

To ensure that the baseline correction window used for single pulse data analysis did not influence the results, we repeated the analysis using a window closer to the pulse (−500 to −10 ms).

3.3.1. TEPs

For ROI analysis, two-way repeated measures ANOVA yielded a significant interaction ($F_{2,18} = 5.967$, $p = 0.010$) in N120 amplitude. Globally, cluster-based statistics across space showed one significant negative cluster ($p = 0.001$) at N120, and one positive cluster ($p = 0.015$) at P200 following iTBS. One significant negative cluster was observed for the change in N120 (Δ N120) [iTBS > cTBS ($p = 0.0004$); iTBS > sham ($p = 0.032$)], and one positive cluster each for the change in P200 (Δ P200) [iTBS > cTBS ($p = 0.015$); iTBS > sham ($p = 0.017$)].

3.3.2. TMS-evoked oscillations

For ROI analysis, two-way repeated measures ANOVA yielded a significant interaction ($F_{2,18} = 7.857$, $p = 0.004$) in TMS-evoked theta power. Globally, one significant positive cluster in the change in theta power (Δ theta) was found between iTBS and cTBS ($p = 0.008$) on the contralateral site of stimulation.

4. Discussion

Results of this study have demonstrated short-term plastic changes by TBS delivered to the left DLPFC. Most notably, iTBS increased N120 TEP peak amplitude, TMS-evoked theta power and LICI of TMS-evoked theta oscillations, while cTBS showed a decrease in these measures. In addition, changes in N120 amplitude following TBS correlated with change in LICI of theta oscillations, suggesting N120 may be linked to TBS-induced modulation of cortical inhibition.

In the current study, we showed that iTBS over DLPFC increased N120 amplitude, whereas we could not find the evidence for a similar effect with cTBS. This is the first study to assess the effects of TBS on DLPFC TEPs, however, plasticity change has been demonstrated in the DLPFC using other stimulation paradigms including cortico-cortical paired associative stimulation (PAS) (Casula et al., 2016a) and peripheral-cortical PAS (Rajji et al., 2013). Modulation of later peaks (120–250 ms) have been demonstrated by PAS in the DLPFC (Casula et al., 2016a), and studies from the motor cortex have found that TEPs with similar latencies were also modulated. For example, 1 Hz rTMS, which has been known to decrease cortical excitability, applied to the primary motor cortex increased TEPs with a latency of 100 ms (i.e. N100) in healthy individuals (Casula et al., 2014), while cTBS resulted in decreased N100 (Harrington and Hammond-Tooke, 2015; Huang and Mouraux, 2015). Harrington and colleagues (2015) have demonstrated effects of TBS on cerebellum using TMS-EEG over motor cortex, and found increased N100 amplitude following iTBS and decreased N100 amplitude following cTBS (Harrington and Hammond-Tooke, 2015), which in part, is similar to the finding of the current study. However, TBS effects were projected through cerebello-thalamo-cortical pathway in the above-mentioned study, and the parameters of the stimulation used were also different (30 Hz, 80–90% rMT). More recently, a similar study with a larger sample size ($n = 20$) showed the opposite effect of TBS on cerebellum to the above mentioned study (i.e. increased amplitude following cTBS, decrease following iTBS), probed from both M1 and posterior parietal cortex (Casula et al., 2016b). The main difference between the two studies is in its frequency of TBS applied, the former study using 30 Hz, and the latter using 50 Hz. Even though a direct comparison of 30 Hz and 50 Hz cTBS has been demonstrated in the motor cortex (Goldsworthy et al., 2012), it is unclear what effect it would have in other brain regions, and requires further investigation.

Overall, changes in N100 amplitude have been observed following TBS in different brain regions, but it remains unclear whether N100 of M1-TEP and N120 of the DLPFC-TEP are analogous responses, and further studies are needed to characterise this negative potential. In addition to the increase in N120 amplitude, we also observed an increase in P200 amplitude following iTBS. Currently, the origin of this late TEP is still unknown, but changes have been observed following tDCS (Pellicciari et al., 2013) and PAS (Huber et al., 2008; Veniero et al., 2013) and TBS (Casula et al., 2016b).

We found an increase in TMS-evoked theta oscillations following iTBS in the prefrontal region, and to a lesser extent, a decrease with cTBS. Furthermore, iTBS also resulted in an increase in LICI of TMS-evoked theta (a paired-pulse measure of cortical inhibition (Daskalakis et al., 2008; Garcia Dominguez et al., 2014)), suggesting TBS can modulate cortical inhibition in the stimulated region. The change in LICI of theta correlated with change in N120 amplitude, suggesting that LICI of theta and N120 amplitude in DLPFC may reflect similar underlying mechanisms. Additional pharmacological studies are required to establish whether N120 amplitude and LICI of theta oscillations in DLPFC are specifically sensitive to changes in $GABA_B$-mediated inhibition.

Our finding of TBS-induced changes in theta oscillations is broadly consistent with the effect of TBS on cognitive performance, especially working memory (WM), where iTBS over DLPFC increases WM performance (Hoy et al., 2015) and cTBS decreases performance (Schicktanz et al., 2015). Theta frequency is thought to reflect active operations of the cortex, such as memory encoding, retention and retrieval (Jacobs et al., 2006; Itthipuripat et al., 2013; Cavanagh and Frank, 2014), suggesting these changes in cognitive performance may result from changes in the capacity to generate theta oscillations.

Contrary to our hypothesis, we did not observe any change in TMS-evoked gamma oscillations. Gamma oscillations reflect coordinated neuronal activity, and are implicated in spike-timing-dependent plasticity (Nyhus and Curran, 2010). In an animal study, when equivalent repeats of the two TBS paradigms were applied to rat cortex, iTBS but not cTBS caused a lasting increase in gamma power of the EEG recorded from the frontal cortex (Benali et al., 2011). It should be noted that TMS-evoked oscillations may not necessarily reflect an increase in gamma power of the cortex, and we did not measure resting EEG data to confirm this finding.

No significant changes in TEPs could be detected following cTBS. This is likely to be due to individual variability to TBS, which may arise from the activation of different interneuronal networks across individuals (Hamada et al., 2013). In addition, 120% rMT was used to probe TBS-induced changes. It has been described that the magnitude and the consistency of MEP suppression induced by cTBS were greatest when probed using stimulus intensities at or above 150% rMT, while facilitation of MEPs following iTBS was strongest and most consistent at 110% rMT (Goldsworthy et al., 2016). Whether a similar relationship exists in the DLPFC requires further investigation. Vernet and colleagues (2013) have demonstrated a decrease in TMS-evoked oscillations in low frequencies (theta and alpha) in the motor cortex following cTBS (Vernet et al., 2013), which is somewhat consistent with our findings. Overall, the changes in N120 and TMS-evoked theta were significantly different between iTBS and cTBS, consistent with differential changes in MEP amplitude observed in motor cortex.

Several limitations of the present study should be acknowledged. It is possible that the TMS click sound was not completely suppressed by the application of white noise. In addition, the click of the coil transmitted via bone conduction could not be avoided in this study. Even though it is unlikely that N100-P180 components are induced by auditory effects alone (ter Braack et al., 2015), any remaining effects of auditory-evoked potentials cannot be ignored for proper inference of physiological meaning of the TBS. It is, however, worth noting that the auditory artefacts should be consistent across time, and therefore changes in TEP amplitude can be attributed to TMS-evoked neural activity. Magnetic artefacts produced by the TMS pulse can affect the measurement of evoked potentials which could confound the interpretation of EEG data. However, as we used a repeated measures, sham-controlled design it is unlikely that confounding factors would have affected the pre- and post-TBS measures unequally unless they specifically impact on the cortical plastic response to TBS. It is reassuring that we saw no significant change in cortical reactivity with sham stimulation. This study was performed on a small number of participants. A larger sample size would be required for more accurate estimation for future comparisons. The removal of magnetic pulse artefact, followed by the artefact rejection from the muscular origin may have removed the information on early TEPs (15–30 ms). The low number of trials collected may have also limited the ability to detect the changes in N40 and P60 due to lower SNR. However, we adopted measuring mean voltage rather than peak voltage, and included neurophysiologically valid time points and sensors into the measurement of mean amplitudes, which would increase the internal consistency of the result despite low SNR (Thigpen et al., 2017), as mean amplitude over a predefined latency range is not biased by the number of trials (Luck, 2005). It is worth noting that peaks we found differences in (N120 and P200) had high SNR. In addition, differences in LICI of TEPs were not found, which may have been impacted by a saturation of LICI at baseline preventing the assessment of increased LICI following TBS. Due to local power-line frequency at 50 Hz, analysis specific to the frequency of interest was limited, and accounted for using a wider window (30–70 Hz), which may have resulted in the negative finding in gamma frequency. Finally,

localisation of DLPFC was estimated using F3 electrode, and this could be improved by using neuronavigation.

5. Conclusion and future directions

This study provides preliminary evidence that TBS produces direct changes in cortical reactivity in the prefrontal cortex, in a manner similar to that seen in motor regions. We have also demonstrated that the TMS – EEG methodology can be used to study the effects of TBS in the prefrontal cortex. This may be a useful approach to pre-clinically optimise stimulation paradigms prior to the conduct of clinical trials.

The continuing optimisation of TBS protocols is imperative in order to facilitate their translation into clinical use. For example, experiments aimed at investigating the effects of change in pulse frequency and intensity are required to define optimal stimulation parameters. Methods such as those applied in this study allow the pre-clinical investigation of optimal stimulation parameters in a manner that can potentially help develop optimal methods for clinical trial applications. Furthermore, whilst the lasting effects of theta burst stimulation have been demonstrated (Nyffeler et al., 2006; Noh et al., 2012; Goldsworthy et al., 2013), further evidence is required to demonstrate the effects of repeated TBS sessions on cortical excitability in non-motor brain regions. Studying the effect of state-dependency factors on TBS-induced cortical excitability is also important. A range of studies has demonstrated the impact of factors such as prior stimulation by TMS (Lang et al., 2004) and antiepileptic medication (Fregni et al., 2006). Examination of the state of the brain prior to TBS administration may offer further advantages in terms of optimisation. A number of studies have suggested a role for matching the stimulation frequency to the specific neural frequency of the brain prior to stimulation (Jin et al., 2006, 2012; Leuchter et al., 2013) and this may yield interesting results in modulating cortical plasticity using TBS.

Conflict of interest

SWC was supported by a Monash Graduate Scholarship. NCR is supported by a NHMRC Early Career Fellowship (1072057). KEH is supported by a NHMRC Career Development Fellowship (1082894). PBF is supported by a NHMRC Practitioner Fellowship (1078567). PBF has received equipment for research from MagVenture A/S, Medtronic Ltd, Cervel Neurotech and Brainsway Ltd and funding for research from Neuronetics and Cervel Neurotech. He is on the scientific advisory board for Bionomics Ltd. There are no other conflicts.

References

Bakker N, Shahab S, Giacobbe P, Blumberger DM, Daskalakis ZJ, Kennedy SH, et al. RTMS of the dorsomedial prefrontal cortex for major depression: safety, tolerability, effectiveness, and outcome predictors for 10 Hz versus intermittent theta-burst stimulation. Brain Stimul 2015;8:208–15.

Benali A, Trippe J, Weiler E, Mix A, Petrasch-Parwez E, Girzalsky W, et al. Theta-burst transcranial magnetic stimulation alters cortical inhibition. J Neurosci 2011;31:1193–203.

Bikmullina R, Kicic D, Carlson S, Nikulin VV. Electrophysiological correlates of short-latency afferent inhibition: a combined EEG and TMS study. Exp Brain Res 2009;194:517–26.

Bortoletto M, Veniero D, Thut G, Miniussi C. The contribution of TMS-EEG coregistration in the exploration of the human cortical connectome. Neurosci Biobehav Rev 2015;49:114–24.

Brunelin J, Szekely D, Costes N, Mondino M, Bougerol T, Saoud M, et al. Theta burst stimulation in the negative symptoms of schizophrenia and striatal dopamine release. An iTBS-[11C]raclopride PET case study. Schizophr Res 2011;131:264–5.

Cardenas-Morales L, Nowak DA, Kammer T, Wolf RC, Schonfeldt-Lecuona C. Mechanisms and applications of theta-burst rTMS on the human motor cortex. Brain Topogr 2010;22:294–306.

Casula EP, Pellicciari MC, Picazio S, Caltagirone C, Koch G. Spike-timing-dependent plasticity in the human dorso-lateral prefrontal cortex. Neuroimage 2016a;143:204–13.

Casula EP, Pellicciari MC, Ponzo V, Stampanoni Bassi M, Veniero D, Caltagirone C, et al. Cerebellar theta burst stimulation modulates the neural activity of interconnected parietal and motor areas. Sci Rep 2016b;6:36191.

Casula EP, Tarantino V, Basso D, Arcara G, Marino G, Toffolo GM, et al. Low-frequency rTMS inhibitory effects in the primary motor cortex: insights from TMS-evoked potentials. Neuroimage 2014;98:225–32.

Cavanagh JF, Frank MJ. Frontal theta as a mechanism for cognitive control. Trends Cogn Sci 2014;18:414–21.

Cheng CM, Juan CH, Chen MH, Chang CF, Lu HJ, Su TP, et al. Different forms of prefrontal theta burst stimulation for executive function of medication-resistant depression: evidence from a randomized sham-controlled study. Prog Neuropsychopharmacol Biol Psychiatry 2016;66:35–40.

Chistyakov AV, Kreinin B, Marmor S, Kaplan B, Khatib A, Darawsheh N, et al. Preliminary assessment of the therapeutic efficacy of continuous theta-burst magnetic stimulation (cTBS) in major depression: a double-blind sham-controlled study. J Affect Disord 2015;170:225–9.

Chung SW, Hill AT, Rogasch NC, Hoy KE, Fitzgerald PB. Use of theta-burst stimulation in changing excitability of motor cortex: a systematic review and meta-analysis. Neurosci Biobehav Rev 2016;63:43–64.

Chung SW, Hoy KE, Fitzgerald PB. Theta-burst stimulation: a new form of TMS treatment for depression? Depress Anxiety 2015a;32:182–92.

Chung SW, Rogasch NC, Hoy KE, Fitzgerald PB. Measuring brain stimulation induced changes in cortical properties using TMS-EEG. Brain Stimul 2015b;8:1010–20.

Colgin LL. Theta-gamma coupling in the entorhinal-hippocampal system. Curr Opin Neurobiol 2015;31:45–50.

Conforto AB, Z'Graggen WJ, Kohl AS, Rosler KM, Kaelin-Lang A. Impact of coil position and electrophysiological monitoring on determination of motor thresholds to transcranial magnetic stimulation. Clin Neurophysiol 2004;115:812–9.

Daskalakis ZJ, Farzan F, Barr MS, Maller JJ, Chen R, Fitzgerald PB. Long-interval cortical inhibition from the dorsolateral prefrontal cortex: a TMS-EEG study. Neuropsychopharmacology 2008;33:2860–9.

Debener S, Strobel A, Sorger B, Peters J, Kranczioch C, Engel AK, et al. Improved quality of auditory event-related potentials recorded simultaneously with 3-T fMRI: removal of the ballistocardiogram artefact. Neuroimage 2007;34:587–97.

Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods 2004;134:9–21.

Demirtas-Tatlidede A, Freitas C, Cromer JR, Safar L, Ongur D, Stone WS, et al. Safety and proof of principle study of cerebellar vermal theta burst stimulation in refractory schizophrenia. Schizophr Res 2010;124:91–100.

Esslinger C, Schuler N, Sauer C, Gass D, Mier D, Braun U, et al. Induction and quantification of prefrontal cortical network plasticity using 5 Hz rTMS and fMRI. Hum Brain Mapp 2014;35:140–51.

Fell J, Axmacher N. The role of phase synchronization in memory processes. Nat Rev Neurosci 2011;12:105–18.

Fitzgerald PB, Maller JJ, Hoy KE, Thomson R, Daskalakis ZJ. Exploring the optimal site for the localization of dorsolateral prefrontal cortex in brain stimulation experiments. Brain Stimul 2009;2:234–7.

Fregni F, Boggio PS, Valle AC, Otachi P, Thut G, Rigonatti SP, et al. Homeostatic effects of plasma valproate levels on corticospinal excitability changes induced by 1Hz rTMS in patients with juvenile myoclonic epilepsy. Clin Neurophysiol 2006;117:1217–27.

Garcia Dominguez L, Radhu N, Farzan F, Daskalakis ZJ. Characterizing long interval cortical inhibition over the time-frequency domain. PLoS ONE 2014;9:e92354.

Goldsworthy MR, Pitcher JB, Ridding MC. A comparison of two different continuous theta burst stimulation paradigms applied to the human primary motor cortex. Clin Neurophysiol 2012;123:2256–63.

Goldsworthy MR, Pitcher JB, Ridding MC. Neuroplastic modulation of inhibitory motor cortical networks by spaced theta burst stimulation protocols. Brain Stimul 2013;6:340–5.

Goldsworthy MR, Vallence AM, Hodyl NA, Semmler JG, Pitcher JB, Ridding MC. Probing changes in corticospinal excitability following theta burst stimulation of the human primary motor cortex. Clin Neurophysiol 2016;127:740–7.

Gosseries O, Sarasso S, Casarotto S, Boly M, Schnakers C, Napolitani M, et al. On the cerebral origin of EEG responses to TMS: insights from severe cortical lesions. Brain Stimul 2015;8:142–9.

Grossheinrich N, Rau A, Pogarell O, Hennig-Fast K, Reinl M, Karch S, et al. Theta burst stimulation of the prefrontal cortex: safety and impact on cognition, mood, and resting electroencephalogram. Biol Psychiat 2009;65:778–84.

Guse B, Falkai P, Wobrock T. Cognitive effects of high-frequency repetitive transcranial magnetic stimulation: a systematic review. J Neural Transm (Vienna) 2010;117:105–22.

Hamada M, Murase N, Hasan A, Balaratnam M, Rothwell JC. The role of interneuron networks in driving human motor cortical plasticity. Cereb Cortex 2013;23:1593–605.

Harrington A, Hammond-Tooke GD. Theta burst stimulation of the cerebellum modifies the TMS-evoked N100 potential, a marker of GABA inhibition. PLoS ONE 2015;10:e0141284.

Hasan A, Brinkmann C, Strube W, Palm U, Malchow B, Rothwell JC, et al. Investigations of motor-cortex cortical plasticity following facilitatory and inhibitory transcranial theta-burst stimulation in schizophrenia: a proof-of-concept study. J Psychiatr Res 2015;61:196–204.

Hill AT, Rogasch NC, Fitzgerald PB, Hoy KE. Effects of prefrontal bipolar and high-definition transcranial direct current stimulation on cortical reactivity and working memory in healthy adults. Neuroimage 2017;152:142–57.
Hinder MR, Goss EL, Fujiyama H, Canty AJ, Garry MI, Rodger J, et al. Inter- and Intra-individual variability following intermittent theta burst stimulation: implications for rehabilitation and recovery. Brain Stimul 2014;7:365–71.
Hoy KE, Bailey N, Michael M, Fitzgibbon B, Rogasch NC, Saeki T, et al. Enhancement of working memory and task-related oscillatory activity following intermittent theta burst stimulation in healthy controls. Cereb Cortex 2015. http://dx.doi.org/10.1093/cercor/bhv193.
Hu L, Mouraux A, Hu Y, Iannetti GD. A novel approach for enhancing the signal-to-noise ratio and detecting automatically event-related potentials (ERPs) in single trials. Neuroimage 2010;50:99–111.
Huang G, Mouraux A. MEP latencies predict the neuromodulatory effect of cTBS delivered to the ipsilateral and contralateral sensorimotor cortex. PLoS ONE 2015;10:e0133893.
Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron 2005;45:201–6.
Huber R, Maatta S, Esser SK, Sarasso S, Ferrarelli F, Watson A, et al. Measures of cortical plasticity after transcranial paired associative stimulation predict changes in electroencephalogram slow-wave activity during subsequent sleep. J Neurosci 2008;28:7911–8.
Itthipuripat S, Wessel JR, Aron AR. Frontal theta is a signature of successful working memory manipulation. Exp Brain Res 2013;224:255–62.
Jacobs J, Hwang G, Curran T, Kahana MJ. EEG oscillations and recognition memory: theta correlates of memory retrieval and decision making. Neuroimage 2006;32:978–87.
Jin Y, Kemp AS, Huang Y, Thai TM, Liu Z, Xu W, et al. Alpha EEG guided TMS in schizophrenia. Brain Stimul 2012;5:560–8.
Jin Y, Potkin SG, Kemp AS, Huerta ST, Alva G, Thai TM, et al. Therapeutic effects of individualized alpha frequency transcranial magnetic stimulation (alphaTMS) on the negative symptoms of schizophrenia. Schizophr Bull 2006;32:556–61.
Korhonen RJ, Hernandez-Pavon JC, Metsomaa J, Maki H, Ilmoniemi RJ, Sarvas J. Removal of large muscle artifacts from transcranial magnetic stimulation-evoked EEG by independent component analysis. Med Biol Eng Comput 2011;49:397–407.
Lang N, Siebner HR, Ernst D, Nitsche MA, Paulus W, Lemon RN, et al. Preconditioning with transcranial direct current stimulation sensitizes the motor cortex to rapid-rate transcranial magnetic stimulation and controls the direction of after-effects. Biol Psychiat 2004;56:634–9.
Larson J, Wong D, Lynch G. Patterned stimulation at the theta frequency is optimal for the induction of hippocampal long-term potentiation. Brain Res 1986;368:347–50.
Lega B, Burke J, Jacobs J, Kahana MJ. Slow-theta-to-gamma phase-amplitude coupling in human hippocampus supports the formation of new episodic memories. Cereb Cortex 2016;26:268–78.
Leonard CJ, Kaiser ST, Robinson BM, Kappenman ES, Hahn B, Gold JM, et al. Toward the neural mechanisms of reduced working memory capacity in schizophrenia. Cereb Cortex 2013;23:1582–92.
Leuchter AF, Cook IA, Jin Y, Phillips B. The relationship between brain oscillatory activity and therapeutic effectiveness of transcranial magnetic stimulation in the treatment of major depressive disorder. Front Hum Neurosci 2013;7:37.
Li CT, Chen MH, Juan CH, Huang HH, Chen LF, Hsieh JC, et al. Efficacy of prefrontal theta-burst stimulation in refractory depression: a randomized sham-controlled study. Brain 2014;137:2088–98.
Luck SJ. Ten simple rules for designing ERP experiments. In: Handy TC, editor. Event-related potentials: a methods handbook. Cambridge: MIT Press; 2005. p. 17–32.
Machado S, Arias-Carrion O, Paes F, Vieira RT, Caixeta L, Novaes F, et al. Repetitive transcranial magnetic stimulation for clinical applications in neurological and psychiatric disorders: an overview. Eurasian J Med 2013;45:191–206.
Noh NA, Fuggetta G, Manganotti P, Fiaschi A. Long lasting modulation of cortical oscillations after continuous theta burst transcranial magnetic stimulation. PLoS ONE 2012;7:e35080.
Nyffeler T, Wurtz P, Luscher HR, Hess CW, Senn W, Pflugshaupt T, et al. Repetitive TMS over the human oculomotor cortex: comparison of 1-Hz and theta burst stimulation. Neurosci Lett 2006;409:57–60.
Nyhus E, Curran T. Functional role of gamma and theta oscillations in episodic memory. Neurosci Biobehav Rev 2010;34:1023–35.
Oostenveld R, Fries P, Maris E, Schoffelen JM. FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Comput Intell Neurosci 2011;2011:156869.
Pellicciari MC, Brignani D, Miniussi C. Excitability modulation of the motor system induced by transcranial direct current stimulation: a multimodal approach. Neuroimage 2013;83:569–80.
Plewnia C, Pasqualetti P, Grosse S, Schlipf S, Wasserka B, Zwissler B, et al. Treatment of major depression with bilateral theta burst stimulation: a randomized controlled pilot trial. J Affect Disord 2014;156:219–23.
Premoli I, Castellanos N, Rivolta D, Belardinelli P, Bajo R, Zipser C, et al. TMS-EEG signatures of GABAergic neurotransmission in the human cortex. J Neurosci 2014;34:5603–12.
Rajji TK, Sun Y, Zomorrodi-Moghaddam R, Farzan F, Blumberger DM, Mulsant BH, et al. PAS-induced potentiation of cortical-evoked activity in the dorsolateral prefrontal cortex. Neuropsychopharmacology 2013;38:2545–52.
Rogasch NC, Daskalakis ZJ, Fitzgerald PB. Mechanisms underlying long-interval cortical inhibition in the human motor cortex: a TMS-EEG study. J Neurophysiol 2013a;109:89–98.
Rogasch NC, Daskalakis ZJ, Fitzgerald PB. Cortical inhibition of distinct mechanisms in the dorsolateral prefrontal cortex is related to working memory performance: a TMS-EEG study. Cortex 2015;64:68–77.
Rogasch NC, Thomson RH, Daskalakis ZJ, Fitzgerald PB. Short-latency artifacts associated with concurrent TMS-EEG. Brain Stimul 2013b;6:868–76.
Rogasch NC, Thomson RH, Farzan F, Fitzgibbon BM, Bailey NW, Hernandez-Pavon JC, et al. Removing artefacts from TMS-EEG recordings using independent component analysis: importance for assessing prefrontal and motor cortex network properties. Neuroimage 2014;101:425–39.
Schicktanz N, Fastenrath M, Milnik A, Spalek K, Auschra B, Nyffeler T, et al. Continuous theta burst stimulation over the left dorsolateral prefrontal cortex decreases medium load working memory performance in healthy humans. PLoS ONE 2015;10:e0120640.
Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. 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. J Clin Psychiatry 1998;59(Suppl. 20):22–33. quiz 4–57.
Silvanto J, Pascual-Leone A. State-dependency of transcranial magnetic stimulation. Brain Topogr 2008;21:1–10.
Spronk D, Arns M, Bootsma A, van Ruth R, Fitzgerald PB. Long-term effects of left frontal rTMS on EEG and ERPs in patients with depression. Clin EEG Neurosci 2008;39:118–24.
ter Braack EM, de Vos CC, van Putten MJ. Masking the auditory evoked potential in TMS-EEG: a comparison of various methods. Brain Topogr 2015;28:520–8.
Thigpen NN, Kappenman ES, Keil A. Assessing the internal consistency of the event-related potential: an example analysis. Psychophysiology 2017;54:123–38.
Thomson RH, Cleve TJ, Bailey NW, Rogasch NC, Maller JJ, Daskalakis ZJ, et al. Blood oxygenation changes modulated by coil orientation during prefrontal transcranial magnetic stimulation. Brain Stimul 2013;6:576–81.
van Ede F, Maris E. Physiological plausibility can increase reproducibility in cognitive neuroscience. Trends Cogn Sci 2016;20:567–9.
Veniero D, Ponzo V, Koch G. Paired associative stimulation enforces the communication between interconnected areas. J Neurosci 2013;33:13773–83.
Vernet M, Bashir S, Yoo WK, Perez JM, Najib U, Pascual-Leone A. Insights on the neural basis of motor plasticity induced by theta burst stimulation from TMS-EEG. Eur J Neurosci 2013;37:598–606.
Wilcox RR. Introduction to robust estimation and hypothesis testing. San Diego, CA: Academic Press; 1997.
Wischnewski M, Schutter DJ. Efficacy and time course of theta burst stimulation in healthy humans. Brain Stimul 2015;8:685–92.
Yang W, Liu TT, Song XB, Zhang Y, Li ZH, Cui ZH, et al. Comparison of different stimulation parameters of repetitive transcranial magnetic stimulation for unilateral spatial neglect in stroke patients. J Neurol Sci 2015;359:219–25.
Zheng C, Zhang T. Synaptic plasticity-related neural oscillations on hippocampus-prefrontal cortex pathway in depression. Neuroscience 2015;292:170–80.

CHAPTER NINE

Effects of intensity of iTBS in the prefrontal cortex

Chung SW, Rogasch NC, Hoy KE, Sullivan CM, Cash RFH, Fitzgerald PB. 2017. Impact of different intensities of intermittent theta burst stimulation on the cortical properties during TMS-EEG and working memory performance.

Preamble to empirical paper

Having established the utility of TMS-EEG in probing TBS-induced changes and the indices of measurement in the prefrontal cortex such as changes in TMS-evoked N100 and TMS-evoked theta power, first optimisation of the stimulation protocol proceeded. Conventional method of applying TBS in the motor cortex uses intensity of 70 – 80% motor threshold (Goldsworthy et al., 2012a; Huang et al., 2005), and a vast majority of the studies has adopted this method of application (Chung et al., 2016; Wischnewski and Schutter, 2015). However, recent reports of the stimulation intensity used in prefrontal TBS for therapeutic intervention have varied quite substantially, some using sub-threshold intensities (Li et al., 2014; Plewnia et al., 2014; Prasser et al., 2015) and others using supra-threshold (Bakker et al., 2015; Desmyter et al., 2016; Duprat et al., 2016). While the optimal intensity of stimulation in the prefrontal cortex remains unknown, it is an important factor to consider (Cardenas-Morales et al., 2010) as changing the intensity of the intervention could change the outcomes of stimulation. In the following paper, the effect of three different intensities of iTBS (50, 75 and 100% of individual resting motor threshold) was examined in the left

prefrontal cortex using TMS-EEG. In addition, the impact of these stimulation conditions on working memory performance and neural activity during working memory was explored. Measurement of improvement in working memory as a behavioural marker of stimulation. It was anticipated that the efficacy of iTBS would increase with increasing intensity which would be reflected in the N100 amplitude. In addition, TMS-evoked oscillations were examined in more detail by examining both total power and evoked power of activity. Total power of activity was computed via converting each epoch (TEPs / ERPs) into the frequency domain prior to averaging. Evoked activity, however, involved averaging the epochs prior to the conversion into the frequency domain. The rationale for the analysis was to explore whether changes in evoked (phase-locked) or induced (non phase-locked) oscillations were driving the changes in total power. iTBS was chosen as more robust changes were observed using TMS-EEG in the previous study (Chapter 8), and due to its beneficial effect on memory performance (Hoy et al., 2016) and in clinical settings (Duprat et al., 2016; Li et al., 2014).

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RESEARCH ARTICLE

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Impact of different intensities of intermittent theta burst stimulation on the cortical properties during TMS-EEG and working memory performance

Sung Wook Chung[1] | Nigel C. Rogasch[2] | Kate E. Hoy[1] | Caley M. Sullivan[1] | Robin F. H. Cash[1] | Paul B. Fitzgerald[1,3]

[1]Monash Alfred Psychiatry Research Centre, Monash University, Central Clinical School and The Alfred, Melbourne, Australia

[2]Brain and Mental Health Laboratory, School of Psychological Sciences and Monash Biomedical Imaging, Monash Institute of Cognitive and Clinical Neuroscience, Monash University, Melbourne, Australia

[3]Epworth Clinic, Epworth Healthcare, Camberwell, VIC, Australia

Correspondence
Sung Wook Chung, Monash Alfred Psychiatry Research Centre, Level 4, 607 St Kilda Road, Melbourne, Victoria, Australia, 3004.
Email: sung.chung@monash.edu

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Abstract

Intermittent theta burst stimulation (iTBS) is a noninvasive brain stimulation technique capable of increasing cortical excitability beyond the stimulation period. Due to the rapid induction of modulatory effects, prefrontal application of iTBS is gaining popularity as a therapeutic tool for psychiatric disorders such as depression. In an attempt to increase efficacy, higher than conventional intensities are currently being applied. The assumption that this increases neuromodulatory may be mechanistically false for iTBS. This study examined the influence of intensity on the neurophysiological and behavioural effects of iTBS in the prefrontal cortex. Sixteen healthy participants received iTBS over prefrontal cortex at either 50, 75 or 100% resting motor threshold in separate sessions. Single-pulse TMS and concurrent electroencephalography (EEG) was used to assess changes in cortical reactivity measured as TMS-evoked potentials and oscillations. The n-back task was used to assess changes in working memory performance. The data can be summarised as an inverse U-shape relationship between intensity and iTBS plastic effects, where 75% iTBS yielded the largest neurophysiological changes. Improvement in reaction time in the 3-back task was supported by the change in alpha power, however, comparison between conditions revealed no significant differences. The assumption that higher intensity results in greater neuromodulatory effects may be false, at least in healthy individuals, and should be carefully considered for clinical populations. Neurophysiological changes associated with working memory following iTBS suggest functional relevance. However, the effects of different intensities on behavioural performance remain elusive in the present healthy sample.

KEYWORDS
intensity, prefrontal cortex, theta burst stimulation (TBS), TMS-EEG, working memory

1 | INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive brain stimulation technique capable of modulating cortical activity beyond the stimulation period. Clinical applications of rTMS have been studied in various neurological and psychiatric disorders (Machado et al., 2013), especially in the treatment of depression (George et al., 2010; George, Taylor, & Short, 2013; O'Reardon et al., 2007). Recently, a modified form of rTMS known as theta-burst stimulation (TBS), has been investigated as a potential treatment of depression, with promising therapeutic effects (Chung, Hoy, & Fitzgerald, 2015a; Duprat et al., 2016; Li et al., 2014). TBS was modified from an animal stimulation paradigm (Larson, Wong, & Lynch, 1986) and elicits long-term potentiation or depression (LTP/LTD)—like changes depending on the stimulation pattern in human (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). In the motor cortex, intermittent TBS (iTBS, 2sec on, 8 sec off, 600 pulses, 3 minutes duration) elicits LTP-like increases in cortical excitability whereas continuous TBS (cTBS, 40 sec on, 600 pulses) evokes LTD-like decreases cortical excitability (Huang et al., 2005; Suppa et al., 2008). Due to the rapid induction of modulatory effects

compared to conventional rTMS, TBS is an attractive option for neuromodulatory treatments in clinical disorders (Chung et al., 2015a; Machado et al., 2013). For psychiatric conditions, this typically involves stimulation delivered to prefrontal cortical regions such as dorsolateral prefrontal cortex (DLPFC) (Desmyter et al., 2016; Li et al., 2014; Plewnia et al., 2014). As adoption of TBS increases in the clinical literature, the lack of consensus with respect to optimal intensity is becoming increasingly evident. Conventionally, TBS in the motor cortex has been applied at 80% of active motor threshold (aMT) (Huang et al., 2005), equivalent to approximately 70% of resting motor threshold (rMT) (Cardenas-Morales et al., 2014; Chen et al., 1998; Gentner, Wankerl, Reinsberger, Zeller, & Classen, 2008). Recent reports of the stimulation intensity used in prefrontal TBS for therapeutic intervention have varied quite substantially in the range of 80–120% of rMT (Bakker et al., 2015; Desmyter et al., 2016; Duprat et al., 2016; Li et al., 2014; Plewnia et al., 2014; Prasser et al., 2015). The underlying assumption is that the efficacy of iTBS will be greater with increasing intensity of stimulation. This is partially supported by linear responses to increases in the intensity of conventional rTMS in healthy individuals (1 Hz [Nahas et al., 2001]) and in clinical populations (10 Hz [Padberg et al., 2002]). Studies using different modulatory paradigms have also shown a shift from LTD- to LTP-like effects at higher intensity (Batsikadze, Moliadze, Paulus, Kuo, & Nitsche, 2013; Cash, Jegatheeswaran, Ni, & Chen, 2017a; Doeltgen & Ridding, 2011), corroborating the idea of increased propensity for LTP-like changes at higher intensity. However, systematic investigation of intensity-dependent effects of iTBS in the prefrontal cortex has not been established.

Another key question concerns the use of TBS for cognitive disorders. TBS was originally developed to mimic the natural firing patterns of neurons in the hippocampus, where high-frequency gamma oscillations (30–80 Hz) were modulated by the phase of lower frequency theta oscillations (4–7 Hz) (Lisman & Jensen, 2013). Applying electrical stimulation to the hippocampus with gamma frequency bursts nested in theta frequency rhythms resulted in robust long-term potentiation (LTP) (Larson et al., 1986). A similar theta-gamma coupling relationship in endogenous brain activity has been observed in human studies using electroencephalography (EEG) during cognitive functions (Lisman, 2010). It is therefore of particular interest whether iTBS in human can facilitate cognitive and memory processes, and to what extent the plastic changes elicited by TBS translate to changes in neurophysiological metrics of cognition and behavioural performance outcomes.

Recent advances in technology have enabled the measurement of plastic neuronal changes following neuromodulatory paradigms using concurrent recording of electroencephalographic responses to TMS (TMS-EEG) (Chung, Rogasch, Hoy, & Fitzgerald, 2015b; Farzan et al., 2016; Hill, Rogasch, Fitzgerald, & Hoy, 2016). Each TMS pulse elicits a TMS-evoked EEG response, and the change in the amplitude of TMS-evoked potentials (TEPs) and the power of TMS-evoked oscillations following TBS provide metric of plasticity in the prefrontal cortex (Chung et al., 2017). TEPs are composed of several components which are thought to represent excitatory and inhibitory postsynaptic potentials. A negative trough at a latency of approximately 100 ms (N100) has been associated with inhibitory mechanisms in motor (Bonnard, Spieser, Meziane, de Graaf, & Pailhous, 2009; Premoli et al., 2014; Rogasch, Daskalakis, & Fitzgerald, 2013a) and prefrontal cortex (Chung et al., 2017; Rogasch, Daskalakis, & Fitzgerald, 2015), and is considered to be the most robust TEP component with the best signal to noise ratio (SNR) (Noda et al., 2016). Modulation of this component has been observed following TBS over the prefrontal cortex (Chung et al., 2017) and cerebellum (Casula et al., 2016b; Harrington & Hammond-Tooke, 2015). Recent studies also suggest that a peak at a latency of 60 ms (P60) may be a correlate of neuronal excitability in motor cortex (Cash et al., 2017b) and DLPFC (Hill, Rogasch, Fitzgerald, & Hoy, 2017).

In the present study, we examined the relationship between iTBS intensity (50, 75 and 100% of individual rMT), LTP-like neural plasticity and the relationship to neurophysiological and behavioural metrics of learning and memory using N-back task (Haatveit et al., 2010). We hypothesized that iTBS would be accompanied by plastic changes in N100 and P60 amplitude. Secondly, we anticipated that the efficacy of iTBS would increase with increasing intensity. Thirdly, we hypothesized that these changes will be mirrored by increasing working memory (WM) performance measured via N-back task and neurophysiological correlates. The modulation of theta and gamma oscillatory activity was of particular interest since these frequency bands are targeted by TBS and involved in WM.

2 | MATERIAL AND METHODS

2.1 | Participants

Sixteen healthy volunteers (7 female, 27.8 ± 8.6 years of age, 16.25 ± 2.11 years of formal education) participated in the study. All subjects were right-handed according to the Edinburgh Handedness Inventory, and the mini international neuropsychiatric interview (MINI) was performed (Sheehan et al., 1998) to confirm no history of mental illness. No participants were smokers. All participants provided informed consent prior to the experiment and the experimental procedures were approved by the Alfred Hospital and Monash University Human Research Ethics Committees.

2.2 | Procedure

Each participant attended 3 sessions receiving iTBS at either 50%, 75% or 100% of their resting motor threshold (rMT). Each session was at least 72 hours apart and the session order was pseudorandomized across participants. The experimental procedures comprised of recording EEG during 50 single TMS pulses before (BL—baseline), 5 min post (T5) and 30 min post (T30) iTBS (Figure 1a). The N-back WM task (2-back and 3-back conditions) was also performed pre (BL) and 15 min post (T15) iTBS with concurrent EEG recording.

2.3 | EEG recording

EEG was recorded with TMS-compatible Ag/AgCl electrodes and a DC-coupled amplifier (SynAmps2, EDIT Compumedics Neuroscan, Texas, USA). 42 electrodes were used on a 64-channel EEG cap (AF3, AF4, F7, F5, F3, F1, Fz, F2, F4, F6, F8, FC5, FC3, FC1, FCz, FC2, FC4,

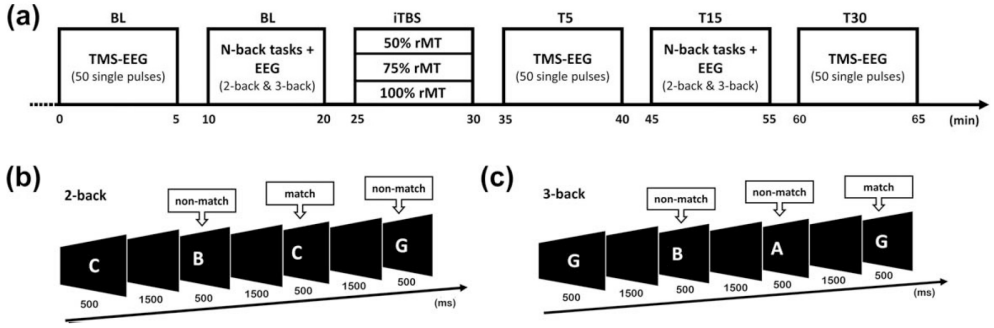

FIGURE 1 Schematic diagram of the experimental design. (a) Concurrent recording of electroencephalogram during transcranial magnetic stimulation (TMS-EEG) and N-back task were performed at baseline (BL). Intermittent theta burst stimulation (iTBS) was then administered at one of three intensities. TMS-EEG was rerepeated at T5 and T30 following iTBS, and the N-back at T15 following iTBS. (b-c) Diagrams illustrating trials of match and nonmatch during 2-back and 3-back tasks

FC6, T7, C5, C3, C1, Cz, C2, C4, C6, T8, P7, P5, P3, P1, Pz, P2, P4, P6, P8, PO3, POz, PO4, O1, Oz, O2), and electrooculography recording was obtained with 4 electrodes, one positioned above and one below the left eye and one on lateral to the outer canthus of either eye. Electrodes were online referenced to CPz and grounded to FPz with exception to the lateral eye electrodes which were referenced to each other. For TMS-EEG, data were recorded with a high acquisition rate (10,000 Hz) using a large operating range (± 200 mV) to avoid amplifier saturation. Signals were amplified (1,000×) and low pass filtered (DC-2,000 Hz). For EEG recording during N-back task, AC acquisition setting was used and the signals were filtered (low pass at 200 Hz, high pass at 0.05 Hz) and sampled at 1,000 Hz with an operating window of ± 950 μV. Electrode impedance levels were kept below 5 kΩ throughout the experiment. During TMS-EEG recording, subjects listened to white noise through intra-auricular earphones (Etymotic Research, ER3–14A, USA) to limit the influence of the auditory processing of the TMS click. The sound level was adjusted for each individual subject until single-pulse TMS at 120% rMT was barely audible.

2.4 | Transcranial magnetic stimulation

Participants sat comfortably with their arms resting on a pillow throughout the experiment. The EEG cap was mounted following the 10–20 standard system and the resting motor threshold (rMT) was obtained from left motor cortex, which was identified as the minimum intensity required to evoke at least 3 out of 6 motor evoked potentials (MEPs) > 0.05 mV in amplitude (Conforto, Z'graggen, Kohl, Rosler, & Kaelin-Lang, 2004) via Ag/AgCl electromyography electrodes attached to the first dorsal interosseous (FDI) muscles. TMS was administered to the left prefrontal cortex at F1 electrode using 10/20 method of placement. The F1 electrode sits over the superior frontal gyrus with Brodmann area (BA) of 6, 8, and 9 (Koessler et al., 2009), and therefore, is part of dorsolateral prefrontal cortex. This electrode was chosen to minimize stimulation of scalp muscles which result in large artefacts in EEG recordings lasting up to 40 ms following the TMS pulse (Rogasch, Thomson, Daskalakis, & Fitzgerald, 2013b). By minimising artefacts, the amount of correction needed in postprocessing for the TMS-EEG signals is reduced. A MagVenture B-65 fluid-cooled coil (a figure-of-eight coil; MagVenture A/S, Denmark) was used for both single-pulse stimulation and iTBS (biphasic pulses, antero-posterior to postero-anterior current direction in the underlying cortex). The coil was positioned at 45° angle relative to midline, which has been shown to produce strongest stimulation in the prefrontal cortex (Thomson et al., 2013). A line was drawn on the coil at 45° angle, which would then sit perpendicular to the midline of the EEG cap to ensure same angle positioning. In addition, the edge of the coil was marked on the cap to reliably re-position the coil within 5 mm (Rogasch et al., 2013b).

Participants received 50 single pulses to left prefrontal cortex at an interval of 5 s (10% jitter) at 120% rMT before and after different stimulation intensities of iTBS. These parameters were chosen to be consistent with our previous study (Chung et al., 2017), and the majority of the TMS-EEG studies in the prefrontal cortex used suprathreshold intensities (Cash et al., 2017b; Daskalakis et al., 2008; Farzan et al., 2009, 2010; Hill et al., 2017; Kahkonen, Wilenius, Nikulin, Ollikainen, & Ilmoniemi, 2003; Rogasch et al., 2014) which may also allowed for better signal-to-noise ratio, given that smaller TEPs are obtained in the prefrontal cortex compared to the motor cortex (Kahkonen, Komssi, Wilenius, & Ilmoniemi, 2005). Across different sessions, participants received iTBS at different intensities (50%, 75%, or 100% rMT). 75% rMT was chosen as smaller EEG responses to TMS have been observed in the prefrontal cortex compared to the motor cortex (Kahkonen et al., 2005) and to be within the range of 70–80% motor threshold as previously been described (Gentner et al., 2008; Goldsworthy, Pitcher, & Ridding, 2012; Jones et al., 2016; Nettekoven et al., 2014; Pedapati et al., 2015, 2016; Tsang et al., 2014). In addition, the intensity was set relative to rMT rather than aMT to avoid potential metaplastic influences related to prior muscle activation (Cash, Mastaglia, & Thickbroom, 2013). With the exception of intensity, iTBS parameters adhered to the originally described method (Huang et al., 2005). iTBS consisted of a burst of 3 pulses given at 50 Hz repeated at a frequency of 5 Hz, with 2 s of stimulation on and 8 s off repeated for a total of 600 pulses. The average stimulation intensity was as follows (% of maximum stimulator output; mean ± SD): 50% condition = 28.5 ± 3.0%; 75% condition = 42.5 ± 5.3%; 100% condition = 57.19 ± 5.6%.

2.5 | Working memory task

Participants were assessed on the N-back task with 5 mins of 2-back and 5 mins of 3-back conditions in a pseudorandomised order. Letters were in a random series of A to J, and participants were requested to respond with a button press when the presented letter was the same as the letter appeared either 2 trials (Figure 1b; 2-back) or 3 trials (Figure 1c; 3-back) earlier. Each letter was presented in white on a black screen for 500 ms with a 1,500 ms interstimulus interval. Each N-back task consisted of 130 trials with 25% targets. Due to technical failure, data was not collected from one participant (complete data from 15 participants; 27.3 ± 8.7 years, 7 female). WM performance was assessed via accurate reaction time and *d* prime sensitivity index (*d'*) (z-transformed values of hit- minus false-alarm rates) (Haatveit et al., 2010).

2.6 | EEG data preprocessing

EEG data were analysed offline using EEGLAB (Delorme & Makeig, 2004), FieldTrip (Oostenveld, Fries, Maris, & Schoffelen, 2011), TESA (Rogasch et al., 2017) and custom scripts on Matlab platform (R2015b, The MathWorks, USA). For TMS-EEG, data were epoched around the test TMS pulse (−1,000 to 1,000 ms), baseline corrected to the TMS-free data (−500 to −50 ms), and data around the large signal from TMS pulse (−5 to 10 ms) were removed and linearly interpolated. The epoched TMS-EEG data from all three time points (BL, T5, T30) were concatenated and analysed concurrently to avoid bias in component rejection. Data were downsampled to 1,000 Hz and visually inspected to remove epochs with excessive noise (i.e., muscle artefact), and bad channels (i.e., disconnected). An average of 47.6 (± 2.7) trials was included in the 50% iTBS condition, 47.4 (± 2.8) trials in the 75% iTBS condition and 48.0 (± 2.7) trials in the 100% iTBS condition across each time point. Two rounds of independent component analysis (FastICA algorithm using the 'tanh' contrast function) were applied to the data; the first to remove large amplitude muscle artefacts, and the second to remove other common artefacts following offline filtering. The first round of independent component analysis (ICA) used a semi-automated component classification algorithm (tesa_compselect function) to remove the remainder of the muscle artefact (Korhonen et al., 2011) (classified if component time course 8 times larger than the mean absolute amplitude across the entire time course). All data were bandpass filtered (second-order, zero-phase, Butterworth filter, 1–80 Hz) and bandstop filtered (48–52 Hz; to remove 50 Hz line noise) and epochs were inspected again to remove any anomalous activity in the EEG trace. The second round of FastICA was conducted, and additional artefactual components were removed based on a previous study (Rogasch et al., 2014) and using TESA toolbox as a guide (Rogasch et al., 2017). Components representing the following artefacts were removed; eye blinks and saccades (mean absolute *z* score of the two electrodes larger than 2.5), persistent muscle activity (high frequency power that is 60% of the total power), decay artefacts and other noise-related artefacts (one or more electrode has an absolute *z* score of at least 4).

For EEG during N-back tasks, data were epoched around the correctly encoded and maintained trials (−1,450 to 1,990 ms), and baseline corrected (−350 to −50 ms). Trials containing a button response in the epochs were excluded to avoid confounds introduced by motor preparation. Epoched EEG data for two time points (BL, T15) and two N-back tasks were concatenated and analysed concurrently to avoid bias in rejecting components. Data were visually inspected to remove epochs with excessive noise, and bad channels removed. An average of trials included in 50% iTBS conditions were—76.6 (± 12.9) for 2-back, 74.5 (± 22.2) for 3-back; in 75% iTBS conditions were—74.6 (± 13.3) for 2-back, 78.1 (± 17.8) for 3-back, and in 100% iTBS conditions were —75.8 (± 14.3) for 2-back, 74.4 (± 24.5) for 3-back tasks. It has been demonstrated that late ERP components such as P300 encounters the risk of being distorted following high-pass filter above 1 Hz (Rousselet, 2012). However, drift in data filtered at 0.1 Hz is not suitable for ICA (Debener & De Vos, 2011). Therefore, steps were taken to minimize the distortion of ERPs; (1) All data were bandpass filtered (second-order, zero-phase, Butterworth filter, 0.1–80 Hz) and bandstop filtered (48–52 Hz), and set aside. (2) Original data were bandpass filtered at 1–80 Hz, and FastICA with artefact component removal was conducted as described above (only one round of ICA). (3) The ICA weight matrix from step 2 was then applied to the data in step 1.

For all EEG data, removed channels were interpolated, and data were re-referenced to common average reference. Finally, data were separated into time point blocks (TMS-EEG: BL, T5 and T30; N-back EEG: BL and T15), conditions (50%, 75% and 100% iTBS) and/or tasks (2-back and 3-back).

2.7 | TMS-evoked potentials (TEPs) and event related potentials (ERPs) during N-back tasks

TEPs and ERPs were analysed using a global scalp analysis (cluster-based permutation statistics) to access the effect of iTBS across the cortex. For TEPs, the MagVenture stimulator has shown to introduce unwanted artefacts on electrodes in contact with the coil (Rogasch et al., 2013b). As such, the FCz electrode was chosen for TEP waveform representation. Amplitudes of TEPs were compared across time and conditions within predetermined time window for N45 (30–55 ms), P60 (55–80 ms), N100 (90–140 ms) and P200 (160–240 ms). These peaks are known to occur following prefrontal TMS-EEG (Chung et al., 2017; Hill et al., 2017; Rogasch et al., 2014, 2015). A signal-to-noise ratio (SNR) analysis was performed on the average of three fronto-central electrodes (FC1, FCz, FC2) for each individual to validate the limited number of TMS pulses available for the analyses (∼47 pulses). The SNR was calculated by dividing the peak amplitude by the standard deviation (SD) of the TEPs in the prestimulus period (−500 to −50 ms) (Chung et al., 2017; Hu, Mouraux, Hu, & Iannetti, 2010).

For ERPs during N-back tasks, the same electrode was used for graphical representation, and peaks were statistically compared within time window for N100 (70–110 ms), P150 (120–180 ms), N200 (190–260 ms) and P300 (280–380 ms) during encoding/maintenance period. These peaks were chosen for the implication of these peaks in visual WM tasks (Coull, 1998; Kok, 2001; Vogel & Luck, 2000).

2.8 | TMS-evoked oscillations and event related oscillations during N-back tasks

TMS-evoked oscillatory power and event related oscillations during N-back tasks were measured by converting TEPs and ERPs into the frequency domain using Morlet wavelet decomposition (3.5 oscillation cycles (Casula et al., 2016b; Hill et al., 2016; Hoy et al., 2016; Rogasch et al., 2015) with steps of 1 Hz between 2 Hz and 50 Hz, 10 ms time resolution on each trial for each electrode. The oscillatory power was then averaged to compute the total power of activity, which contained both evoked and induced oscillations. In line with recent discussions on the different approaches to the analysis of oscillatory activity in TMS-EEG (Pellicciari, Veniero, & Miniussi, 2017b), we explored the effects of iTBS on evoked neural oscillations alone. Normalised oscillatory power was then obtained by dividing all power bins by a mean baseline value (−650 to −350 ms). This baseline window was chosen to avoid the temporal smearing of poststimulus activity into the baseline as the lowest frequency of interest (i.e., 5 Hz–200 ms) would require at least 350 ms (3.5 oscillation cycles × 200 ms (5 Hz) = 700 ms; Half of the wavelet length—700/2 = 350 ms). Power values were averaged in frequency bands of interest; theta (5–7 Hz) and gamma (30–45 Hz), and in time (50–250 ms for theta, 50–150 ms for gamma) prior to the computation of cluster-based statistics. Focused analyses were conducted on theta and gamma frequencies as theta-burst stimulation is comprised of these two frequency bands, and also due to the implication of synaptic plasticity by the interaction between theta and gamma frequency bands (Zheng & Zhang, 2015). For the N-back tasks, oscillations were investigated in two blocks; during the letter presentation (50–450 ms) and after the letter presentation (550–950 ms), and averaged across these time windows for both theta and gamma oscillations prior to the cluster-based statistics. Similar to the examination of oscillatory activity during TMS-EEG, evoked oscillations were also investigated.

Additional multi-dimensional cluster-based statistics were performed [time (50–500 ms for TMS-EEG; 50–950 ms for N-back tasks) × frequency (5–45 Hz) × space], as it is recommended to analyse the data in all possible dimensions (van Ede & Maris, 2016). Further subgroup analyses on alpha (8–12 Hz) and beta (13–29 Hz) bands were also conducted to explore any iTBS-induced change in these frequencies.

2.9 | Source estimation

In order to establish the spread of activity following single-pulse TMS on F1 electrode, source estimation was performed. All source localisation was performed using depth-weighted minimum norm estimation (MNE) implemented in Brainstorm software (Tadel, Baillet, Mosher, Pantazis, & Leahy, 2011) which is documented and freely available for download online under the GNU general public licence (http://neuroimage.usc.edu/brainstorm/). A template anatomy (ICBM 152) in Brainstorm software was used as individual MRI scans were not obtained. The forward model used the Symmetric Boundary Element Method provided by OpenMEEG (Gramfort, Papadopoulo, Olivi, & Clerc, 2010), and the inverse model was computed with dipole orientations constrained to be normal to the cortex.

2.10 | Addition of control condition

Twelve age and gender matched participants (5 female, 27.8 ± 7.4 years of age, 16.5 ± 2.35 years of formal education) were included in this study as a control condition for a secondary analysis where no active stimulation was applied. Sham iTBS was applied at 90° tilt with the bottom of the TMS coil facing away from the scalp. An average of 48.9 (± 1.2) trials were included in the TMS-EEG data, 73.1 (± 18.8) trials in the 2-back, and 72.5 (± 20.6) trials in the 3-back EEG data across each time point.

2.11 | Statistics

Statistical analysis was performed in SPSS (Version 22) and Matlab. Data did not meet the requirement for normality (Shapiro-Wilk test) in behaviour measures, and therefore nonparametric statistics were used. The Wilcoxon signed-rank tests were conducted for comparison between different pre- and post-iTBS measures to assess whether iTBS conditions altered WM performance. To assess whether iTBS conditions differentially affected WM, Friedman's Analysis of Variance by Ranks was used with a factor of condition (50%, 75%, 100%) to compare the change-from-baseline scores (post–pre; Δ) between conditions. For the comparison between active ($n = 15$) and sham ($n = 12$) conditions, the Mann-Whitney U test was performed on the Δ scores.

For analysis of electrophysiological data, nonparametric cluster-based statics were used (Oostenveld et al., 2011). Monte Carlo p-values were calculated on 5000 random permutations and a value of $p < .05$ was used as the cluster-statistical significance for all analyses, controlling for multiple comparisons across space and time ($p < .025$; two-tailed test). Within condition comparison was first conducted over time to assess whether iTBS conditions altered peak amplitudes/oscillatory power over time (post-iTBS vs pre-iTBS). To assess whether iTBS conditions differentially modulated these measure, Δ values (post–pre) were calculated and compared between conditions (dependent t-tests between active conditions (within groups), independent t-tests between active and sham conditions (between groups)).

To assess the relationship between the changes in TMS-evoked activities, N-back related electrophysiology and WM performances, Spearman's rank correlations were used.

3 | RESULTS

3.1 | Single-pulse TMS

An overview of TEP waveforms following single-pulse TMS over left prefrontal cortex (F1 electrode) and the source estimation at the peaks of interest (N45, P60, N100 and P200) are illustrated in Figure 2. The scalp topography and the source estimation of these peaks conform to other TMS-EEG studies in the prefrontal cortex (Chung et al., 2017; Hill et al., 2017; Rogasch et al., 2014).

The analysis of SNR can be found in the Supporting Information Table S1. Qualitatively N45 peaks showed moderate values (~2.5 SDs), but other peaks, especially latter peaks (N100 and P200) showed high/acceptable SNR.

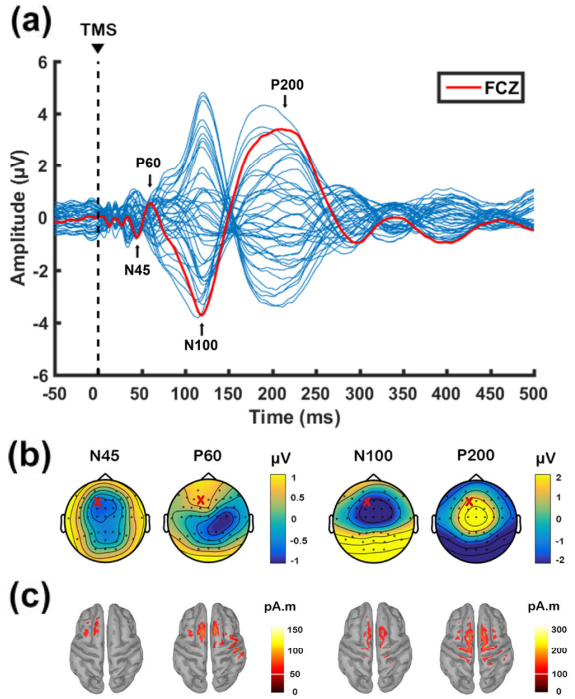

FIGURE 2 Transcranial magnetic stimulation (TMS)-evoked potentials following single-pulse stimulation over left prefrontal cortex (F1 electrode) before theta-burst stimulation (data combined across conditions at baseline). (a) Butterfly plot of all electrodes with peaks of interest (N45, P60, N100, P200) shown in text. The red line indicates the waveform obtained from FCz electrode for graphical representation. (b) Voltage distribution and (c) Minimum Norm Estimates (MNEs) of the source level activity at the cortex for each peak of interest. 'X' on topoplots represents stimulation site [Color figure can be viewed at wileyonlinelibrary.com]

3.2 | The effect of different iTBS intensities on TMS-evoked activity

We first assessed the after-effects of iTBS by comparing the amplitudes of TEPs over time, and across conditions. Using the cluster-based permutation tests between pre-iTBS (BL) and 5-min post iTBS (T5), we found that both 50% (115–140 ms, $p = .011$, right frontal; Figure 3a) and 75% iTBS (110–140 ms, $p = .010$, bilateral frontal; Figure 3b) resulted in an increased N100 amplitude. This change, however, was absent following 100% iTBS ($p > .025$; Figure 3c), and no other peaks showed any significant changes (all $p > .025$). We compared the TEPs between BL and 30-min post iTBS (T30), but no significant persistent effect remained (all $p > .025$). In order to evaluate the differences between conditions, iTBS-induced changes in TEP amplitude were calculated (post – pre) and compared. As our experimental design was not sham-controlled, this method of comparison would minimize the confounding factor (e.g., change over time unrelated to stimulation). We found that the change in N100 amplitude (Δ N100) was the largest with 75% iTBS, but less following 100% iTBS (75% > 100% iTBS: T5, 112–140 ms, $p = .008$), which was observed in fronto-central sensors (Figure 3d). Source estimation of N100 in these stimulation conditions supported the findings of the scalp-level analyses, where increased electrical activity was found in fronto-central region following 75% iTBS, but minimal change was seen following 100% iTBS (Figure 3d). The differences were not apparent when these conditions were compared with 50% iTBS (all $p > .025$), placing the strength of the after-effect of 50% iTBS in the middle of 75% and 100% iTBS.

Given the implication of P60 and N100 peaks in excitatory-inhibitory balance, we explored the relationship between these peaks modulated by iTBS. Correlation analysis was conducted on the data combined across different conditions ($n = 48$) using the average of 3 fronto-central electrodes (FC1, FCz, FC2) as these electrodes were close to the stimulation, and often showed significant changes following iTBS. Spearman's rank correlation revealed a significant correlation between Δ P60 and Δ N100 at T5 ($r = -0.385$, $p = .007$) and a trend toward significance at T30 ($r = -0.257$, $p = .077$) (Figure 4).

iTBS-induced changes in TMS-evoked oscillations (averaged across all electrodes) are illustrated in Figure 5. We assessed whether different iTBS conditions altered TMS-evoked theta and gamma power (total activity: evoked + induced) in a similar fashion. The cluster-based permutation test revealed a significant increase in TMS-evoked theta power at T5 compared to BL in close proximity to the stimulation site following 75% iTBS ($p = .024$), but not with 50% or 100% iTBS ($p > .025$). Between conditions, the change in theta power (Δ theta) was larger following 75% iTBS compared to 100% iTBS (75% > 100% iTBS: T5, $p = .020$; Figure 5d, top row). However, no prolonged theta change was observed at T30 (all $p > .025$).

Initially, TMS-evoked gamma power showed slightly different changes, with significantly decreased gamma power following 100% iTBS at T5 ($p = .023$), which was most pronounced over the frontal sensors. On the other hand, 75% iTBS exhibited nonsignificant increase in the frontal and parietal regions. Even though no significant differences between BL and T30 were observed in gamma frequency band in any stimulation conditions (all $p > .025$), between condition comparisons revealed the change in gamma power (Δ gamma) was significantly different between 75% and 100% iTBS at both T5 and T30, which resulted from polarity-specific changes following the two stimulation conditions. At T5, the difference was most pronounced over bilateral frontal sensors ($p = .006$) and parieto-occipital sensors ($p = .015$), and at T30, the differences were observed at left frontal ($p = .019$) and left parietal region ($p = .006$) (Figure 5e, top row). Again, no significant differences were found between 50% and 75% iTBS, or 50% and 100% iTBS for changes in theta or gamma power (all $p > .025$).

Examination of evoked oscillations revealed that only 75% iTBS significantly increased both theta ($p = .019$, fronto-central) and gamma power ($p = .016$, parieto-occipital) at T5, but not at T30. Neither 50% nor 100% iTBS showed any significant change in these frequency bands (all $p > .025$). For between condition comparisons, Δ theta showed significant difference between 75% and 100% iTBS at T5 (75% > 100% iTBS: $p = .009$, fronto-central) (Figure 5d, bottom row), but not in Δ gamma (Figure 5e, bottom row). No significant differences in Δ theta or Δ gamma were found between 50% and 75% iTBS, or 50% and 100% iTBS at any time point (all $p > .025$).

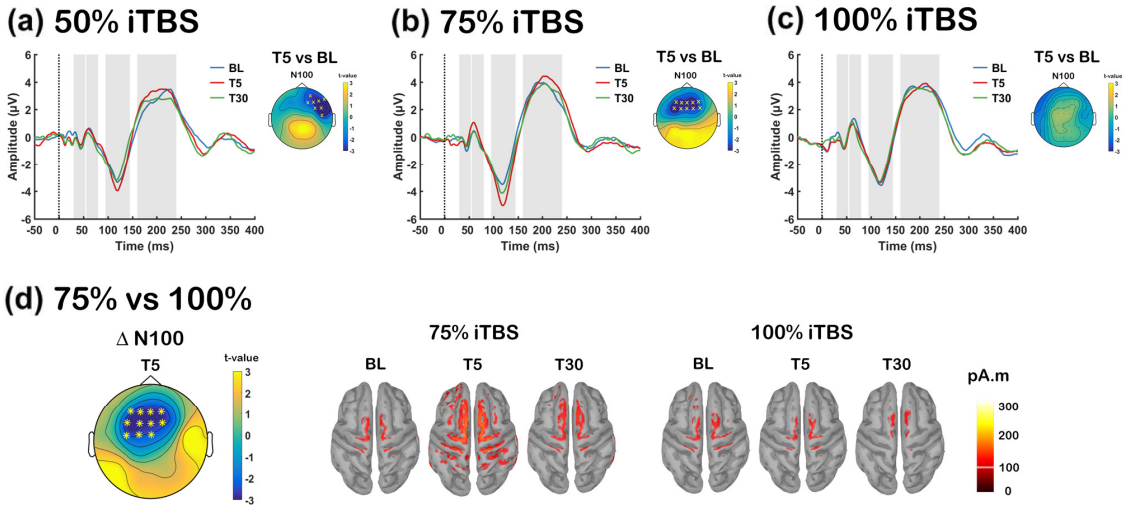

FIGURE 3 Assessment of transcranial magnetic stimulation (TMS)-evoked potentials (TEPs) before and after each stimulation condition [a: Intermittent theta-burst stimulation (iTBS) at 50% rMT (50% iTBS); b: iTBS at 75% rMT (75% iTBS); c: iTBS at 100% rMT (100% iTBS)]. Grand average TEP waveforms before (BL: blue), 5-min post (T5: red) and 30-min post (T30: green) iTBS at FCz electrode for each stimulation conditions, with significant differences across the scalp illustrated in topoplots. (d) Global scalp differences of iTBS-induced change in N100 amplitude (TEP Δ N100) between 75% and 100% iTBS at T5 and Minimum Norm Estimates (MNEs) of the source level activity at the cortex for the N100 peak. Asterisks and 'X' s on topoplots indicate significant clusters between comparisons (cluster-based statistics, $^{*}p < .01$, $^{X}p < .025$) [Color figure can be viewed at wileyonlinelibrary.com]

Exploratory analyses including all dimensions of the data (time × frequency × space) were conducted to investigate iTBS-induced changes in all oscillatory bands and time windows. However, we found no significant differences within or between stimulation conditions (all $p > .025$). Subgroup analysis on alpha (8–12 Hz) and beta (13–29 Hz) frequency bands [time × alpha/beta (frequency range averaged prior to cluster-statistics) × space] also resulted in no significant changes (all $p > .025$).

A recent study using prefrontal-parietal paired associative stimulation (PAS) protocol demonstrated increased cortical responses to TMS-induced plastic effects in subjects with higher gamma power (Casula, Pellicciari, Picazio, Caltagirone, & Koch, 2016a), and we explored whether observed changes in theta and gamma power had any relationship with each peak of interest. Spearman's rank correlation revealed significant correlations between Δ gamma and Δ P60 (T5: $r = 0.353$, $p = .014$) and Δ N100 (T5: $r = -0.347$, $p = .016$; T30: $r = -0.326$, $p = .024$), and between Δ theta and Δ P200 (T5: $r = 0.597$, $p = .001$) (Supporting Information Figure S1), but not with Δ N45 (all $p > .05$). These findings indicate increased amplitude of multiple peaks are associated with stronger oscillatory activity in either theta or gamma range. This is in agreement with previous findings for PAS, but also demonstrates the specificity to theta and gamma for iTBS.

3.3 | The effect of different iTBS intensities on working memory neurophysiology

Before we examined the effect of iTBS on ERPs during WM task, the effect of memory load on the ERPs was first established in our dataset

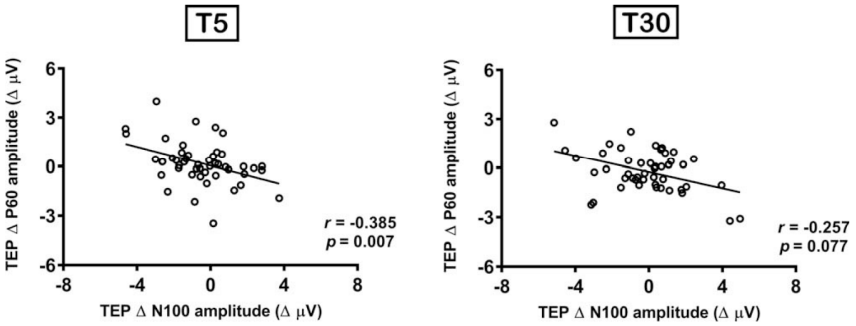

FIGURE 4 Correlation between intermittent theta burst stimulation (iTBS)-induced changes in transcranial magnetic stimulation (TMS)-evoked potential (TEP) N100 and P60 amplitude

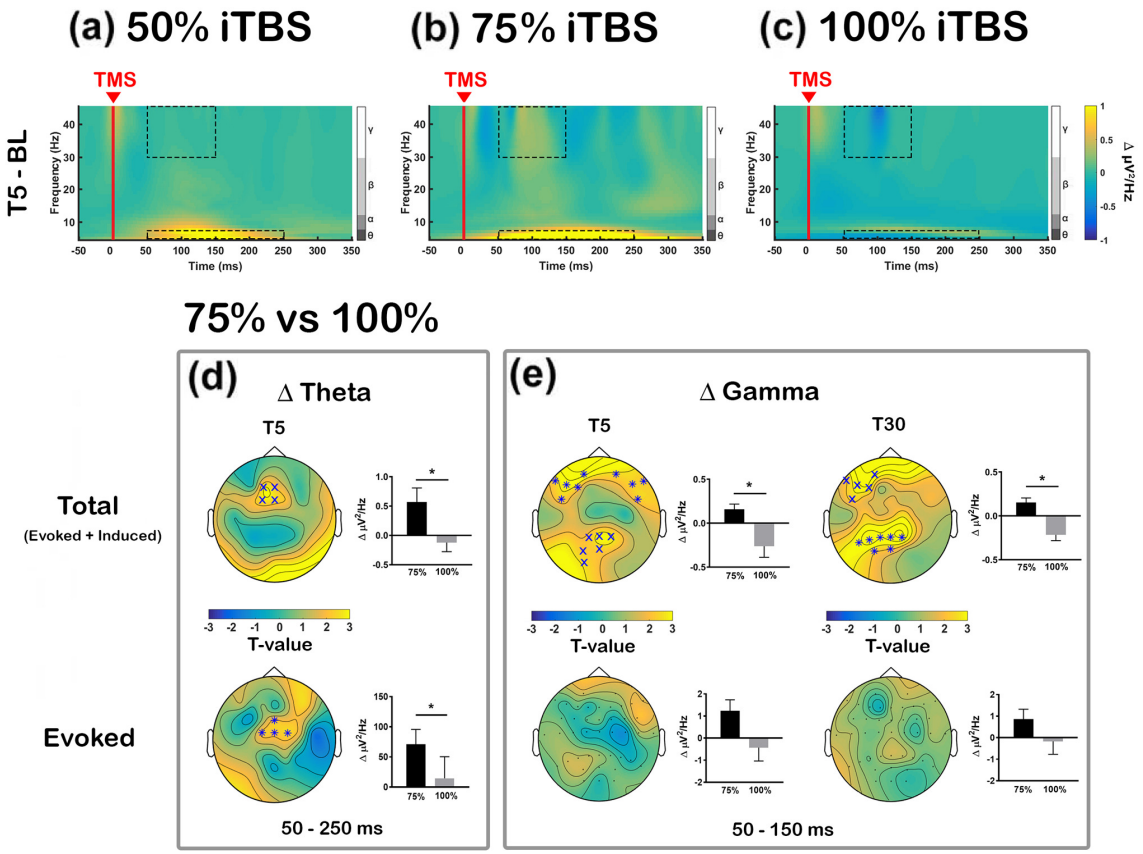

FIGURE 5 Comparison of transcranial magnetic stimulation (TMS)-evoked oscillations in iTBS-induced changes [a: Intermittent theta-burst stimulation (iTBS) at 50% rMT (50% iTBS); b: iTBS at 75% rMT (75% iTBS); c: iTBS at 100% rMT (100% iTBS)]. Grand average time-frequency plots are illustrated using average of all electrodes and displayed the difference between baseline and T5 (Δ power; T5 – BL). Dotted boxes represent time-frequency windows for gamma (50–150 ms) and theta (50–250 ms) bands where statistical analyses were conducted. Comparison between 75% and 100% iTBS conditions in (d) Δ theta at T5 and (e) Δ gamma at T5 and T30 across the scalp. Both total power (evoked + induced; top row) and evoked power alone (bottom row) were examined separately. Asterisks and 'X' s on topoplots indicate significant clusters between comparisons (cluster-based statistics, $^{*}p < .01$, $^{X}p < .025$). Bar graphs were plotted using the values extracted from the significant sensors (when not significant, using same sensors as total power) to examine the directional changes [Color figure can be viewed at wileyonlinelibrary.com]

using BL measurement (Supporting Information Figure S2A). To test if iTBS-induced changes measured by TEPs were consistent with electrophysiology recordings during WM task, we investigated the ERPs during 2-back and 3-back tasks in a similar manner to TEPs. Supporting the outcome in the TEPs measurement, 75% iTBS significantly increased the amplitude ERP N200 (198–218 ms, $p = .022$, fronto-central) during 2-back task (Figure 6a). The change in N200 amplitude (ERP Δ N200) was the largest with 75% iTBS compared to 100% iTBS (ERP Δ N200: 190–228 ms, $p = .018$, fronto-central). Source estimation of ERP N200 in these stimulation conditions revealed activity of parieto-occipital origin, and 75% iTBS resulted in increased activity including fronto-central region, whereas minimal change was observed following 100% iTBS (Figure 6c). Similar to TEPs, the differences were not significant when these conditions were compared with 50% iTBS (all $p > .025$). During the 3-back task, cluster-based statistics revealed 50% and 75% iTBS, but not 100% iTBS, resulted in significant differences between BL and T15 in ERP P300 amplitude, which was observed over anterior (50% iTBS: 310–333 ms, $p = .023$; 75% iTBS: 315–343 ms, $p = .015$) sensors, indicating increased amplitude following 50% and 75% iTBS (Figure 6b). However, no significant differences were seen between different stimulation conditions in P300 or any other peaks (all $p > .025$).

As both the TEP N100 and cognitive task related N200 peaks have been associated with inhibitory mechanisms [TEP N100 (Farzan et al., 2013; Premoli et al., 2014; Rogasch et al., 2015); ERP N200 (Aron, 2007; Kopp, Rist, & Mattler, 1996; Sasaki, Gemba, & Tsujimoto, 1989)], correlation analysis was performed on the data combined across different conditions ($n = 45$) using the average of 3 fronto-central electrodes (FC1, FCz, FC2). These electrodes were close to the stimulation, and the significant changes were most often observed in these electrodes across different measures. Spearman's rank correlation revealed TEP Δ N100 amplitude following iTBS (T5) correlated

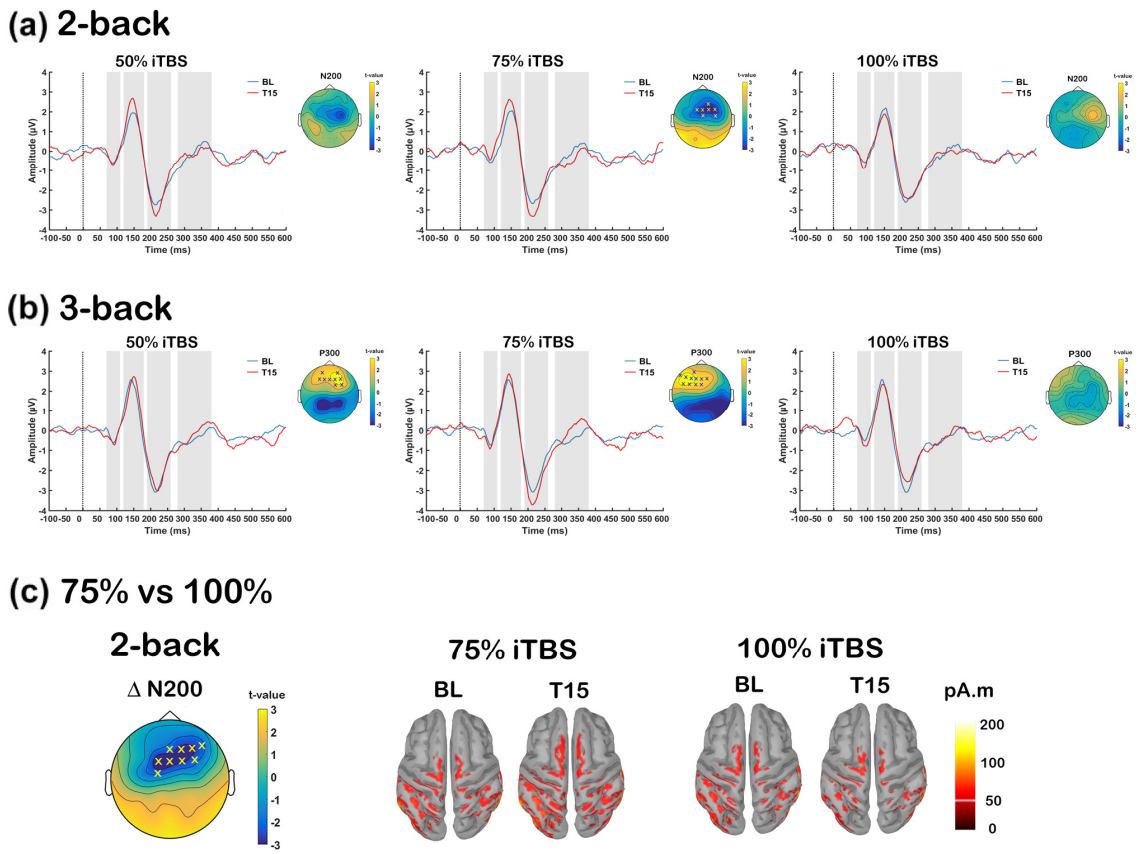

FIGURE 6 Effect of different intensities of intermittent theta-burst stimulation (iTBS) on the event related potentials (ERPs) during working memory tasks. Grand average ERP waveforms at baseline (BL: blue) and 15-min post (T15: red) iTBS at FCz electrode for each stimulation conditions (50%, 75%, and 100% iTBS) in (a) 2-back and (b) 3-back tasks, with significant differences across scalp shown in topoplots. (c) Global scalp differences of iTBS-induced change in N200 amplitude (ERP Δ N200) during 2-back task between 75% and 100% iTBS at T15 and Minimum Norm Estimates (MNEs) of the source level activity at the cortex for the N200 peak. 'X' s on topoplots indicate significant clusters between comparisons (cluster-based statistics, $^{X}p < .025$) [Color figure can be viewed at wileyonlinelibrary.com]

with ERP Δ N200 amplitude during 2-back task (T15) ($r = 0.572$, $p = .001$; Figure 7). We also explored if TEP Δ N100 correlated with ERP Δ P150 during 2-back task, or ERP Δ 300 during 3-back task, however, no significant correlations were found (all $p > .05$). The correlation between TEP Δ N100 and ERP Δ N200 during 2-back task supports the evidence that iTBS alters cortical inhibition in human prefrontal cortex at subthreshold intensities.

We also assessed the effect of different iTBS intensities on theta and gamma oscillations during WM. The effect of memory load on these oscillations was again examined using BL measurement (Supporting Information Figure S2B). As N-back task involves continuous mix of encoding, updating and maintaining of the letters, we divided each trial into two blocks—during letter presentation (50–450 ms: encoding) and after letter presentation (550–950 ms: maintenance).

To assess whether iTBS was able to modulate these frequency bands during WM task, both theta and gamma power were compared across time, and the changes between conditions. During letter presentation, iTBS did not change any frequency band during 2-back task (all $p > .025$). However, during 3-back task, significant increases in theta power were found at T15 compared to BL following both 50% ($p = .013$, right prefrontal) and 75% iTBS ($p = .023$, left prefrontal), but not 100% iTBS, indicating theta oscillations increased with subthreshold intensities. When Δ theta power were compared between conditions, differences were observed only between 75% and 100% iTBS (75% > 100% iTBS, $p = .022$) over left prefrontal sensors (Figure 8a, top row). While gamma power changes were not observed in any stimulation conditions in any N-back task, Δ gamma was significantly different between 75% and 100% iTBS (75% > 100% iTBS, $p = .022$) over left posterior sensors during 2-back task (Figure 8b, top row), but not during 3-back task. These findings suggest that iTBS differentially modulates cortical oscillations during letter presentation across task loads. After the letter presentation, however, iTBS resulted in no change in either theta or gamma band during either memory task (all $p > .025$), which suggests iTBS was not able to alter the processing involved in maintenance of memory.

Analysis of evoked oscillations resulted in a different pattern to the evoked oscillatory activity during TMS-EEG. We found no

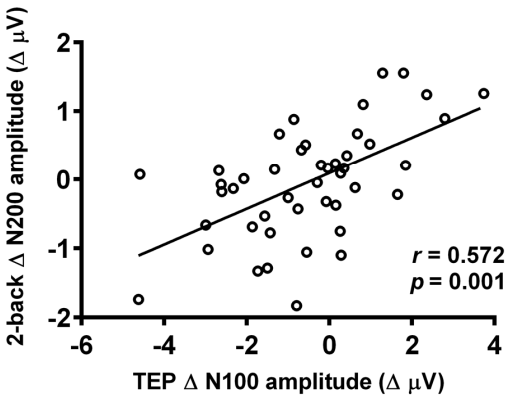

FIGURE 7 Correlation between iTBS-induced changes in TMS-evoked potential (TEP) N100 amplitude and 2-back task related N200 amplitude

significant differences in any frequency bands within or between conditions in any task (all $p > .025$). However, we observed nonsignificant increase in theta power following 75% iTBS, which was absent following 100% iTBS in 3-back task (Figure 8a, bottom row). We were unable to detect any changes in gamma power in the evoked activity in 2-back task (Figure 8b, bottom row).

Similar to TMS-EEG time-frequency analyses, exploratory analyses including all dimensions of the data (time × frequency × space) were conducted to investigate iTBS-induced changes in all oscillatory bands and time windows. However, no significant differences were found within or between stimulation conditions both in 2-back and 3-back task (all $p > .025$). In addition, we found no significant differences in alpha or beta frequency band (all $p > .025$).

We tested if TMS-evoked oscillations (Δ theta and Δ gamma) shared similar mechanisms to N-back task related oscillations (Δ theta with 3-back, Δ gamma with 2-back). For gamma oscillations, average of 3 left/mid parietal electrodes (P3, P1, Pz) were used for correlation analysis as these were found significant in cluster-based analysis of both TMS-evoked and 2-back task. Spearman's rank correlation revealed the TMS-evoked Δ gamma power following iTBS (T5) correlated with Δ gamma power during 2-back task (T15) ($r = 0.420$, $p = .004$; Figure 9). For theta oscillations, average of 3 fronto-central electrodes (FC1, FCz, FC2) were used. However, no significant correlation was found in Δ theta power between TMS-evoked and 3-back task ($r = 0.078$, $p = .609$).

3.4 | The effect of iTBS intensity on working memory

N-back WM performance (accuracy d', reaction time and effect sizes (Hedges' g [Hedges & Olkin, 1985]) is shown in Table 1.

3.4.1 | Performance at baseline

Initial statistical analysis was conducted on pre-iTBS (BL) data (combined across sessions, $n = 45$) to determine if WM performance differed between different memory load conditions (2-back vs 3-back) in accuracy (d') and reaction time. The Wilcoxon signed-rank tests revealed d' scores decreased [$Z = -5.108$, $r = -0.35$, $p = .001$ (3-back- < 2-back)] and reaction times increased [$Z = 2.523$, $r = 0.18$, $p = .012$

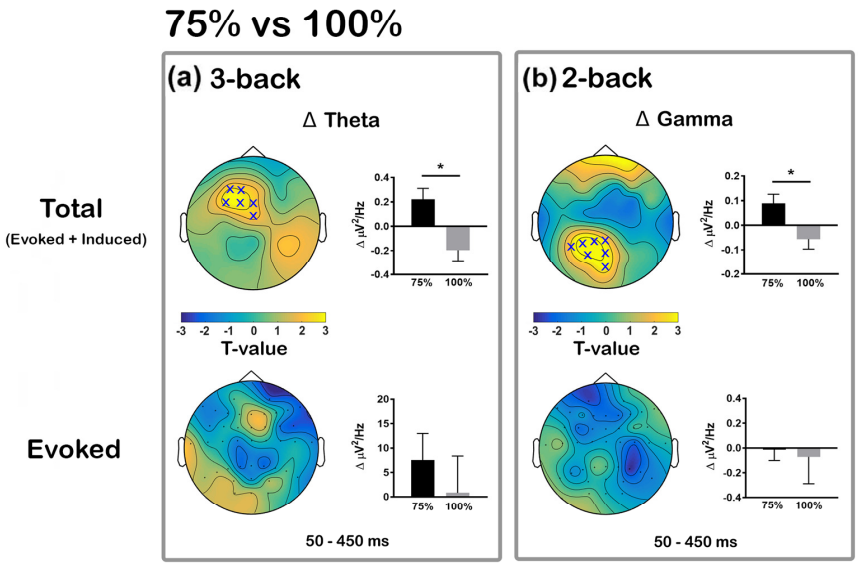

FIGURE 8 Comparison of intermittent theta-burst stimulation (iTBS)-induced changes in theta and gamma oscillations during different working memory tasks between 75% and 100% iTBS conditions. Significant differences in iTBS-induced change in (a) Δ theta power during 3-back task and in (b) Δ gamma power during 2-back task across the scalp. Both total power (evoked + induced; top row) and evoked power alone (bottom row) were examined separately. 'X' s on topoplots indicate significant clusters between comparisons (cluster-based statistics, $^{X}p < .025$). Bar graphs were plotted using the values extracted from the significant sensors (when not significant, using same sensors as total power) to examine the directional changes [Color figure can be viewed at wileyonlinelibrary.com]

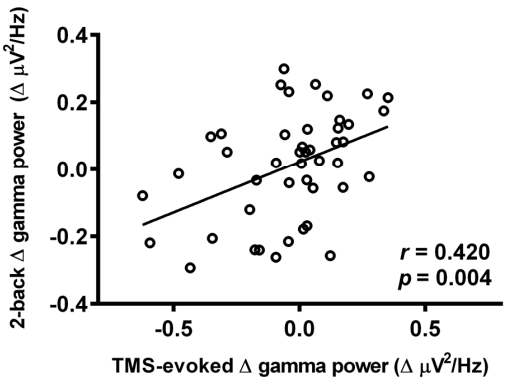

FIGURE 9 Correlation between iTBS-induced changes in TMS-evoked gamma power and 2-back task related gamma power

(3-back > 2-back)] with increasing WM load. We also conducted order effect analysis to confirm the effectiveness of the counter-balancing of stimulation conditions. Friedman's ANOVA showed no significant session effects in either *d'* (2-back: $x^2 = 0.037$, $p = .982$; 3-back: $x^2 = 0.036$, $p = .982$) or accurate reaction time (2-back: $x^2 = 3.448$, $p = .178$; 3-back: $x^2 = 1.793$, $p = .408$) for WM tasks at baseline measure.

3.4.2 | Performance following iTBS

Following 75% iTBS there was a significant decrease in reaction time (Wilcoxon signed rank test; $p = .031$) of small-to-moderate effect size (−0.42) during 3-back task. No other stimulation conditions showed any significant differences in WM performance (Wilcoxon signed rank test; all $p > .05$).

3.4.3 | Comparison pre- and post-iTBS

When compared across conditions using the change-from-baseline scores (post − pre; Δ), we could not detect any significant differences in reaction time or *d'* (Friedman's ANOVA; all $p > .05$).

We next tested if physiological changes were related to improved reaction time following 75% iTBS. The correlation analyses were performed between significant changes observed following 75% iTBS in TMS-EEG (Δ N100, Δ theta, Δ gamma) and during 3-back task (Δ P300, Δ theta) against Δ reaction time in 75% iTBS condition during 3-back task. However, there was no significant correlation between any change in physiological measure and 3-back reaction time (all $p > .05$).

3.5 | Control analyses

3.5.1 | Assessment of carryover effect

Studies have used 72 hours as a wash-out period for various noninvasive brain stimulation techniques (Chung et al., 2017; Hameed et al., 2017; Hill et al., 2017; Kumpulainen, Mrachacz-Kersting, Peltonen, Voigt, & Avela, 2012; Vossen, Gross, & Thut, 2015). To test if 72 hours were sufficient to avoid carryover effect of iTBS, baseline (BL) neurophysiological data were rearranged in the order of session and statistical analyses were performed on both TMS-EEG and N-back EEG data.

TABLE 1 Mean (SD) *d'*, accurate reaction time (ms) and the effect sizes (hedges' *g*) of 2-back and 3-back after different stimulation conditions

	2-back BL	T15	*Z* (*p*)	Hedges' *g* (95% CI)	3-back BL	T15	*Z* (*p*)	Hedges' *g* (95% CI)
d' (SD)								
50%	3.53 (0.95)	3.59 (1.09)	0.078 (0.937)	0.06 (−0.65 0.78)	2.57 (1.24)	2.72 (1.39)	1.161 (0.245)	0.11 (−0.61 0.83)
75%	3.34 (0.96)	3.49 (1.04)	0.848 (0.397)	0.14 (−0.57 0.86)	2.67 (1.18)	2.75 (1.20)	0.094 (0.925)	0.07 (−0.65 0.75)
100%	3.47 (1.21)	3.58 (0.96)	0.471 (0.638)	0.09 (−0.62 0.81)	2.62 (1.15)	2.86 (1.30)	0.909 (0.363)	0.19 (−0.53 0.91)
Friedman's Anova			$x^2 = 0.441$, $p = .802$				$x^2 = 1.458$, $p = .482$	
Reaction time (SD)								
50%	537.07 (136.31)	524.78 (131.21)	−1.420 (0.156)	−0.09 (−0.81 0.63)	583.67 (159.92)	575.22 (146.42)	−0.454 (0.650)	−0.05 (−0.77 0.66)
75%	521.74 (104.68)	518.81 (121.44)	0.000 (1.000)	−0.03 (−0.74 0.69)	561.35 (117.92)	517.01 (87.14)	−2.158 (0.031)[a]	−0.42 (−1.14 0.31)
100%	487.26 (104.79)	514.59 (80.28)	1.022 (0.307)	0.28 (−0.43 1.00)	538.80 (146.16)	520.09 (108.04)	0.000 (1.000)	−0.14 (−0.86 0.57)
Friedman's Anova			$x^2 = 2.678$, $p = .262$				$x^2 = 1.458$, $p = .482$	

[a]indicates significant difference ($p < .05$).

We found no significant differences between any sessions in any neurophysiological data (all $p > .025$) (Supporting Information Figure S3), suggesting the absence of carryover effect.

3.5.2 | Secondary analyses of sham condition

Neurophysiology

No significant differences were observed in the amplitudes of any TEPs or ERPs (both the 2-back and 3-back tasks) across time (Supporting Information Figure S4A–C), as well as in the oscillatory power in these measures (all $p > .025$) following sham iTBS.

When compared to active conditions, cluster-based permutation test (independent t-test) between 75% iTBS and sham iTBS showed a significant difference in TEP Δ N100 (75% > sham iTBS: T5, 109–140 ms, $p = .009$; fronto-central sensors). Similarly, a significantly larger TMS-evoked theta power was seen following 75% iTBS compared to sham (T5, $p = .019$, fronto-central sensors). During the 2-back task, a significantly larger gamma power was observed following 75% iTBS compared to sham ($p = .024$; parietal sensors) during the letter presentation. During the 3-back task, a significantly larger alpha power was seen following 75% iTBS compared to sham ($p = .024$; left prefrontal sensors) during the maintenance period (550–950 ms) (Supporting Information Figure S4D). A comparison between 100% iTBS and sham yielded a significantly difference only in TMS-evoked gamma power (100% < sham iTBS: T30, $p = .020$; left-prefrontal sensors) (Supporting Information Figure S4E). No other change in peaks or oscillatory power showed any significant differences either in TMS-EEG or N-back EEG (all $p > .025$).

Behaviour

Table 2 summarises the N-back performance and the effect size of sham control iTBS and its comparison to active stimulation conditions. While no significant differences were found between BL and T15 following sham stimulation in either d' or accurate reaction time for both the 2-back and the 3-back tasks (Wilcoxon signed rank test; all $p > .05$), between condition comparisons using the Mann-Whiney U test indicated that 75% iTBS elicited a greater improvement in accurate reaction time than sham stimulation during the 3-back task ($U = 44$, $p = .025$).

3.5.3 | Association of alpha power and reaction time

Increased alpha power has been associated with faster reaction time in a motor task (Moore, Gale, Morris, & Forrester, 2008) and in working memory (Bonnefond & Jensen, 2012; Nenert, Viswanathan, Dubuc, & Visscher, 2012). Similarly, Δ alpha (Figure 10a,b) resembled closely to Δ accurate reaction time (Figure 10c). Therefore, we explored if these changes were related. Correlation analysis was conducted on the data combined across active iTBS conditions ($n = 45$) using the average of all electrodes. Spearman's rank correlation revealed the Δ alpha power significantly correlated with Δ accurate reaction time during 3-back task ($r = -0.603$, $p = .001$) (Figure 10d), suggesting increased alpha power leads to faster reaction time.

TABLE 2 Mean (SD) d', accurate reaction time (ms) and the effect sizes (hedges' g) of 2-back and 3-back task following sham stimulation and its comparison to active stimulation conditions using change-from-baseline scores

	2-back				3-back			
	BL	T15	Z (p)	Hedges' g (95% CI)	BL	T15	Z (p)	Hedges' g (95% CI)
d' (SD)								
Sham	3.03 (0.89)	3.25 (0.89)	0.863 (0.388)	0.14 (−0.66 0.95)	2.44 (1.05)	2.45 (1.14)	−0.471 (0.638)	−0.04 (−0.84 0.76)
Δ d'	**Mann-Whiney Test**			**Hedges' g (95% CI)**	**Mann-Whiney Test**			**Hedges' g (95% CI)**
50% vs Sham	$U = 74$, $p = .456$			−0.29 (−1.05 0.47)	$U = 73$, $p = .427$			−0.22 (−0.98 0.54)
75% vs Sham	$U = 89$, $p = .981$			−0.24 (−1.00 0.53)	$U = 83$, $p = .755$			0.39 (−0.37 1.16)
100% vs Sham	$U = 84$, $p = .792$			0.01 (−0.75 0.77)	$U = 75$, $p = .486$			0.07 (−0.69 0.83)
	2-back				**3-back**			
	BL	**T15**	**Z (p)**	**Hedges' g (95% CI)**	**BL**	**T15**	**Z (p)**	**Hedges' g (95% CI)**
Reaction time (SD)								
Sham	472.68 (65.80)	456.53 (96.49)	−1.412 (0.158)	−0.19 (−0.99 0.61)	518.26 (118.05)	559.97 (168.51)	1.177 (0.239)	0.28 (−0.53 1.08)
Δ Reaction time	**Mann-Whiney Test**			**Hedges' g (95% CI)**	**Mann-Whiney Test**			**Hedges' g (95% CI)**
50% vs Sham	$U = 71$, $p = .373$			0.06 (−0.70 0.82)	$U = 60$, $p = .152$			−0.65 (−1.43 0.13)
75% vs Sham	$U = 70$, $p = .347$			0.19 (−0.57 0.95)	**$U = 44$, $p = .025$**[a]			**-1.09 (-1.91 −0.28)**
100% vs Sham	$U = 58$, $p = .126$			0.51 (−0.26 1.28)	$U = 69$, $p = .323$			−0.54 (−1.31 0.23)

[a]indicates significant difference ($p < .05$).

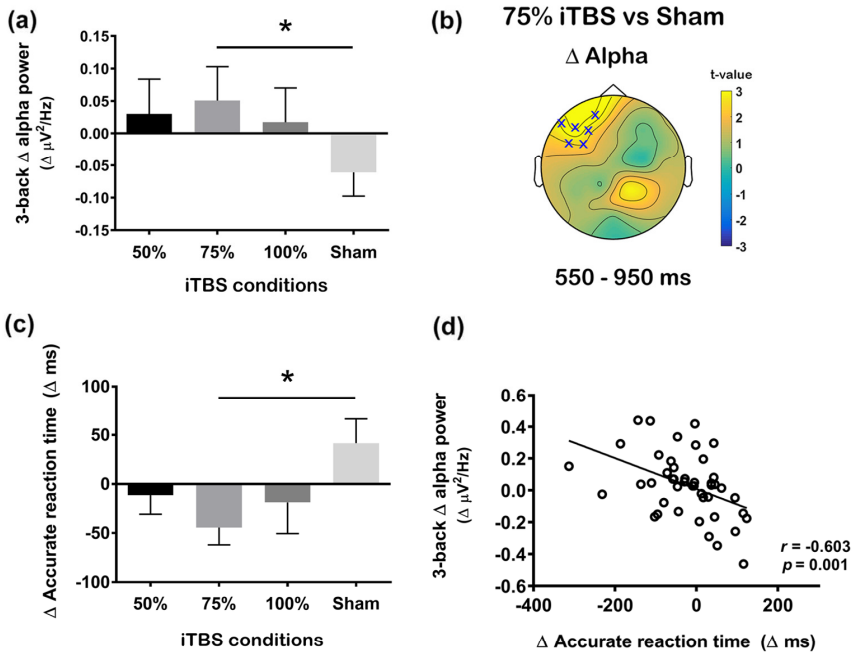

FIGURE 10 Comparison of the change (Δ) in alpha power between different stimulation condition during the 3-back task and its association to working memory performance. (a) Comparison of global scalp Δ alpha power between 50%, 75%, 100% and sham intermittent theta burst stimulation (iTBS) and (b) scalp map representing *t*-values for the significant differences (cluster-based statistics, $^{X}p < .025$). (c) Comparison of Δ accurate reaction time between different stimulation condition and (d) correlation between Δ alpha power and Δ accurate reaction time following active iTBS. Error bars indicate standard error of means (SEM) [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

This study examined the link between iTBS intensity and LTP-like neural plasticity, and the association to neurophysiological and behavioural metrics of WM in the prefrontal cortex. The data indicate an inverse U-shaped relationship between iTBS intensity and neurophysiological changes following single-pulse TMS and during working memory, whereby these effects were maximal at an intermediate intensity of 75% rMT. However, no differences in working memory performances were seen between active conditions. The plastic effects correlated with changes in neurophysiological aspects of cognition (ERPs), however these changes did not have a direct relationship with the behavioural outcomes of the WM task (accuracy and reaction time). Instead, iTBS-induced change in alpha power during the 3-back task demonstrated close association to the change in reaction time. The data suggest using subthreshold intensities is important in order to achieve desirable after-effects following iTBS in the prefrontal cortex, and highlight potential benefits in the application of iTBS for clinical treatment.

4.1 | Influence of iTBS intensity on plastic effects in DLPFC

iTBS modulated N100 amplitude, and the increase in this component was maximal when iTBS was delivered at 75% rMT compared to lower (50% rMT) or higher intensity (100% rMT). These findings raise interesting aspects of the relationship between intensity and plasticity induction. Increased N100 following iTBS over prefrontal cortex is in line with previous studies which also showed modulation of this component following iTBS (Chung et al., 2017; Harrington & Hammond-Tooke, 2015) or cTBS (Harrington & Hammond-Tooke, 2015; Huang & Mouraux, 2015), however, opposite outcome (i.e., decreased following iTBS, increase following cTBS) has also been described in cerebellar stimulation (Casula et al., 2016b). The N100 deflection is considered to be the most prominent and robust TMS-EEG component and is understood to have the greatest inter-individual and inter-session reproducibility compared to other TEPs both in motor and prefrontal cortex (Lioumis, Kicic, Savolainen, Makela, & Kahkonen, 2009). The N100 is also considered to have a high degree of sensitivity to small changes in cortical excitability (Nikulin, Kicic, Kahkonen, & Ilmoniemi, 2003). These factors enhance the value of N100 as a marker of cortical processing in basic and clinical research, and make it ideal for exploration of the effects of TMS plasticity paradigms (Chung et al., 2015b; Ilmoniemi & Kicic, 2010; Noda et al., 2016). Recent studies have provided evidence that N100 may also be associated with $GABA_B$-mediated postsynaptic inhibition in motor (Farzan et al., 2013; Premoli et al., 2014; Rogasch et al., 2013a) and prefrontal (Rogasch et al., 2015) cortex. These findings raise the prospect of current data reflecting an increase in cortical inhibition following iTBS. This account is difficult to reconcile with the absence of effects of iTBS on $GABA_B$-mediated inhibitory measures such as long intracortical inhibition (LICI) (Goldsworthy, Pitcher, &

Ridding, 2013; Suppa et al., 2008) or the cortical silent period (Brownjohn, Reynolds, Matheson, Fox, & Shemmell, 2014; Di Lazzaro et al., 2011) in the motor cortex. However, we did recently observe an increase in LICI of theta oscillations which correlated with increased N100 amplitude following iTBS over DLPFC (Chung et al., 2017), supporting possible modulation of cortical inhibition following stimulation.

The present data did not show a significant increase in P60 amplitude following iTBS. Recent studies suggest that P60 provides a marker of neural excitability (Cash et al., 2017b; Hill et al., 2017). It should be noted that the SNR for P60 is substantially lower than for N100, and the current protocol with ~47 single TMS pulses may have been insufficient to capture significant changes. The data, however, demonstrated evidence of a relationship between the change in amplitude of N100 and P60 following iTBS. If N100 is related to inhibition, and P60 to neural excitability, this finding suggests that the change in excitation was balanced by a similar change in inhibition, maintaining the excitatory-inhibitory balance following iTBS. This is in agreement with the concept of homeostatic plasticity mechanisms involving a dynamic adjustment of excitatory and inhibitory circuits (Turrigiano & Nelson, 2004). In summary, it appears that the most reliable TMS-EEG metric of plasticity is the modulation of N100 amplitude and iTBS-induced change in this component was greatest at an intermediate intensity of 75% rMT.

The relationship between iTBS intensity and the level of plasticity induction is likely explained by the unique mechanistic features underlying iTBS. Typically, the propensity for LTP-like effects increases with increasing intensity (Artola, Brocher, & Singer, 1990; Cash et al., 2017a), whereby greater postsynaptic depolarisation leads to higher levels of N-methyl-D-aspartate receptor (NDMA-R) activation, and consequently regulating the processes leading to LTP (Luscher & Malenka, 2012). A similar relationship has been demonstrated across a range of noninvasive NMDA-R dependent brain stimulation protocols in human (Batsikadze et al., 2013; Cash et al., 2017a; Doeltgen & Ridding, 2011; Moliadze, Atalay, Antal, & Paulus, 2012). However, the present findings demonstrate an exception to this relationship, showing an inverse U-shaped influence of stimulus intensity on plastic effects. This may be explained by the unique temporal aspects that underlie the fundamental mechanism of TBS (Larson & Munkacsy, 2015). It is thought that the robust after-effect of TBS is achieved through targeting a late period of presynaptic $GABA_B$-mediated disinhibition, which may itself help sustain the theta rhythm (Davies, Starkey, Pozza, & Collingridge, 1991; Larson & Munkacsy, 2015; Mott & Lewis, 1991). More specifically, stimulation elicits both postsynaptic $GABA_B$-mediated inhibition (inhibitory postsynaptic potentials) and presynaptic $GABA_B$ autoreceptor-mediated disinhibition (temporary blockade of further GABA release). It has been shown that presynaptic disinhibition outlasts postsynaptic inhibition, resulting in a late temporal window (~200 ms) during which disinhibition dominates (Deisz, 1999; Otis, De Koninck, & Mody, 1993) and plasticity induction is enhanced (Davies & Collingridge, 1996; Larson & Lynch, 1986; Mott & Lewis, 1991; Pacelli, Su, & Kelso, 1989). Delivery of stimulus bursts at this interval (i.e., TBS) results in a rapid induction of plastic effects (Davies et al., 1991; Mott & Lewis, 1991). A similar late phase of disinhibition has recently been described in humans at ~200 ms latency (Cash, Ziemann, Murray, & Thickbroom, 2010), during which excitability (Cash, Ziemann, & Thickbroom, 2011) and plasticity induction were enhanced (Cash, Murakami, Chen, Thickbroom, & Ziemann, 2016). Importantly, the latency of this period increases with increasing stimulus intensity (Cash et al., 2010) and stimulation outside this window does not result in plastic effects in humans (Cash et al., 2016) or animals (Larson & Munkacsy, 2015). Consequently, higher TBS intensities may miss this plastic window. This unique plasticity mechanism may account for the inverse U-shaped relationship between intensity and plasticity observed in this study.

4.2 | The effect of iTBS on neural oscillations is modulated by stimulus intensity

The spectral characteristics elicited by single-pulse TMS are commonly modulated following TBS in a manner that may depend on the area being stimulated. Cerebellar stimulation (iTBS and cTBS) were found to modulate alpha and beta power (Casula et al., 2016b), while cTBS of motor cortex produced modulation of theta, alpha and beta power (Vernet et al., 2013). In the prefrontal cortex, polarity-specific changes in TMS-evoked theta power (increase following iTBS, decrease following cTBS) were demonstrated (Chung et al., 2017), and modulation of theta and gamma power were also observed in a resting EEG study (Wozniak-Kwasniewska, Szekely, Aussedat, Bougerol, & David, 2014), suggesting TBS may be targeting the natural frequency of oscillations in the stimulated region. Our data indicate the additional dimension of iTBS intensity in modulating these spectral changes. Theta power was increased following iTBS, consistent with our previous study (Chung et al., 2017), and this effect was maximal at 75% rMT. Previous findings in relation to gamma power have been somewhat inconsistent, showing no change (Chung et al., 2017), or an increase following cTBS (Vernet et al., 2013), and this may relate to low SNR of gamma and/or discrepancies in analysis methods such as the total power vs evoked power, and the level of spatial dynamics (region of interest vs global scalp analysis). Here, we examined both total and evoked activity, and the analysis of total power provided additional information about the spread of activity following iTBS in distant yet interconnected regions. In the present study, the direction of change in TMS-evoked gamma was further shown to depend on the intensity of the stimulation (increase with 75% iTBS, decrease with 100%), and this change remained significant at T30. This was an interesting observation as iTBS on rat cortex also resulted in long-lasting gamma power increase (Benali et al., 2011), and this finding may indicate that the persistent difference in after-effects of iTBS could be observed in the gamma frequency band in humans. The increase in theta and gamma power following iTBS at 75% rMT would seemingly suggest that this intensity might be advantageous for enhancing performance on cognitive tasks.

4.3 | Relationship to neurophysiological and behavioural metrics during cognitive performance

Similar to TMS-EEG findings, iTBS modulated neurophysiological metrics during the performance of the cognitive task in an intensity-

dependent manner. With 75% rMT and 50% rMT to some extent, iTBS increased N200 amplitude in the 2-back task, and P300 amplitude in the 3-back task, while no changes were evident at a higher intensity. N200 has been linked to executive control (Kopp et al., 1996) and cognitive and inhibitory processing (Folstein & Van Petten, 2008; Sasaki et al., 1989; Schmajuk, Liotti, Busse, & Woldorff, 2006). The change in ERP N200 amplitude correlated with plastic changes in TEP N100 amplitude, suggesting that these may be modulated by iTBS in a similar manner or have a degree of functional overlap. This link was not present with ERP P150 or ERP P300, further strengthening the selective link for possible inhibitory processing involved in two different measures following iTBS. In the frequency domain, frontal theta power was enhanced following 75% iTBS during the 3-back task. There was also a trend for an increase in parietal gamma power during 2-back WM task, which was maximal following iTBS at 75% rMT. These results are consistent with a maximal effect of iTBS at 75% rMT observed in TMS-EEG data. A significant correlation between the change in TMS-evoked gamma power and event-related gamma power during 2-back task provides further evidence of a relationship between the neural elements modulated by TBS, probed by single-pulse TMS and functionally recruited during a WM task. These results support the notion that iTBS can likely enhance the neurophysiological mechanisms mediating working memory (Hoy et al., 2016), and does so in an intensity-dependent manner. Theta and gamma oscillations are important in WM (Howard et al., 2003; Hsieh & Ranganath, 2014) and these oscillation frequencies are targeted by iTBS. The involvement of fronto-parietal network control system (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008) is also supported by the observation of the influence of TBS on visuo-spatial attention (Xu et al., 2013) and in WM task (Hoy et al., 2016).

We observed a significant correlation between Δ alpha power and Δ reaction time following active iTBS conditions during the maintenance period of the 3-back task. Alpha power has been associated with the gating and maintenance of relevant information during working memory (Manza, Hau, & Leung, 2014), and protects against distractions (Bonnefond & Jensen, 2012). Alpha power decreases with increasing load in the N-back task (Chen & Huang, 2015; Scharinger, Soutschek, Schubert, & Gerjets, 2017), and increased alpha power may reflect an ease of performance. In addition, faster reaction time resulted in stronger alpha power in frontal and posterior regions during visual memory task (Nenert et al., 2012), which is in line with the current study.

We were unable to replicate the previous study of iTBS demonstrating a significant increase in the accuracy of 2-back task following iTBS compared to sham stimulation (Hoy et al., 2016). The reason for this discrepancy remains unclear, and further research is required as currently only a few studies have been performed in this area to date (Cheng et al., 2016; Debarnot et al., 2015; Demeter, Mirdamadi, Meehan, & Taylor, 2016; Hoy et al., 2016; Ryals, Rogers, Gross, Polnaszek, & Voss, 2016). A recent study investigated the effect of prefrontal TBS on a series of cognitive tasks, such as Digits Backward, 3-back task, Stroop Colour and Word Test, and the Tower of Hanoi (Viejo-Sobera et al., 2017). Only subtle behavioural changes were found in these measures in the absence of statistical differences between iTBS, cTBS and sham condition, and with no clear bi-directional changes (i.e., enhanced or impaired performance following iTBS or cTBS, respectively). It is interesting to note that for pre- and post-TBS comparison, iTBS showed improvement in Digits Backward and Stroop WR score.

The absence of strong behavioural changes in the presence of robust neurophysiological effects has also been described following tDCS (Hill et al., 2016), suggesting neurophysiological measures may provide a more sensitive index for assessing changes following neuromodulatory paradigms. It is possible that the marginal behavioural differences between active stimulation conditions may be due to a ceiling effect of performance in healthy individuals. A recent meta-analysis of the working memory performance following noninvasive brain stimulation demonstrates only small effect sizes in improvement in healthy controls compared to clinical populations that showed medium effect sizes (Brunoni & Vanderhasselt, 2014). Greater behavioural effects may be detected in disorders of WM, such as schizophrenia, in which considerable differences in physiological measures are often observed compared to a control group (Ferrarelli et al., 2012; Noda et al., 2017). However, it is also conceivable that other cognitive tasks may provide more robust behavioural outcome and should further be investigated. The use of TBS as a cognitive enhancer is still at its early stage, and future studies should examine a different variety of cognitive tests in combination with physiological measurement to better characterise the modulatory capacity and the neurobiological basis of TBS on cognition.

4.4 | Limitations

Our study design did not include a control site for single-pulse TMS besides the area directly under the iTBS location. Several studies have included the use of a control site such as vertex for TMS (Foltys et al., 2001; Garcia, Grossman, & Srinivasan, 2011; Silvanto, Cattaneo, Battelli, & Pascual-Leone, 2008; Taylor, Walsh, & Eimer, 2008), and this method may provide additional information in future studies. It may be important to note that the spread of neural activity from the vertex stimulation can be observed in brain regions associated with default mode network (DMN) (Jung, Bungert, Bowtell, & Jackson, 2016), and certain regions of DMN are connected to the working memory network (WMN; DLPFC) in functional connectivity (Piccoli et al., 2015). The highly interconnected nature of prefrontal cortex (Paus, Castro-Alamancos, & Petrides, 2001; Petrides & Pandya, 2002; Yeterian, Pandya, Tomaiuolo, & Petrides, 2012) may limit localisation of functionally distant control site. Our TEP data mainly indicate changes in the TEP components which had a high SNR (Supporting Information Table S1). It is possible that increasing the number of stimuli would also have revealed changes in other TEP components. In addition, TMS-EEG at high intensity (120% rMT) may introduce additional muscle artefacts (Lioumis et al., 2009), which was in part mitigated by stimulating over the F1 electrode to minimise muscle activation (Rogasch et al., 2013b). Muscle artefacts can also be removed effectively via current cleaning method using ICA (Korhonen et al., 2011; Rogasch et al., 2014). Finally, consistency of stimulation site localisation between sessions could be improved by using MRI-guided neuronavigation, however, this was not feasible in the present study. Nevertheless, the TEP waveforms in this study are consistent with previous studies in DLPFC (Chung et al.,

2017; Hill et al., 2017; Rogasch et al., 2014), and comparable results have been reported using EEG-guided methods (Rogasch et al., 2014) and MRI-guided neuronavigation (Lioumis et al., 2009).

5 | CONCLUSION

The present data provide the first evidence that for iTBS, unlike rTMS (Nahas et al., 2001; Padberg et al., 2002), using higher intensities may not be optimal for maximal neuromodulation, and instead, maximal effects are observed at an intermediate intensity of 75% rMT. Further research is required to explore whether the present intensity relationship extends to clinical efficacy. The data also indicate that the link between neurophysiological and behavioural effects may not be as direct as hoped, however, it is also possible that repeated sessions are necessary to elicit more robust behavioural outcomes. Despite the modest behavioural outcome in this study, the change in cortical oscillatory activity evoked by TMS has been implicated in clinical improvement in a patient with MDD (a case study) (Pellicciari, Ponzo, Caltagirone, & Koch, 2017a), and we were able to demonstrate different effects the stimulation intensity has on the oscillatory properties following iTBS over the left prefrontal cortex, which may be useful indices for treatment regime. Other short paradigms of similar duration to TBS are now available (Cash et al., 2016, 2017a), and may offer another option for clinical trials.

In conclusion, the current study indicates that iTBS at 75% rMT produces the strongest effect on physiological measures in the prefrontal cortex, and increasing the intensity may not necessarily result in a corresponding change. These findings highlight the importance of intensity in administering iTBS and paves the path for more efficacious outcome in patients with neurological and psychiatric disorders.

CONFLICT OF INTEREST

There are no other conflict.

ORCID

Sung Wook Chung http://orcid.org/0000-0001-8022-8037

REFERENCES

Aron, A. R. (2007). The neural basis of inhibition in cognitive control. *The Neuroscientist*, *13*, 214–228.

Artola, A., Brocher, S., & Singer, W. (1990). Different voltage-dependent thresholds for inducing long-term depression and long-term potentiation in slices of rat visual cortex. *Nature*, *347*, 69–72.

Bakker, N., Shahab, S., Giacobbe, P., Blumberger, D. M., Daskalakis, Z. J., Kennedy, S. H., & Downar, J. (2015). rTMS of the dorsomedial prefrontal cortex for major depression: safety, tolerability, effectiveness, and outcome predictors for 10 Hz versus intermittent theta-burst stimulation. *Brain Stimulation*, *8*, 208–215.

Batsikadze, G., Moliadze, V., Paulus, W., Kuo, M. F., & Nitsche, M. A. (2013). Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. *The Journal of Physiology*, *591*, 1987–2000.

Benali, A., Trippe, J., Weiler, E., Mix, A., Petrasch-Parwez, E., Girzalsky, W., … Funke, K. (2011). Theta-burst transcranial magnetic stimulation alters cortical inhibition. *Journal of Neuroscience*, *31*, 1193–1203.

Bonnard, M., Spieser, L., Meziane, H. B., de Graaf, J. B., & Pailhous, J. (2009). Prior intention can locally tune inhibitory processes in the primary motor cortex: direct evidence from combined TMS-EEG. *European Journal of Neuroscience*, *30*, 913–923.

Bonnefond, M., & Jensen, O. (2012). Alpha oscillations serve to protect working memory maintenance against anticipated distracters. *Current Biology*, *22*, 1969–1974.

Brownjohn, P. W., Reynolds, J. N., Matheson, N., Fox, J., & Shemmell, J. B. (2014). The effects of individualized theta burst stimulation on the excitability of the human motor system. *Brain Stimulation*, *7*, 260–268.

Brunoni, A. R., & Vanderhasselt, M. A. (2014). Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: a systematic review and meta-analysis. *Brain and Cognition*, *86*, 1–9.

Cardenas-Morales, L., Volz, L. J., Michely, J., Rehme, A. K., Pool, E. M., Nettekoven, C., … Grefkes, C. (2014). Network connectivity and individual responses to brain stimulation in the human motor system. *Cerebral Cortex*, *24*, 1697–1707.

Cash, R. F., Jegatheeswaran, G., Ni, Z., & Chen, R. (2017a). Modulation of the direction and magnitude of hebbian plasticity in human motor cortex by stimulus intensity and concurrent inhibition. *Brain Stimulation*, *10*, 83–90.

Cash, R. F., Mastaglia, F. L., & Thickbroom, G. W. (2013). Evidence for high-fidelity timing-dependent synaptic plasticity of human motor cortex. *Journal of Neurophysiology*, *109*, 106–112.

Cash, R. F., Murakami, T., Chen, R., Thickbroom, G. W., & Ziemann, U. (2016). Augmenting plasticity induction in human motor cortex by disinhibition stimulation. *Cerebral Cortex*, *26*, 58–69.

Cash, R. F., Noda, Y., Zomorrodi, R., Radhu, N., Farzan, F., Rajji, T. K., … Blumberger, D. M. (2017b). Characterization of glutamatergic and GABAA-mediated neurotransmission in motor and dorsolateral prefrontal cortex using paired-pulse TMS-EEG. *Neuropsychopharmacology*, *42*, 502–511.

Cash, R. F., Ziemann, U., Murray, K., & Thickbroom, G. W. (2010). Late cortical disinhibition in human motor cortex: a triple-pulse transcranial magnetic stimulation study. *Journal of Neurophysiology*, *103*, 511–518.

Cash, R. F., Ziemann, U., & Thickbroom, G. W. (2011). Inhibitory and disinhibitory effects on I-wave facilitation in motor cortex. *Journal of Neurophysiology*, *105*, 100–106.

Casula, E. P., Pellicciari, M. C., Picazio, S., Caltagirone, C., & Koch, G. (2016a). Spike-timing-dependent plasticity in the human dorso-lateral prefrontal cortex. *Neuroimage*, *143*, 204–213.

Casula, E. P., Pellicciari, M. C., Ponzo, V., Stampanoni Bassi, M., Veniero, D., Caltagirone, C., & Koch, G. (2016b). Cerebellar theta burst stimulation modulates the neural activity of interconnected parietal and motor areas. *Scientific Reports*, *6*, 36191.

Chen, R., Tam, A., Butefisch, C., Corwell, B., Ziemann, U., Rothwell, J. C., & Cohen, L. G. (1998). Intracortical inhibition and facilitation in different representations of the human motor cortex. *Journal of Neurophysiology*, *80*, 2870–2881.

Chen, Y., & Huang, X. (2015). Modulation of alpha and beta oscillations during an n-back task with varying temporal memory load. *Frontiers in Psychology*, *6*, 2031.

Cheng, C. M., Juan, C. H., Chen, M. H., Chang, C. F., Lu, H. J., Su, T. P., … Li, C. T. (2016). Different forms of prefrontal theta burst

stimulation for executive function of medication- resistant depression: Evidence from a randomized sham-controlled study. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *66*, 35–40.

Chung, S. W., Hoy, K. E., & Fitzgerald, P. B. (2015a). Theta-burst stimulation: a new form of TMS treatment for depression? *Depression and Anxiety*, *32*, 182–192.

Chung, S. W., Lewis, B. P., Rogasch, N. C., Saeki, T., Thomson, R. H., Hoy, K. E., … 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*, 1117–1126.

Chung, S. W., Rogasch, N. C., Hoy, K. E., & Fitzgerald, P. B. (2015b). Measuring brain stimulation induced changes in cortical properties using TMS-EEG. *Brain Stimulation*, *8*, 1010–1020.

Conforto, A. B., Z'graggen, W. J., Kohl, A. S., Rosler, K. M., & Kaelin-Lang, A. (2004). Impact of coil position and electrophysiological monitoring on determination of motor thresholds to transcranial magnetic stimulation. *Clinical Neurophysiology*, *115*, 812–819.

Coull, J. T. (1998). Neural correlates of attention and arousal: insights from electrophysiology, functional neuroimaging and psychopharmacology. *Progress in Neurobiology*, *55*, 343–361.

Daskalakis, Z. J., Farzan, F., Barr, M. S., Maller, J. J., Chen, R., & Fitzgerald, P. B. (2008). Long-interval cortical inhibition from the dorsolateral prefrontal cortex: a TMS-EEG study. *Neuropsychopharmacology*, *33*, 2860–2869.

Davies, C. H., & Collingridge, G. L. (1996). Regulation of EPSPs by the synaptic activation of GABAB autoreceptors in rat hippocampus. *The Journal of Physiology*, *496*(Pt 2), 451–470.

Davies, C. H., Starkey, S. J., Pozza, M. F., & Collingridge, G. L. (1991). GABA autoreceptors regulate the induction of LTP. *Nature*, *349*, 609–611.

Debarnot, U., Crepon, B., Orriols, E., Abram, M., Charron, S., Lion, S., … Piolino, P. (2015). Intermittent theta burst stimulation over left BA10 enhances virtual reality-based prospective memory in healthy aged subjects. *Neurobiol Aging*, *36*, 2360–2369.

Debener, S., & De Vos, M. (2011). The benefits of simultaneous EEG-fMRI for EEG analysis. *Clinical Neurophysiology*, *122*, 217–218.

Deisz, R. A. (1999). The GABA(B) receptor antagonist CGP 55845A reduces presynaptic GABA(B) actions in neocortical neurons of the rat in vitro. *Neuroscience*, *93*, 1241–1249.

Delorme, A., & Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods*, *134*, 9–21.

Demeter, E., Mirdamadi, J. L., Meehan, S. K., & Taylor, S. F. (2016). Short theta burst stimulation to left frontal cortex prior to encoding enhances subsequent recognition memory. *Cognitive, Affective, & Behavioral Neuroscience*, *16*, 724–735.

Desmyter, S., Duprat, R., Baeken, C., Van Autreve, S., Audenaert, K., & van Heeringen, K. (2016). Accelerated intermittent theta burst stimulation for suicide risk in therapy-resistant depressed patients: A randomized, sham-controlled trial. *Frontiers in Human Neuroscience*, *10*, 480.

Di Lazzaro, V., Dileone, M., Pilato, F., Capone, F., Musumeci, G., Ranieri, F., … Profice, P. (2011). Modulation of motor cortex neuronal networks by rTMS: comparison of local and remote effects of six different protocols of stimulation. *Journal of Neurophysiology*, *105*, 2150–2156.

Doeltgen, S. H., & Ridding, M. C. (2011). Low-intensity, short-interval theta burst stimulation modulates excitatory but not inhibitory motor networks. *Clinical Neurophysiology*, *122*, 1411–1416.

Dosenbach, N. U., Fair, D. A., Cohen, A. L., Schlaggar, B. L., & Petersen, S. E. (2008). A dual-networks architecture of top-down control. *Trends in Cognitive Sciences*, *12*, 99–105.

Duprat, R., Desmyter, S., Rudi de, R., van Heeringen, K., Van den Abbeele, D., Tandt, H., … Baeken, C. (2016). Accelerated intermittent theta burst stimulation treatment in medication-resistant major depression: A fast road to remission? *Journal of Affective Disorders*, *200*, 6–14.

Farzan, F., Barr, M. S., Hoppenbrouwers, S. S., Fitzgerald, P. B., Chen, R., Pascual-Leone, A., & Daskalakis, Z. J. (2013). The EEG correlates of the TMS-induced EMG silent period in humans. *Neuroimage*, *83*, 120–134.

Farzan, F., Barr, M. S., Levinson, A. J., Chen, R., Wong, W., Fitzgerald, P. B., & Daskalakis, Z. J. (2010). Reliability of long-interval cortical inhibition in healthy human subjects: a TMS-EEG study. *Journal of Neurophysiology*, *104*, 1339–1346.

Farzan, F., Barr, M. S., Wong, W., Chen, R., Fitzgerald, P. B., & Daskalakis, Z. J. (2009). Suppression of gamma-oscillations in the dorsolateral prefrontal cortex following long interval cortical inhibition: a TMS-EEG study. *Neuropsychopharmacology*, *34*, 1543–1551.

Farzan, F., Vernet, M., Shafi, M. M., 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*, 73.

Ferrarelli, F., Sarasso, S., Guller, Y., Riedner, B. A., Peterson, M. J., Bellesi, M., … Tononi, G. (2012). Reduced natural oscillatory frequency of frontal thalamocortical circuits in schizophrenia. *Archives of General Psychiatry*, *69*, 766–774.

Folstein, J. R., & Van Petten, C. (2008). Influence of cognitive control and mismatch on the N2 component of the ERP: a review. *Psychophysiology*, *45*, 152–170.

Foltys, H., Sparing, R., Boroojerdi, B., Krings, T., Meister, I. G., Mottaghy, F. M., & Topper, R. (2001). Motor control in simple bimanual movements: a transcranial magnetic stimulation and reaction time study. *Clinical Neurophysiology*, *112*, 265–274.

Garcia, J. O., Grossman, E. D., & Srinivasan, R. (2011). Evoked potentials in large-scale cortical networks elicited by TMS of the visual cortex. *Journal of Neurophysiology*, *106*, 1734–1746.

Gentner, R., Wankerl, K., Reinsberger, C., Zeller, D., & Classen, J. (2008). Depression of human corticospinal excitability induced by magnetic theta-burst stimulation: evidence of rapid polarity-reversing metaplasticity. *Cerebral Cortex*, *18*, 2046–2053.

George, M. S., Lisanby, S. H., Avery, D., McDonald, W. M., Durkalski, V., Pavlicova, M., … Sackeim, H. A. (2010). Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Archives of General Psychiatry*, *67*, 507–516.

George, M. S., Taylor, J. J., & Short, E. B. (2013). The expanding evidence base for rTMS treatment of depression. *Current Opinion in Psychiatry*, *26*, 13–18.

Goldsworthy, M. R., Pitcher, J. B., & Ridding, M. C. (2012). The application of spaced theta burst protocols induces long-lasting neuroplastic changes in the human motor cortex. *European Journal of Neuroscience*, *35*, 125–134.

Goldsworthy, M. R., Pitcher, J. B., & Ridding, M. C. (2013). Neuroplastic modulation of inhibitory motor cortical networks by spaced theta burst stimulation protocols. *Brain Stimulation*, *6*, 340–345.

Gramfort, A., Papadopoulo, T., Olivi, E., & Clerc, M. (2010). OpenMEEG: opensource software for quasistatic bioelectromagnetics. *Biomedical Engineering Online*, *9*, 45.

Haatveit, B. C., Sundet, K., Hugdahl, K., Ueland, T., Melle, I., & Andreassen, O. A. (2010). The validity of d prime as a working memory index: results from the "Bergen n-back task. *Journal of Clinical and Experimental Neuropsychology*, *32*, 871–880.

Hameed, M. Q., Dhamne, S. C., Gersner, R., Kaye, H. L., Oberman, L. M., Pascual-Leone, A., & Rotenberg, A. (2017). Transcranial magnetic and direct current stimulation in children. *Current Neurology and Neuroscience Reports*, *17*, 11.

Harrington, A., & Hammond-Tooke, G. D. (2015). Theta burst stimulation of the cerebellum modifies the TMS-Evoked N100 potential, a marker of GABA inhibition. *PLoS One*, *10*, e0141284.

Hedges, L. V., & Olkin, I. (1985). *Statistical methods for meta-analysis*. Orlando, FL: Academic Press.

Hill, A. T., Rogasch, N. C., Fitzgerald, P. B., & Hoy, K. E. (2016). TMS-EEG: A window into the neurophysiological effects of transcranial electrical stimulation in non-motor brain regions. *Neuroscience & Biobehavioral Reviews*, *64*, 175–184.

Hill, A. T., Rogasch, N. C., Fitzgerald, P. B., & Hoy, K. E. (2017). Effects of prefrontal bipolar and high-definition transcranial direct current stimulation on cortical reactivity and working memory in healthy adults. *Neuroimage*, *152*, 142–157.

Howard, M. W., Rizzuto, D. S., Caplan, J. B., Madsen, J. R., Lisman, J., Aschenbrenner-Scheibe, R., … Kahana, M. J. (2003). Gamma oscillations correlate with working memory load in humans. *Cerebral Cortex*, *13*, 1369–1374.

Hoy, K. E., Bailey, N., Michael, M., Fitzgibbon, B. M., Rogasch, N. C., Saeki, T., & Fitzgerald, P. B. (2016). Enhancement of working memory and task-related oscillatory activity following intermittent theta burst stimulation in healthy controls. *Cerebral Cortex*, *26*, 4563–4573.

Hsieh, L. T., & Ranganath, C. (2014). Frontal midline theta oscillations during working memory maintenance and episodic encoding and retrieval. *Neuroimage*, *85 Pt 2*, 721–729.

Hu, L., Mouraux, A., Hu, Y., & Iannetti, G. D. (2010). A novel approach for enhancing the signal-to-noise ratio and detecting automatically event-related potentials (ERPs) in single trials. *Neuroimage*, *50*, 99–111.

Huang, G., & Mouraux, A. (2015). MEP latencies predict the neuromodulatory effect of cTBS delivered to the ipsilateral and contralateral sensorimotor cortex. *PLoS One*, *10*, e0133893.

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*, 201–206.

Ilmoniemi, R. J., & Kicic, D. (2010). Methodology for combined TMS and EEG. *Brain Topography* , *22*, 233–248.

Jones, C. B., Lulic, T., Bailey, A. Z., Mackenzie, T. N., Mi, Y. Q., Tommerdahl, M., & Nelson, A. J. (2016). Metaplasticity in human primary somatosensory cortex: effects on physiology and tactile perception. *Journal of Neurophysiology*, *115*, 2681–2691.

Jung, J., Bungert, A., Bowtell, R., & Jackson, S. R. (2016). Vertex stimulation as a control site for transcranial magnetic stimulation: A concurrent TMS/fMRI study. *Brain Stimulation*, *9*, 58–64.

Kahkonen, 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 (Berl)*, *181*, 16–20.

Kahkonen, S., Wilenius, J., Nikulin, V. V., Ollikainen, M., & Ilmoniemi, R. J. (2003). Alcohol reduces prefrontal cortical excitability in humans: a combined TMS and EEG study. *Neuropsychopharmacology*, *28*, 747–754.

Koessler, L., Maillard, L., Benhadid, A., Vignal, J. P., Felblinger, J., Vespignani, H., & Braun, M. (2009). Automated cortical projection of EEG sensors: anatomical correlation via the international 10-10 system. *Neuroimage*, *46*, 64–72.

Kok, A. (2001). On the utility of P3 amplitude as a measure of processing capacity. *Psychophysiology*, *38*, 557–577.

Kopp, B., Rist, F., & Mattler, U. (1996). N200 in the flanker task as a neurobehavioral tool for investigating executive control. *Psychophysiology*, *33*, 282–294.

Korhonen, R. J., Hernandez-Pavon, J. C., Metsomaa, J., Maki, H., Ilmoniemi, R. J., & Sarvas, J. (2011). Removal of large muscle artifacts from transcranial magnetic stimulation-evoked EEG by independent component analysis. *Medical & Biological Engineering & Computing*, *49*, 397–407.

Kumpulainen, S., Mrachacz-Kersting, N., Peltonen, J., Voigt, M., & Avela, J. (2012). The optimal interstimulus interval and repeatability of paired associative stimulation when the soleus muscle is targeted. *Experimental Brain Research*, *221*, 241–249.

Larson, J., & Lynch, G. (1986). Induction of synaptic potentiation in hippocampus by patterned stimulation involves two events. *Science*, *232*, 985–988.

Larson, J., & Munkacsy, E. (2015). Theta-burst LTP. *Brain Research*, *1621*, 38–50.

Larson, J., Wong, D., & Lynch, G. (1986). Patterned stimulation at the theta frequency is optimal for the induction of hippocampal long-term potentiation. *Brain Research*, *368*, 347–350.

Li, C. T., Chen, M. H., Juan, C. H., Huang, H. H., Chen, L. F., Hsieh, J. C., … Su, T. P. (2014). Efficacy of prefrontal theta-burst stimulation in refractory depression: a randomized sham-controlled study. *Brain*, *137*, 2088–2098.

Lioumis, P., Kicic, D., Savolainen, P., Makela, J. P., & Kahkonen, S. (2009). Reproducibility of TMS-Evoked EEG responses. *Human Brain Mapping*, *30*, 1387–1396.

Lisman, J. (2010). Working memory: the importance of theta and gamma oscillations. *Current Biology*, *20*, R490–R492.

Lisman, J. E., & Jensen, O. (2013). The theta-gamma neural code. *Neuron*, *77*, 1002–1016.

Luscher, C., & Malenka, R. C. (2012). NMDA receptor-dependent long-term potentiation and long-term depression (LTP/LTD). *Cold Spring Harbor Perspectives in Biology*, *4*,

Machado, S., Arias-Carrion, O., Paes, F., Vieira, R. T., Caixeta, L., Novaes, F., … Nardi, A. E. (2013). Repetitive transcranial magnetic stimulation for clinical applications in neurological and psychiatric disorders: an overview. *The Eurasian Journal of Medicine*, *45*, 191–206.

Manza, P., Hau, C. L., & Leung, H. C. (2014). Alpha power gates relevant information during working memory updating. *Journal of Neuroscience*, *34*, 5998–6002.

Moliadze, V., Atalay, D., Antal, A., & Paulus, W. (2012). Close to threshold transcranial electrical stimulation preferentially activates inhibitory networks before switching to excitation with higher intensities. *Brain Stimulation*, *5*, 505–511.

Moore, R. A., Gale, A., Morris, P. H., & Forrester, D. (2008). Alpha power and coherence primarily reflect neural activity related to stages of motor response during a continuous monitoring task. *International Journal of Psychophysiology*, *69*, 79–89.

Mott, D. D., & Lewis, D. V. (1991). Facilitation of the induction of long-term potentiation by GABAB receptors. *Science*, *252*, 1718–1720.

Nahas, Z., Lomarev, M., Roberts, D. R., Shastri, A., Lorberbaum, J. P., Teneback, C., … Bohning, D. E. (2001). Unilateral left prefrontal transcranial magnetic stimulation (TMS) produces intensity-dependent bilateral effects as measured by interleaved BOLD fMRI. *Biological Psychiatry*, *50*, 712–720.

Nenert, R., Viswanathan, S., Dubuc, D. M., & Visscher, K. M. (2012). Modulations of ongoing alpha oscillations predict successful short-term visual memory encoding. *Frontiers in Human Neuroscience*, *6*, 127.

Nettekoven, C., Volz, L. J., Kutscha, M., Pool, E. M., Rehme, A. K., Eickhoff, S. B., … Grefkes, C. (2014). Dose-dependent effects of theta burst rTMS on cortical excitability and resting-state connectivity of the human motor system. *Journal of Neuroscience*, *34*, 6849–6859.

Nikulin, V. V., Kicic, D., Kahkonen, S., & Ilmoniemi, R. J. (2003). Modulation of electroencephalographic responses to transcranial magnetic stimulation: evidence for changes in cortical excitability related to movement. *European Journal of Neuroscience*, *18*, 1206–1212.

Noda, Y., Barr, M.S., Zomorrodi, R., Cash, R. F., Rajji, T. K., Farzan, F., … Blumberger, D. M. (2017). Reduced short-latency afferent inhibition in prefrontal but not motor cortex and its association with executive function in schizophrenia: a combined TMS-EEG study. *Schizophrenia Bulletin*, sbx041.

Noda, Y., Cash, R. F., Zomorrodi, R., Dominguez, L. G., Farzan, F., Rajji, T. K., … Blumberger, D. M. (2016). A combined TMS-EEG study of short-latency afferent inhibition in the motor and dorsolateral prefrontal cortex. *Journal of Neurophysiology*, *116*, 938–948.

O'Reardon, J. P., Cristancho, P., Pilania, P., Bapatla, K. B., Chuai, S., & Peshek, A. D. (2007). Patients with a major depressive episode responding to treatment with repetitive transcranial magnetic stimulation (rTMS) are resistant to the effects of rapid tryptophan depletion. *Depression and Anxiety*, *24*, 537–544.

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.

Otis, T. S., De Koninck, Y., & Mody, I. (1993). Characterization of synaptically elicited GABAB responses using patch-clamp recordings in rat hippocampal slices. *The Journal of Physiology*, *463*, 391–407.

Pacelli, G. J., Su, W., & Kelso, S. R. (1989). Activity-induced depression of synaptic inhibition during LTP-inducing patterned stimulation. *Brain Research*, *486*, 26–32.

Padberg, F., Zwanzger, P., Keck, M. E., Kathmann, N., Mikhaiel, P., Ella, R., … Moller, H. J. (2002). Repetitive transcranial magnetic stimulation (rTMS) in major depression: relation between efficacy and stimulation intensity. *Neuropsychopharmacology*, *27*, 638–645.

Paus, T., Castro-Alamancos, M. A., & Petrides, M. (2001). Cortico-cortical connectivity of the human mid-dorsolateral frontal cortex and its modulation by repetitive transcranial magnetic stimulation. *European Journal of Neuroscience*, *14*, 1405–1411.

Pedapati, E. V., Gilbert, D. L., Erickson, C. A., Horn, P. S., Shaffer, R. C., Wink, L. K., … Wu, S. W. (2016). Abnormal cortical plasticity in youth with autism spectrum disorder: A transcranial magnetic stimulation case-control pilot study. *Journal of Child and Adolescent Psychopharmacology*, *26*, 625–631.

Pedapati, E. V., Gilbert, D. L., Horn, P. S., Huddleston, D. A., Laue, C. S., Shahana, N., & Wu, S. W. (2015). Effect of 30 Hz theta burst transcranial magnetic stimulation on the primary motor cortex in children and adolescents. *Frontiers in Human Neuroscience*, *9*, 91.

Pellicciari, M. C., Ponzo, V., Caltagirone, C., & Koch, G. (2017a). Restored asymmetry of prefrontal cortical oscillatory activity after bilateral theta burst stimulation treatment in a patient with major depressive disorder: A TMS-EEG study. *Brain Stimulation*, *10*, 147–149.

Pellicciari, M. C., Veniero, D., & Miniussi, C. (2017b). Characterizing the cortical oscillatory response to TMS pulse. *Frontiers in Cellular Neuroscience*, *11*, 38.

Petrides, M., & Pandya, D. N. (2002). Comparative cytoarchitectonic analysis of the human and the macaque ventrolateral prefrontal cortex and corticocortical connection patterns in the monkey. *European Journal of Neuroscience*, *16*, 291–310.

Piccoli, T., Valente, G., Linden, D. E., Re, M., Esposito, F., Sack, A. T., & Di Salle, F. (2015). The default mode network and the working memory network are not anti-correlated during all phases of a working memory task. *PLoS One*, *10*, e0123354.

Plewnia, C., Pasqualetti, P., Grosse, S., Schlipf, S., Wasserka, B., Zwissler, B., & Fallgatter, A. (2014). Treatment of major depression with bilateral theta burst stimulation: a randomized controlled pilot trial. *Journal of Affective Disorders*, *156*, 219–223.

Prasser, J., Schecklmann, M., Poeppl, T. B., Frank, E., Kreuzer, P. M., Hajak, G., … Langguth, B. (2015). Bilateral prefrontal rTMS and theta burst TMS as an add-on treatment for depression: a randomized placebo controlled trial. *World Journal of Biological Psychiatry*, *16*, 57–65.

Premoli, I., Rivolta, D., Espenhahn, S., Castellanos, N., Belardinelli, P., Ziemann, U., & Muller-Dahlhaus, F. (2014). Characterization of GABAB-receptor mediated neurotransmission in the human cortex by paired-pulse TMS-EEG. *Neuroimage*, *103*, 152–162.

Rogasch, N. C., Daskalakis, Z. J., & Fitzgerald, P. B. (2013a). Mechanisms underlying long-interval cortical inhibition in the human motor cortex: a TMS-EEG study. *Journal of Neurophysiology*, *109*, 89–98.

Rogasch, N. C., Daskalakis, Z. J., & Fitzgerald, P. B. (2015). Cortical inhibition of distinct mechanisms in the dorsolateral prefrontal cortex is related to working memory performance: a TMS-EEG study. *Cortex*, *64*, 68–77.

Rogasch, N. C., Sullivan, C., Thomson, R. H., Rose, N. S., Bailey, N. W., Fitzgerald, P. B., … Hernandez-Pavon, J. C. (2017). Analysing concurrent transcranial magnetic stimulation and electroencephalographic data: a review and introduction to the open-source TESA software. *Neuroimage*.

Rogasch, N. C., Thomson, R. H., Daskalakis, Z. J., & Fitzgerald, P. B. (2013b). Short-latency artifacts associated with concurrent TMS-EEG. *Brain Stimulation*, *6*, 868–876.

Rogasch, N. C., Thomson, R. H., Farzan, F., Fitzgibbon, B. M., Bailey, N. W., Hernandez-Pavon, J. C., … 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.

Rousselet, G. A. (2012). Does filtering preclude us from studying ERP time-courses? *Frontiers in Psychology*, *3*, 131.

Ryals, A. J., Rogers, L. M., Gross, E. Z., Polnaszek, K. L., & Voss, J. L. (2016). Associative recognition memory awareness improved by theta-burst stimulation of frontopolar cortex. *Cerebral Cortex*, *26*, 1200–1210.

Sasaki, K., Gemba, H., & Tsujimoto, T. (1989). Suppression of visually initiated hand movement by stimulation of the prefrontal cortex in the monkey. *Brain Research*, *495*, 100–107.

Scharinger, C., Soutschek, A., Schubert, T., & Gerjets, P. (2017). Comparison of the working memory load in N-Back and working memory span tasks by means of EEG frequency band power and P300 amplitude. *Frontiers in Human Neuroscience*, *11*, 6.

Schmajuk, M., Liotti, M., Busse, L., & Woldorff, M. G. (2006). Electrophysiological activity underlying inhibitory control processes in normal adults. *Neuropsychologia*, *44*, 384–395.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., … 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. quiz 34–57.

Silvanto, J., Cattaneo, Z., Battelli, L., & Pascual-Leone, A. (2008). Baseline cortical excitability determines whether TMS disrupts or facilitates behavior. *Journal of Neurophysiology*, *99*, 2725–2730.

Suppa, A., Ortu, E., Zafar, N., Deriu, F., Paulus, W., Berardelli, A., & Rothwell, J. C. (2008). Theta burst stimulation induces after-effects on

contralateral primary motor cortex excitability in humans. *The Journal of Physiology*, *586*, 4489–4500.

Tadel, F., Baillet, S., Mosher, J. C., Pantazis, D., & Leahy, R. M. (2011). Brainstorm: a user-friendly application for MEG/EEG analysis. *Computational Intelligence and Neuroscience*, *2011*, 879716.

Taylor, P. C., Walsh, V., & Eimer, M. (2008). Combining TMS and EEG to study cognitive function and cortico-cortico interactions. *Behavioural Brain Research*, *191*, 141–147.

Thomson, R. H., Cleve, T. J., Bailey, N. W., Rogasch, N. C., Maller, J. J., Daskalakis, Z. J., & Fitzgerald, P. B. (2013). Blood oxygenation changes modulated by coil orientation during prefrontal transcranial magnetic stimulation. *Brain Stimulation*, *6*, 576–581.

Tsang, P., Jacobs, M. F., Lee, K. G., Asmussen, M. J., Zapallow, C. M., & Nelson, A. J. (2014). Continuous theta-burst stimulation over primary somatosensory cortex modulates short-latency afferent inhibition. *Clinical Neurophysiology*, *125*, 2253–2259.

Turrigiano, G. G., & Nelson, S. B. (2004). Homeostatic plasticity in the developing nervous system. *Nature Reviews Neuroscience*, *5*, 97–107.

van Ede, F., & Maris, E. (2016). Physiological plausibility can increase reproducibility in cognitive neuroscience. *Trends in Cognitive Sciences*, *20*, 567–569.

Vernet, M., Bashir, S., Yoo, W. K., Perez, J. M., Najib, U., & Pascual-Leone, A. (2013). Insights on the neural basis of motor plasticity induced by theta burst stimulation from TMS-EEG. *European Journal of Neuroscience*, *37*, 598–606.

Viejo-Sobera, R., Redolar-Ripoll, D., Boixados, M., Palaus, M., Valero-Cabre, A., & Marron, E. M. (2017). Impact of Prefrontal Theta Burst Stimulation on Clinical Neuropsychological Tasks. *Frontiers in Neuroscience*, *11*, 462.

Vogel, E. K., & Luck, S. J. (2000). The visual N1 component as an index of a discrimination process. *Psychophysiology*, *37*, 190–203.

Vossen, A., Gross, J., & Thut, G. (2015). Alpha power increase after transcranial alternating current stimulation at alpha frequency (alpha-tACS) reflects plastic changes rather than entrainment. *Brain Stimulation*, *8*, 499–508.

Wozniak-Kwasniewska, A., Szekely, D., Aussedat, P., Bougerol, T., & David, O. (2014). Changes of oscillatory brain activity induced by repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex in healthy subjects. *Neuroimage*, *88*, 91–99.

Xu, G., Lan, Y., Huang, D., Chen, S., Chen, L., Zeng, J., & Pei, Z. (2013). The study on the frontoparietal networks by continuous theta burst stimulation in healthy human subjects. *Behavioural Brain Research*, *240*, 60–68.

Yeterian, E. H., Pandya, D. N., Tomaiuolo, F., & Petrides, M. (2012). The cortical connectivity of the prefrontal cortex in the monkey brain. *Cortex*, *48*, 58–81.

Zheng, C., & Zhang, T. (2015). Synaptic plasticity-related neural oscillations on hippocampus-prefrontal cortex pathway in depression. *Neuroscience*, *292*, 170–180.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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Supplementary Material

Results

SNR analysis

Table S1 shows the SNR of single-pulse TMS before and after different iTBS conditions. Mean SNR values were averaged across individual for grand average values. Values greater than 3 SDs (99.7% of the baseline distribution) are considered as good SNR. Qualitatively only N45 peaks showed moderate values (~2.5 SDs), but other peaks, especially latter peaks (N100 and P200) showed excellent SNR.

Table S1. Signal-to-noise ratio (SNR) of each peak before (BL), 5-min post (T5) and 30-min post (T30) stimulation (mean ± SD)

	50% iTBS			**75% iTBS**			**100% iTBS**		
	BL	T5	T40	BL	T5	T30	BL	T5	T30
N45	2.53 (±1.82)	2.42 (±2.57)	2.43 (±1.83)	2.58 (±2.01)	2.64 (±3.26)	2.38 (±2.07)	2.51 (±2.05)	2.67 (±1.80)	2.55 (±1.72)
P60	3.33 (±2.32)	3.45 (±2.07)	3.27 (±1.11)	3.19 (±1.93)	3.37 (±1.91)	3.17 (±2.27)	3.39 (±2.40)	3.25 (±2.22)	3.08 (±1.85)
N100	9.98 (±5.16)	11.22 (±5.96)	9.29 (±5.19)	9.18 (±5.62)	12.35 (±4.86)	9.64 (±4.31)	10.03 (±4.41)	9.59 (±4.13)	9.29 (±4.10)
P200	11.33 (±4.85)	12.96 (±7.67)	11.27 (±6.56)	10.66 (±2.69)	11.13 (±3.73)	10.56 (±4.63)	11.27 (±6.05)	10.71 (±4.90)	11.32 (±5.35)

Correlational analyses between Δ gamma and Δ TEPs

A recent study using prefrontal-parietal paired associative stimulation (PAS) protocol demonstrated increased cortical responses to TMS-induced plastic effects in subjects with higher gamma power (Casula et al., 2016a), and we explored whether observed gamma power had any relationship with each peak of interest. Spearman's rank correlation revealed significant correlations between Δ gamma and Δ P60 (T5: r = 0.353, p = 0.014) (Fig S2A) and Δ N100 (T5: r = -0.347, p = 0.016; T30: r = -0.326, p = 0.024) (Fig S1B & C), and between Δ theta and Δ P200 (T5: r = 0.597, p = 0.001) (Fig S1D), but not with Δ N45 (all p > 0.05). These findings indicate increased amplitude of multiple peaks are associated with stronger oscillatory activity in either theta or gamma range. This is in agreement with previous findings for PAS, but also demonstrates the specificity to theta and gamma for iTBS.

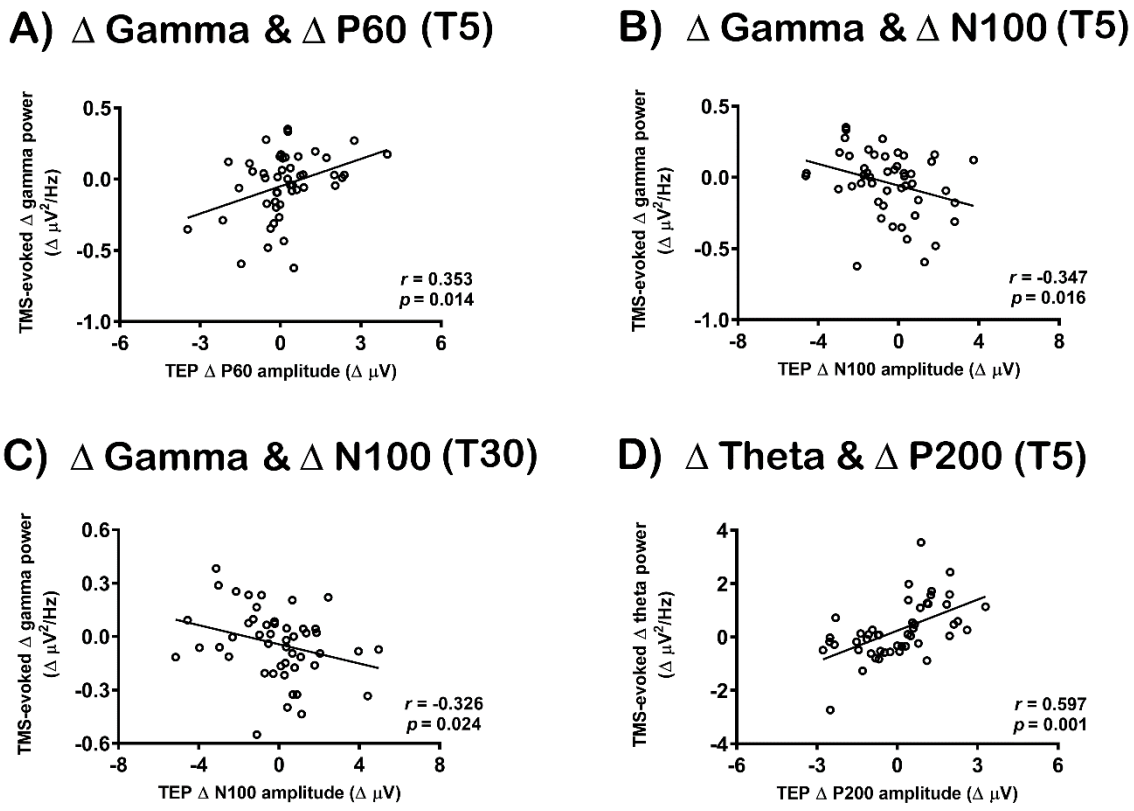

Figure S1. Correlation between iTBS-induced changes in TMS-evoked gamma power and TMS-evoked potentials (TEPs) (A) P60 at T5, (B) N100 at T5 and (C) N100 at T30, and (D) between TMS-evoked theta power and TEP P200.

Neurophysiology of different working memory load

Event-related potentials (ERPs)

In order to establish the effect of memory load on the ERPs in our dataset, each task performed before iTBS (BL) was combined across sessions (n = 45) and the amplitude of ERPs during 2-back and 3-back tasks were compared. Visual representations during 2-back and 3-back tasks resulted in a series of consistent negative [N100 (~90 ms) – associated with discrimination processing (Itier and Taylor, 2004); N200 (~215 ms) – attention and inhibition (Coull, 1998; Kopp et al., 1996)] and positive peaks [P150 (~145 ms) – associated with perceptual priming mechanism (Gosling et al., 2016); P300 (~350 ms) – availability of processing resources (McEvoy et al., 1998)] at FCz electrode (Fig S2A). Cluster-based statistics across space revealed significant differences around these peaks [N100 (3-back < 2-back) over left fronto-temporal (p = 0.002) and right posterior sensors (p = 0.002); P150 (3-back > 2-back) over anterior (p = 0.0004) and posterior sensors (p = 0.002); N200 (3-back > 2-back) over anterior (p = 0.002) and posterior sensors (p = 0.016); P300 (3-back < 2-back) over fronto-central sensors (p = 0.003)] (Fig S2A).

Event-related oscillations

To test if the power of these frequencies differed based on memory load, BL measures were again combined across sessions (n = 45) and the power of theta and gamma bands was compared between 2-back and 3-back task. As N-back task involves continuous mix of encoding, updating and maintaining of the letters, we divided each trial into two blocks – during letter presentation (50 – 450 ms: encoding) and after letter presentation (550 – 950 ms: maintenance).

During letter presentation, cluster-based permutation tests revealed an increase in theta power over left frontal sensors (p = 0.024), and in gamma power over frontal (p = 0.0004) and posterior sensors (p = 0.0004) in 3-back compared to 2-back conditions (Fig S2B). After letter presentation, more prominent increases were observed in theta power (p = 0.022, left frontal; p = 0.002, posterior) in 3-back conditions, whereas less pronounced increases were also observed in gamma power (p = 0.030, right frontal; p = 0.038, left posterior) (Fig S2B).

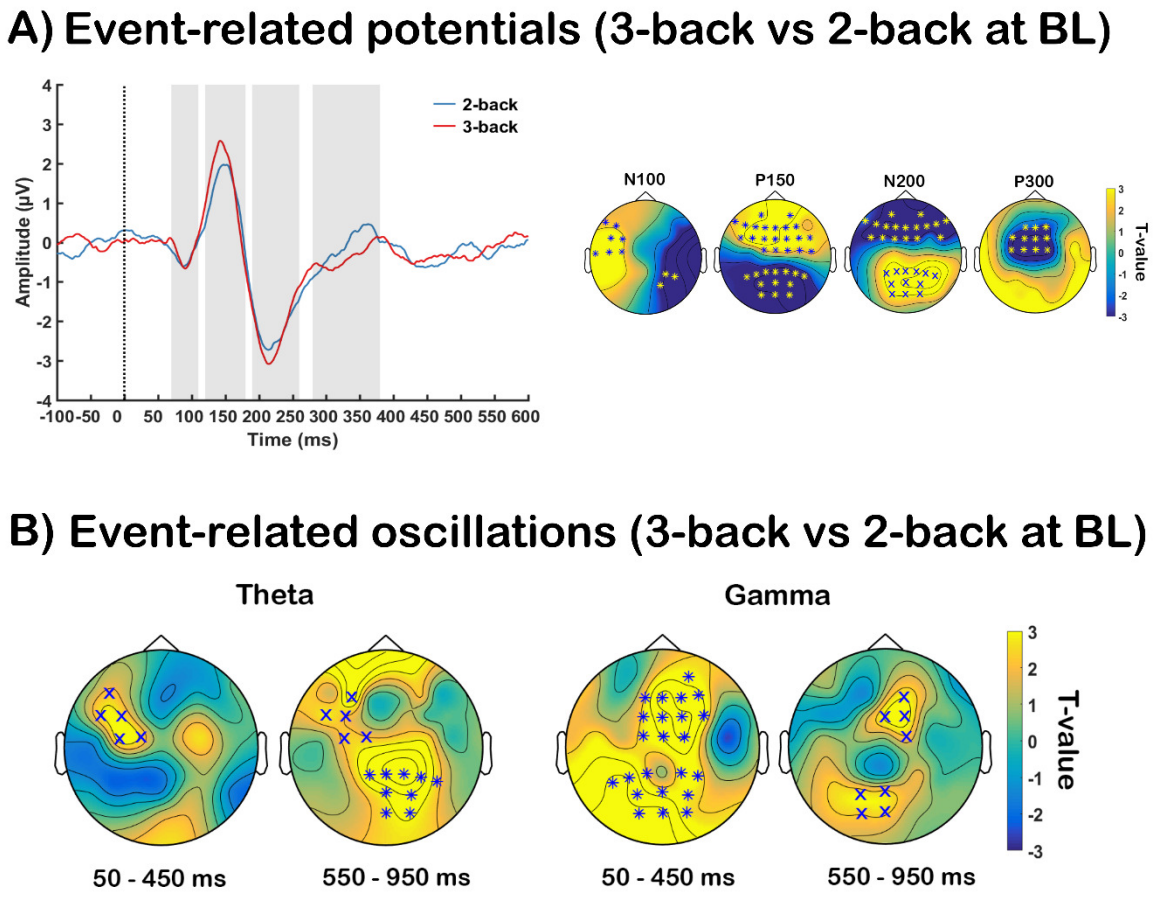

Figure S2. Comparison of event-related potentials and oscillations between different memory loads during working memory tasks at baseline (BL). (A) Grand average ERP waveforms at FCz electrode and (B) differences in theta and gamma power between 2-back (blue) and 3-back (red) tasks before iTBS, with significant differences across the scalp illustrated in topoplots. Asterisks and 'X's on topoplots indicate significant clusters between comparisons (cluster-based statistics, $*p < 0.01$, $^{X}p < 0.05$).

Assessment of carryover effect

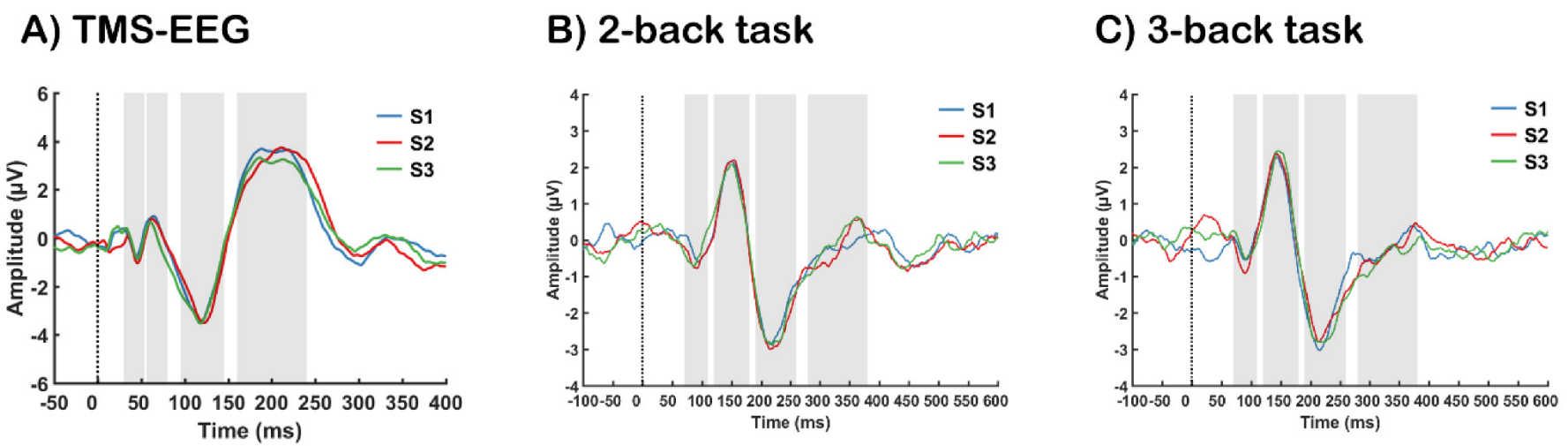

Figure S3. Assessment of carryover effect. Grand average waveforms at baseline using FCz electrode for (A) TMS-EEG, (B) 2-back task and (C) 3-back task at baseline in the order of session (S1 – 3: Session 1 – 3).

Addition of sham condition

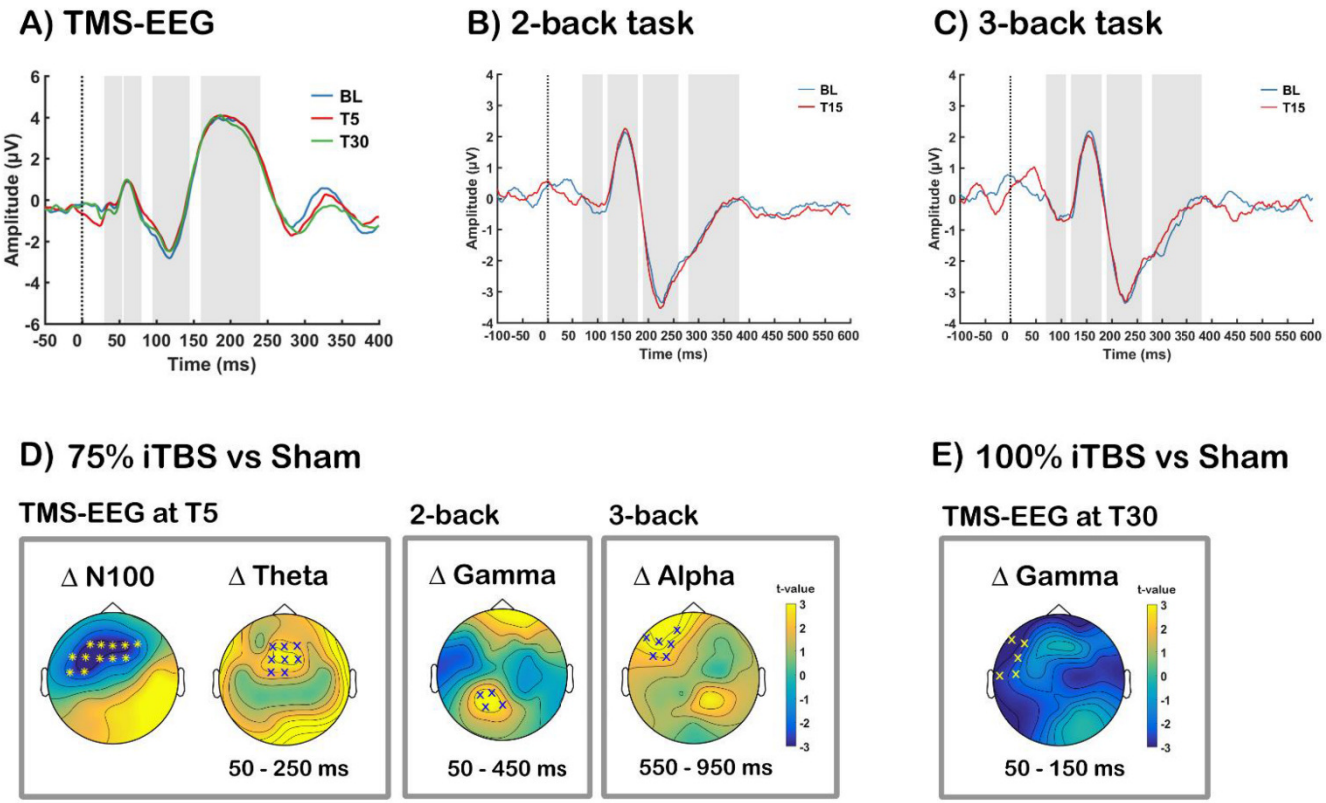

Figure S4. Assessment of sham iTBS and comparison to active conditions. Grand average waveforms at FCz electrode for (A) TMS-EEG, (B) 2-back task and (C) 3-back task across time show no significant differences following sham control stimulation in comparison to baseline. Comparison of sham with active iTBS revealed further evidence for significant global scalp differences whereby (D) 75% iTBS showed greater change in TMS-evoked N100 and theta power, 2-back task related gamma and 3-back task related alpha power. Additionally, (E) 100% iTBS showed reduced TMS-evoked gamma power compared to sham. Asterisks and 'X's on topoplots indicate significant clusters between comparisons (cluster-based statistics, *$p < 0.01$, X$p < 0.025$).

References

Casula, E.P., Pellicciari, M.C., Picazio, S., Caltagirone, C., Koch, G., 2016. Spike-timing-dependent plasticity in the human dorso-lateral prefrontal cortex. Neuroimage 143, 204-213.

Coull, J.T., 1998. Neural correlates of attention and arousal: insights from electrophysiology, functional neuroimaging and psychopharmacology. Prog Neurobiol 55, 343-361.

Gosling, A., Thoma, V., de Fockert, J.W., Richardson-Klavehn, A., 2016. Event-Related Potential Effects of Object Repetition Depend on Attention and Part-Whole Configuration. Front Hum Neurosci 10, 478.

Itier, R.J., Taylor, M.J., 2004. N170 or N1? Spatiotemporal differences between object and face processing using ERPs. Cereb Cortex 14, 132-142.

Kopp, B., Rist, F., Mattler, U., 1996. N200 in the flanker task as a neurobehavioral tool for investigating executive control. Psychophysiology 33, 282-294.

McEvoy, L.K., Smith, M.E., Gevins, A., 1998. Dynamic cortical networks of verbal and spatial working memory: effects of memory load and task practice. Cereb Cortex 8, 563-574.

CHAPTER TEN

Effect of repeated application of iTBS in the prefrontal cortex

Chung SW, Rogasch NC, Hoy KE, Fitzgerald PB. 2017. The effect of single and repeated prefrontal intermittent theta burst stimulation on cortical reactivity and working memory.

Preamble to empirical paper

The results from Chapter 9 provide the evidence that more may not always be better, with intermediate stimulation intensity of iTBS (75% resting motor threshold) showing the strongest physiological changes in the prefrontal cortex, and improved accurate reaction time in the 3-back task compared to sham stimulation. In particular, changes in TMS-evoked N100, TMS-evoked theta and gamma power were differentially modulated by the intensity of stimulation, supporting the results of the previous study (Chapter 8) that these indices are useful in determining the efficacy of stimulation. However, only a marginal differences in working memory performance was observed between active stimulation conditions possibly due to a ceiling effect in healthy individuals. Having established the optimal intensity of stimulation for the subsequent studies, second optimisation step of repeated application of iTBS followed. Studies in the motor cortex have demonstrated a more robust change in MEPs of TBS following repeated applications (cTBS (Goldsworthy et al., 2012a), iTBS (Nettekoven et al., 2014)), however, these findings have been contradicted by others (Gamboa et al., 2010; Murakami et al., 2012). In clinical settings, prefrontal TBS is often delivered in multiple blocks (Bakker et al., 2015; Desmyter et al., 2016; Duprat et al., 2016)

with the assumption that more pulses will lead to greater efficacy. A systematic comparison of single and repeated application of iTBS in the prefrontal cortex has not been conducted in either healthy or clinical population. In the following paper, the same method of measuring iTBS-induced changes in TMS-evoked activity and working memory performance was adopted as Chapter 9. It was predicted that the repeated application of iTBS would result in greater changes in the electrophysiological measures, particularly in N100 amplitude. It was also anticipated that such changes would lead to improved working memory performance surpassing sham and a single iTBS application.

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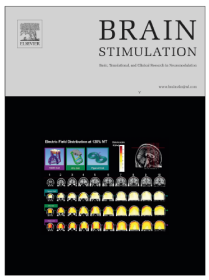

The effect of single and repeated prefrontal intermittent theta burst stimulation on cortical reactivity and working memory

Sung Wook Chung, Nigel C. Rogasch, Kate E. Hoy, Paul B. Fitzgerald

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The effect of single and repeated prefrontal intermittent theta burst stimulation on cortical reactivity and working memory

Sung Wook Chung[1]
Nigel C. Rogasch[2]
Kate E. Hoy[1]
Paul B. Fitzgerald[1, 3]

1. Monash Alfred Psychiatry Research Centre, Monash University, Central Clinical School and The Alfred, Melbourne, Australia

2. Brain and Mental Health Laboratory, School of Psychological Sciences and Monash Biomedical Imaging, Monash Institute of Cognitive and Clinical Neuroscience, Monash University, Melbourne, Australia

3. Epworth Clinic, Epworth Healthcare, Camberwell VIC, Australia

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Correspondence: Sung Wook Chung
Monash Alfred Psychiatry Research Centre
[redacted]

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Abstract

Background: With an increasing interest in the use of theta burst stimulation (TBS) as a cognitive enhancer and a potential therapeutic tool for psychiatric disorders, there is a need to identify optimal parameters of TBS in the prefrontal cortex.

Objective/Hypothesis: This study examined the effect of two blocks of prefrontal intermittent TBS (iTBS) on cortical reactivity and working memory performance, compared to one block of iTBS and sham stimulation. We hypothesized that greater cortical effects would be obtained with two blocks of iTBS.

Methods: Eighteen healthy participants attended three experimental sessions and received either sham, one block or two blocks of iTBS with a 15-min interval. Concurrent transcranial magnetic stimulation with electroencephalography (TMS-EEG) was used to assess the change in cortical reactivity via TMS-evoked potentials. Working memory performance was assessed using the N-back task. Cluster-based permutation statistics and two-way ANOVAs were used for neurophysiological and behavioural data, respectively.

Results: Both single and two blocks of iTBS resulted in a significant increase in the amplitude of TMS-evoked N100 and P200. No significant differences were observed between active conditions in either neurophysiological changes or working memory performance, and both failed to improve working memory performance relative to sham.

Abbreviations: Ag/AgCl, silver-silver chloride; EEG, electroencephalography; ERP, event-related potential; FDI, first dorsal interosseous; ICA, independent component analysis; LICI, long-interval intracortical inhibition; MEP, motor evoked potential; MNE, minimum norm estimates; rMT, resting motor threshold; SH, sham; SNR, signal-to-noise ratio; (c/i) TBS, (continuous/intermittent) theta burst stimulation; TEP, TMS-evoked potential; TMS, transcranial magnetic stimulation

Conclusions: Two blocks of iTBS did not result in stronger measured effects as compared to one block of iTBS. Future studies are needed to identify the optimal stimulation pattern in order to achieve a desired effect. It is also important to establish the best approach in quantifying neuromodulatory effects targeting the prefrontal cortex.

Key words: theta burst stimulation, TMS-EEG, repeated blocks, prefrontal cortex, working memory

Abbreviations: Ag/AgCl, silver-silver chloride; EEG, electroencephalography; ERP, event-related potential; FDI, first dorsal interosseous; ICA, independent component analysis; LICI, long-interval intracortical inhibition; MEP, motor evoked potential; MNE, minimum norm estimates; rMT, resting motor threshold; SH, sham; SNR, signal-to-noise ratio; (c/i) TBS, (continuous/intermittent) theta burst stimulation; TEP, TMS-evoked potential; TMS, transcranial magnetic stimulation

1. Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive technique used to study the physiology of the human brain. Theta-burst stimulation (TBS) is one TMS paradigm, which has a major advantage over conventional repetitive TMS due to its short stimulation duration (20 – 192s vs >20min). An intermittent pattern of TBS (iTBS; 2s on, 8s off, 600 pulses) increases the amplitude of motor-evoked potentials (MEPs), while a continuous pattern of TBS (cTBS, 600 pulses) results in the opposite outcome [1]. Efforts have been made to understand the mechanisms involved in the neuroplastic responses to TBS and to enhance the efficacy of TBS in the motor cortex by varying the parameters of stimulation such as intensity [2], frequency [3-4] and number of pulses [5-7]. Studies have found additive after-effects following repeated applications of cTBS [6] and iTBS [7]. However, these dose-dependent findings are not consistent, and reduced [8] or even the opposite effects [5] have been reported depending on the duration of the interval between each block. These findings suggest the after-effects of TBS may not simply be accumulative. Beyond the motor cortex, there is a paucity of information on the neurophysiological basis of the effects of TBS and the impact of different stimulation parameters on the after-effect. Studies have reported that TBS to the prefrontal cortex can affect cognitive function. For example, prefrontal iTBS has resulted in enhanced working memory performance [9], whereas cTBS has resulted in the opposite outcome [10]. However, such findings are also inconsistent with limited behavioural changes [11-12]. It remains to be determined if repeated application of TBS would promote physiological changes in a dose-dependent manner in the prefrontal cortex, and whether such changes would also result in concurrent behavioural outcomes.

TBS-induced changes in the prefrontal cortex can be probed using concurrent TMS and electroencephalography (TMS-EEG) by examining the changes in TMS-evoked potentials (TEPs) [13]. For instance, iTBS to the prefrontal cortex increases the amplitude of the TMS-evoked N100 [13].

In the present study, we examined whether there were differences in the effects of repeated iTBS stimulation blocks applied to the left prefrontal cortex on cortical reactivity and working memory performance. The experimental procedure involved comparing the effect of two blocks (600 pulses x 2, 15-min interval) of prefrontal iTBS to one block (600 pulses) and sham stimulation on TEPs. The impact of iTBS on working memory performance and task-related electrophysiology (event-related potentials (ERPs)) were also examined. We hypothesized that greater changes in these measures would be obtained with the repeated stimulation blocks/increased number of pulses, and lead to improved working memory performance compared to the application of a single iTBS block or sham stimulation.

2. Material and methods

2.1. Participants

Eighteen healthy subjects volunteered (25.6 ± 7.0 years, 10 female) in the study. All subjects were right-handed according to the Edinburgh Handedness Inventory [14], and average education duration was 16.5 ± 2.3 years. Prior to the experiment, volunteers provided informed consent and were screened with the mini international neuropsychiatric interview (MINI) to confirm no history of mental illness [15]. The experimental procedures were approved by the Alfred Hospital and Monash University Human Research Ethics Committees.

2.2. Procedure

Each participant attended 3 sessions with each session at least 1 week apart to avoid carry-over effect. Stimulation conditions were pseudorandomized. The experimental procedures consisted of concurrent recording of EEG during 50 single TMS pulses before (baseline; BL), 5-min post (T5) and 30-min post (T30) iTBS in the prefrontal cortex. Subjects received either sham stimulation (sham iTBS + sham iTBS; SH+SH), a single block of iTBS (sham iTBS + iTBS 600; SH+iTBS) or two blocks of iTBS (iTBS 600 + iTBS 600; iTBS+iTBS) with 15-min interval between each block of iTBS (Fig 1A). This interval was chosen based on studies that demonstrated the additive effects of TBS when reapplied after 15 minutes in animals [16] and humans [7, 17]. Discomfort level was assessed using 10cm length numerical rating scale (0: No pain – 10: Worst pain) before the first block of iTBS (at BL) and immediately after the second block. The N-back working memory task (2-back and 3-back) was performed before (BL), 15-min post (T15) and 40-min post (T40) iTBS while EEG was recording. Alertness was also measured using 10cm numerical rating scale (0: Alert – 10: Vague) at BL and T40 following working memory tasks to assess attention level.

Insert Figure 1 Here

2.3. Transcranial magnetic stimulation

Biphasic TMS pulses (AP-PA current direction in the underlying cortex) were delivered using a figure-of-eight MagVenture B-65 fluid-cooled coil (MagVenture A/S, Denmark) for both single-pulse TMS and iTBS. Resting motor threshold (rMT) was obtained from left motor cortex and identified as the minimum intensity needed to evoke at least 3 out of 6 motor evoked potentials (MEPs) > 0.05mV in amplitude [18] recorded from the first dorsal interosseous muscles using Ag/AgCl electromyography electrodes. TMS was administered to the left prefrontal cortex at the F1 electrode with the coil positioned at 45° angle relative to midline. This electrode was chosen to minimize the activation of scalp muscles [19], and hence reduce the need for the amount of correction in post-processing of the TMS-EEG data. The edge of the coil was marked on the cap for reliable repositioning of the coil (~5mm) as has been described as a suitable method when neuronavigation is unavailable [19].

50 single pulses with a 5s interval (10% jitter) were applied to the same left prefrontal region at 120% rMT before and after spaced iTBS. Studies have shown reliable TMS-evoked responses with 50 TMS pulses at supra-threshold intensities [13, 20] and a high signal-to-noise ratio (SNR) was obtained particularly for latter peaks (N100 and P200) [13]. Each iTBS block consisted of a burst of 3 pulses (20ms interval) repeated every 200ms for 2s with an 8s break for a total of 600 pulses, given at an intensity of 75% rMT. The rMT was measured on each session, and the average intensity for each condition was as follows: SH+SH: 54.28 ± 6.5%; SH+iTBS: 54.39 ± 6.6%; and iTBS+iTBS: 54.33 ± 6.9%. The rMT for each individual at each session can be found in Supplementary Material, Table S1. The

average of coefficient of variation for rMT between session was 1.14% (range: 0 – 3.03%). For sham iTBS, the coil was rotated 90° around the handle so that the right wing was touching the F1 electrode. In this position, the magnetic field is tangential to the scalp and does not result in cortical stimulation.

2.4. Working memory performance (N-back tasks)

Participants performed 5min of both the 2-back and 3-back task in a pseudorandomised (e.g. either 2-back followed by 3-back or vice versa) at three time points during each experimental session. A random series of white letters from A to J were presented for 500ms every 2000ms on a black screen in a consecutive manner. Participants were required to respond with a button press when the presented letter corresponded to the letter that appeared either 2 (Fig 1B) or 3 trials before (Fig 1C). Each task contained 130 trials with 25% targets. Working memory performance was assessed using *d* prime (*d'*) and accurate reaction time. *d'* quantifies performance with regards to hits and false alarms (*d'*=*Z* (hit rate)–*Z* (false alarm rate)) [21].

2.5. EEG recording and data preprocessing

A detailed procedure for the recording and preprocessing of the EEG data can be found in Supplementary Material, Methods section 1 & 2. Briefly, EEG was recorded using 48 TMS-compatible Ag/AgCl electrodes on a 64-channel EEG cap, referenced to CPz and grounded to FPz. The sampling rate for TMS-EEG and N-back task were 10,000 Hz and 1000 Hz, respectively. Electrode impedance was kept below 5 kΩ and white noise was used to mask TMS click sound.

TMS-EEG data: Data were epoched around the TMS pulse, baseline corrected, and the TMS pulse artefact was removed and interpolated. Data were downsampled and were visually inspected for

104 excessive noise in the signal. Two rounds of independent component analysis (FastICA) was used to
105 remove non-neural components using TESA toolbox [22]. Filters were applied between the two
106 FastICAs.

107 *N-back EEG data*: Continuous data were filtered, epoched around correctly encoded and maintained
108 trials and baseline corrected. Data were concatenated across epochs from three time points (BL, T15,
109 T40) and underwent preprocessing steps with only one round of ICA.

110 For all EEG data, any removed channels were interpolated and data were re-referenced to common
111 average reference. The averaged evoked potentials were analysed separately for each time point
112 (TMS-EEG: BL, T5, T30; N-back: BL, T15, T40).

113

114 *2.6. TMS-evoked potentials (TEPs) and event related potentials (ERPs) during N-back tasks*

115 Both TEPs and ERPs were analysed using cluster-based permutation statistics at a global scalp level.
116 Pre-determined time window for each peak of interest was used for TEPs [N45 (35-55 ms), P60 (55-
117 80ms), N100 (95-135ms) and P200 (160-240ms)] and ERPs [N100 (75-125ms), P150 (125-175ms),
118 N200 (190-260ms) and P300 (280-380ms)], and data were averaged across time prior to the
119 statistical comparisons across the scalp. These peaks are commonly described in the literature (TEPs
120 [13, 20, 23-24]; ERPs [25-27]). The waveforms were graphically represented using the average of 3
121 fronto-central electrodes (FC1, FCz and FC2), as these electrodes were close to the site of stimulation,
122 and electrodes in contact with the MagVenture coil contain unwanted artefacts [19]. Source
123 estimation was computed using Brainstorm software [28] (Supplementary Material, Methods
124 section 3). An SNR analysis was conducted on these electrodes to verify the number of pulses
125 included in the study (~48 pulses) was adequate. The SNR was determined by dividing the amplitude
126 of peaks by the standard deviation (SD) of the signals in the pre-stimulus duration (-500 to -50ms)
127 [13, 29].

2.7. *Statistics*

Statistical analysis was performed in SPSS (Version 22) and Matlab. Non-parametric cluster-based permutation statistics were used for the analysis of all electrophysiological data at a global scalp level, which provides a robust method of controlling for multiple comparisons in space (EEG electrodes) and time [30]. Within-condition comparisons were first assessed for each TBS condition over time (between BL and T5/T30 for TMS-EEG, between BL and T15/T40 for N-back EEG). Between-condition comparisons were then investigated using the change-from-baseline scores following iTBS (post–pre; Δ). Monte Carlo *p*-values were calculated on 2500 randomizations and a value of $p<0.05$ was used as the cluster statistical significance for two or more neighbouring electrodes for all analyses, controlling for multiple comparisons across space and time ($p<0.025$; two-tailed test).

For behavioural measures, repeated measure 3 (time: BL, T15 and T40) x 3 (stimulation conditions – SH+SH, SH+iTBS and iTBS+iTBS) analysis of variance (ANOVAs) were conducted for working memory performance in *d'* and accurate reaction time, and 2 (time: BL and T40) x 3 (stimulation conditions) ANOVAs for numeric ratings. Pearson's correlations were used to assess the relationship between the changes in TMS-evoked activities, N-back task related electrophysiology and working memory performances.

3. Results

3.1. Tolerability of iTBS

Subjects reported no side-effects, such as headaches or dizziness. The average pain rating (0: No pain – 10: Worst pain) in the stimulated area for each condition were as follows (pre & post): SH+SH: 0.14 ± 0.3 & 0.22 ± 0.6; SH+iTBS: 0.38 ± 0.8 & 0.54 ± 1.5; iTBS+iTBS: 0.73 ± 1.3 & 0.58 ± 0.9. Repeated measures ANOVA showed no significant main effect of condition ($F_{2,34}$=1.958, p=0.157), time ($F_{1,17}$=0.072, p=0.791), nor interaction ($F_{2,34}$=0.370, p=0.694). Overall, iTBS was safe with negligible pain rating.

3.2. Single-pulse TMS

Figure 2 illustrates an overview of TEP waveforms following single-pulse TMS over left prefrontal cortex (F1 electrode, marked as 'X' on topoplots) and the estimated source of the peaks of interest (N45, P60, N100 and P200). The waveform, scalp topography and source estimation were consistent with other TMS-EEG studies in the prefrontal cortex [13, 20, 24].

Insert Figure 2 Here

The SNR of single-pulse TMS included in the analyses can be found in the Supplementary Material, Table S2. Qualitatively N45 and P60 peaks displayed a moderate-to-good SNR, but N100 and P200 exhibited excellent SNR.

3.3. The effect of spaced iTBS on TMS-evoked activity

The aftereffects of iTBS were first assessed by comparing the amplitude of TEPs over time in each stimulation condition. Testing for an N100 effect in the pre-defined latency range (as stated in section 2.7), the cluster-based permutation tests revealed significant differences between pre-iTBS (BL) and 5-min post iTBS (T5) following SH+iTBS (p=0.003; Fig 3A), and between BL and 30-min post iTBS (T30) following iTBS+iTBS (p=0.008; Fig 3B), which were observed in fronto-central sensors.

For P200, significant differences were found between BL and T5 (p=0.007), and between BL and T30 for SH+iTBS (p=0.023), whereas a significant difference was found between BL and T5 (p=0.011) and a trend between BL and T30 (p=0.032) for iTBS+iTBS. These differences were most pronounced over fronto-central sensors. No significant changes were observed in SH+SH condition for any peaks (p>0.025; Fig 3C), and no other peaks showed any significant changes in any of the conditions (all p>0.025).

For comparison across conditions, we calculated the iTBS-induced changes in TEP amplitude by subtracting pre-signals (BL) from post-signals (T5 and T30) (change-from-baseline scores; Δ) and compared Δ between each stimulation condition. We found that ΔN100 and ΔP200 were larger following SH+iTBS than SH+SH (N100: SH+iTBS > SH+SH – T5, p=0.006; T30, p=0.012; P200: SH+iTBS > SH+SH – T30, p=0.012), which was observed in fronto-central sensors (Fig 3D). The comparisons between iTBS+iTBS and SH+SH in ΔN100 and ΔP200 were trending towards significance (N100: iTBS+iTBS > SH+SH – T5, p=0.048; T30, p=0.053; P200: SH+iTBS > SH+SH – T5, p=0.052). No significant differences in iTBS-induced change were observed between SH+iTBS and iTBS+iTBS conditions (all p>0.025).

A power analysis was performed on ΔN100 and ΔP200 to determine if the current study was powered to detect subtle differences between two active conditions using G*Power software [7]. A large effect size was required for the detection of differences, which was not present in the

comparison between active conditions (Supplementary Material, Fig S1). In order to obtain power of 0.80 with an alpha of 0.025 for the active condition comparisons, 865 and 495 subjects would be required for ΔN100 at T5 and T30, respectively. For ΔP200, 557 subjects would be needed for T5 and 76 for T30.

The change in N100 and P200 were examined at a single-subject level to determine whether variability in response to stimulation had an impact on the TMS-EEG results (Supplementary Material, Fig S2). The majority of the subjects responded in one direction (i.e. increased amplitude) following active iTBS conditions whereas such specific directional change was not present following the sham condition (Supplementary Material, Fig S3 & Table S3).

Insert Figure 3 Here

3.4. The effect of spaced iTBS on neurophysiology during N-back tasks

During the 2-back task, we were unable to detect any significant changes in event-related potentials (ERPs) following any iTBS condition (all $p>0.025$) (Supplementary Material, Fig S4). However, during the 3-back task, the amplitude of N200 increased following both SH+iTBS ($p=0.009$, frontal; $p=0.022$, posterior; Fig 4A) and iTBS+iTBS ($p=0.008$, frontal; Fig 4B) at T15. No significant differences were seen in any other peaks, and SH+SH condition did not alter the amplitude of any peak (Fig 4C) (all $p>0.025$).

For the comparison across conditions, ΔN200 was larger following both SH+iTBS ($p=0.002$) and iTBS+iTBS ($p=0.016$) compared to SH+SH at T15, and the differences were most pronounced over

fronto-central sensors (Fig 4A & 4B). No significant differences were observed between SH+iTBS and iTBS+iTBS in any peak (all p>0.025).

Insert Figure 4 Here

3.5. The link between TEP N100 and ERP N200

TMS-evoked N100 [13, 23, 31] and task-related N200 [32-33] have been linked to inhibitory processing. These peaks were strongly modulated by active iTBS conditions, and therefore, we conducted exploratory correlation analyses between TMS-evoked ΔN100 (T5 & T30) and ERP ΔN200 during 3-back task (T15 & T40). Significant correlations were observed between the two different measures in SH+iTBS condition (T5/T15: r=0.663, p=0.003; T30/T40: r=0.607, p=0.008), a trend toward significance in iTBS+iTBS (T5/T15: r=0.430, p=0.075) and no significance in sham condition (p>0.05) (Supplementary Material, Fig S5).

3.6. The effect of spaced iTBS on working memory performance

We first conducted order effect analysis to confirm the effectiveness of the counter-balancing of stimulation conditions. One-way repeated measures ANOVA showed no significant session effects in either accuracy (d' – 2-back: $F_{2,34}$=0.477, p=0.625; 3-back: $F_{2,34}$=0.180, p=0.836) or accurate reaction

time (2-back: $F_{2,34}$=0.758, p=0.476; 3-back: $F_{2,34}$=0.259, p=0.774) for both working memory tasks at baseline measure.

Mean *d'*, accurate reaction time and the effect sizes for 2-back and 3-back tasks before and after each stimulation condition can be found in Supplementary Material, Table S4 and S5. A significant overall improvement in *d'* was seen for both the 2-back (Fig 5A) and 3-back (Fig 5B) tasks with no differences between the groups (no main effect of condition or interaction). In addition, no significant effect of iTBS on alertness rating was observed (Fig 5C; Supplementary Material, Table S6).

Insert Figure 5 Here

4. Discussion

This study investigated electrophysiological and cognitive effects of the repeated application of iTBS over the left prefrontal cortex. The findings demonstrate that two blocks of iTBS with a 15-minute interval does not increase iTBS-induced changes in cortical properties measured via evoked potentials and working memory performance compared to a single block of iTBS. We also found that changes in working memory performance following a single and two blocks of iTBS were related to changes in cortical activity, however, the size of these performance changes was subtle. Although our observation suggests that the two active stimulation conditions produced similar effect over the prefrontal cortex in healthy individuals, methodological limitations need to be accounted for when interpreting the results.

4.1. Effects of iTBS on TMS-evoked activity

Within-group comparisons revealed both one block (SH+iTBS) and two blocks of iTBS (iTBS+iTBS) over the prefrontal cortex increased N100 TEP amplitude. Increasing the size of the N100 TEP following iTBS is in line with our previous study in the prefrontal cortex [13], and TMS-EEG studies of iTBS in other brain regions [34-35], which may represent increased cortical inhibition [13, 36-39]. We also observed increased P200 following both active iTBS conditions, which is consistent with our previous study [13]. The underlying physiology of this component is still unknown and further characterization is required. Examination of ΔN100 and ΔP200 in each individual did not reveal substantial difference in the number of responders (i.e. increased N100 & P200) to iTBS+iTBS compared to SH+iTBS (Supplementary Material, Table S3). It is possible that the comparison between iTBS+iTBS and SH+SH did not reach significance due to small, non-specific directional change in the amplitude of these peaks following sham stimulation, and therefore, larger effects may have been necessary following active stimulation conditions to observe statistical differences.

The lack of any noticeable difference between cortical changes following SH+iTBS and iTBS+iTBS suggests cortical reactivity does not increase with dose.

4.2. Effects of iTBS on neurophysiology during N-back tasks

The N200 ERP during working memory has been associated with cognitive control [40], attention [25] and inhibition [33]. We observed a significant increase in N200 amplitude during the 3-back task following both active iTBS conditions. A similar pattern was observed during the 2-back task, but it was not significant. During the 3-back task, within condition comparison showed that N200 amplitude increased following both SH+iTBS and iTBS+iTBS at T15, and both stimulation conditions resulted in an ERP ΔN200 that was larger than sham stimulation. No apparent differences between two active conditions again indicate no dose-dependent effect following two blocks of stimulation. The positive correlations between TEP ΔN100 and ERP ΔN200 suggest the involvement of similar mechanism, possibly cortical inhibition, and N100 in this study is therefore unlikely to be attributed to auditory processing as described in a previous study [41].

4.3. Effects of iTBS on working memory performance

Despite no observable change in electrophysiology during 2-back task, we found improvement in working memory performance (*d'*) over time regardless of stimulation condition. This suggests that the enhancement may have been due to practice effects. Previous studies have shown working memory improvements following iTBS over prefrontal cortex [9] or deficits following cTBS [10] in the 2-back condition. In this study, similar yet non-significant behavioural outcomes were seen in the 3-back task, which were accompanied by robust changes in cortical neurophysiology following active stimulation conditions. This is in contrast with a previous study which demonstrated particularly

large effect size of approximately *d*=1.5 [9]. In the current study, the effect sizes for 3-back task following SH+iTBS was *g*=0.43 (Supplementary Table S5), which is distinctly lower than aforementioned study. However, the effect size in this study is comparable to a recent meta-analysis on working memory performance improvement following non-invasive brain stimulation (confidence interval *g*=0.112 and 0.395), particularly in healthy individuals [42]. Therefore, more study is needed to verify the effectiveness of iTBS in enhancement of cognitive performance.

Even though changes in working memory performance were not statistically different between active and sham conditions, significant correlations were found between $\Delta d'$ and both TMS-evoked ΔN100 and 3-back task related ΔN200 (increased amplitude related to improved accuracy) only in the SH+iTBS condition (Supplementary Material, Fig S6 & S7). It is possible that when neurophysiological change is strong enough, changes in behavioural response can be observed. However, the variability of neurobiological response may be washing out what is likely a more subtle behavioural impact of stimulation.

4.4. Possible reasons for the negative outcome

Overall, stronger effects were not observed following two blocks of iTBS in the prefrontal cortex compared to one block of iTBS. Homeostatic mechanisms may be a possible explanation for the results as have been reported in motor cortex studies using iTBS at varying intervals [8, 43]. The lack of differences between SH+iTBS and iTBS+iTBS could result from the second iTBS block having less novelty when preceded by another block after 15 minutes, thus leading to habituation of the measured effects. Similar outcomes using two blocks of iTBS have been demonstrated in a rat model [16] and in the human motor cortex [7] where the same duration of stimulation break (15-min) was used. However, markedly increased dose-dependent effects were observed following the third application of iTBS (3 x iTBS, 15-min break) in these studies. Future studies should consider

extending the number of iTBS blocks to investigate whether more efficacious after-effects of stimulation can be obtained. Despite different stimulation paradigms, other studies have shown more robust changes following two blocks of cTBS (2 x 600 pulses; 10-min interval) over motor cortex [6] and parietal cortex (15-min interval [17]). Differences in stimulation parameters limit a systematic comparison between studies. It is unclear what impact the interval between the doses has on the after-effects of TBS in the prefrontal cortex, and the possibility that the effects of single block of iTBS are short lasting and therefore may not accumulate with 15-min interval should not be disregarded. On the other hand, enhancement of previously saturated LTP was observed only when TBS was repeated 1 hour or longer, but not when shorter intervals were used in rats [44]. It remains to be determined what interval would be optimal and how many blocks of stimulation would be sufficient in order to obtain the most robust outcome. Another possible reason for not observing a dose-dependent effect following iTBS+iTBS is the limited time point of measurement (30 min for TMS-EEG, 40 min for N-back task) which may have been too short to capture the full effect. Monte-Silva and colleagues [45] observed elevated amplitude of MEPs for more than 24 hours following two blocks of anodal tDCS (3 or 20 min interval) compared to a single block. The effects within 120 minutes were similar, if not smaller than a single block of stimulation. Therefore, future studies should investigate the extended effects of repeated application of iTBS in the prefrontal cortex. Finally, it is also possible that the statistical approach adopted in this study may have limited the sensitivity to detect subtle differences between conditions, particularly between two active stimulation conditions. The current method is widely utilised in the electrophysiological studies and has a very high precision, however the sensitivity may be low and requires larger sample sizes as indicated in the power analysis, trials per TEP/ERP or larger effect sizes in order to observe significant differences [46]. Establishing an optimal method of quantifying neuromodulatory changes targeting the prefrontal cortex would benefit future studies.

5. Limitations

There are several limitations of the study. Even though the experimental protocol was sham-controlled, it was not blinded. It is currently difficult to truly blind both the TMS administrator and the subject. In addition, only one baseline recording was performed using TMS-EEG with limited number of trials which may have affected the ability to detect any difference in the early TEP components due to lower signal-to-noise ratio compared to late TEPs. Results have been consistent with our previous studies, however, increasing the number of TMS-EEG pulses may shed a new light on the after-effects of iTBS. It has been shown that TMS click sound can induce N100-P200 component, even in the presence of noise masking [41]. As we used a repeated measures, possible auditory artefacts would be consistent across time, and any change in TEPs is likely to be attributed to neural activity. The sham condition did not alter the overall amplitude of this component, which confirms the validity of the results. Increasing the number of EEG channels would also provide better spatial resolution. The use of neuronavigation, which was not feasible in this study, could improve the localisation of stimulation site between sessions. Lastly, despite its common use in EEG studies, the statistical method used in this study may not be sensitive to subtle differences between conditions given small number of participants.

6. Conclusions

In conclusion, two blocks of iTBS did not yield stronger measured effects as compared to one block of iTBS within 40-min post stimulation. The results, however, should be interpreted with caution due to methodological and analytical limitations.

7. References

[1] Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron 2005;45(2):201-6.

[2] McAllister SM, Rothwell JC, Ridding MC. Selective modulation of intracortical inhibition by low-intensity Theta Burst Stimulation. Clin Neurophysiol 2009;120(4):820-6.

[3] Goldsworthy MR, Pitcher JB, Ridding MC. A comparison of two different continuous theta burst stimulation paradigms applied to the human primary motor cortex. Clin Neurophysiol 2012;123(11):2256-63.

[4] Wu SW, Shahana N, Huddleston DA, Gilbert DL. Effects of 30Hz theta burst transcranial magnetic stimulation on the primary motor cortex. J Neurosci Methods 2012;208(2):161-4.

[5] Gamboa OL, Antal A, Moliadze V, Paulus W. Simply longer is not better: reversal of theta burst after-effect with prolonged stimulation. Exp Brain Res 2010;204(2):181-7.

[6] Goldsworthy MR, Pitcher JB, Ridding MC. The application of spaced theta burst protocols induces long-lasting neuroplastic changes in the human motor cortex. Eur J Neurosci 2012;35(1):125-34.

[7] Nettekoven C, Volz LJ, Kutscha M, Pool EM, Rehme AK, Eickhoff SB, et al. Dose-dependent effects of theta burst rTMS on cortical excitability and resting-state connectivity of the human motor system. J Neurosci 2014;34(20):6849-59.

[8] Murakami T, Muller-Dahlhaus F, Lu MK, Ziemann U. Homeostatic metaplasticity of corticospinal excitatory and intracortical inhibitory neural circuits in human motor cortex. J Physiol 2012;590(22):5765-81.

[9] Hoy KE, Bailey N, Michael M, Fitzgibbon B, Rogasch NC, Saeki T, et al. Enhancement of Working Memory and Task-Related Oscillatory Activity Following Intermittent Theta Burst Stimulation in Healthy Controls. Cereb Cortex 2016;26(12):4563-73.

[10] Schicktanz N, Fastenrath M, Milnik A, Spalek K, Auschra B, Nyffeler T, et al. Continuous theta burst stimulation over the left dorsolateral prefrontal cortex decreases medium load working memory performance in healthy humans. PLoS One 2015;10(3):e0120640.

[11] Grossheinrich N, Rau A, Pogarell O, Hennig-Fast K, Reinl M, Karch S, et al. Theta burst stimulation of the prefrontal cortex: safety and impact on cognition, mood, and resting electroencephalogram. Biol Psychiatry 2009;65(9):778-84.

[12] Viejo-Sobera R, Redolar-Ripoll D, Boixados M, Palaus M, Valero-Cabre A, Marron EM. Impact of Prefrontal Theta Burst Stimulation on Clinical Neuropsychological Tasks. Front Neurosci 2017;11:462.

[13] Chung SW, Lewis BP, Rogasch NC, Saeki T, Thomson RH, Hoy KE, et al. Demonstration of short-term plasticity in the dorsolateral prefrontal cortex with theta burst stimulation: A TMS-EEG study. Clin Neurophysiol 2017;128(7):1117-26.

[14] Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1971;9(1):97-113.

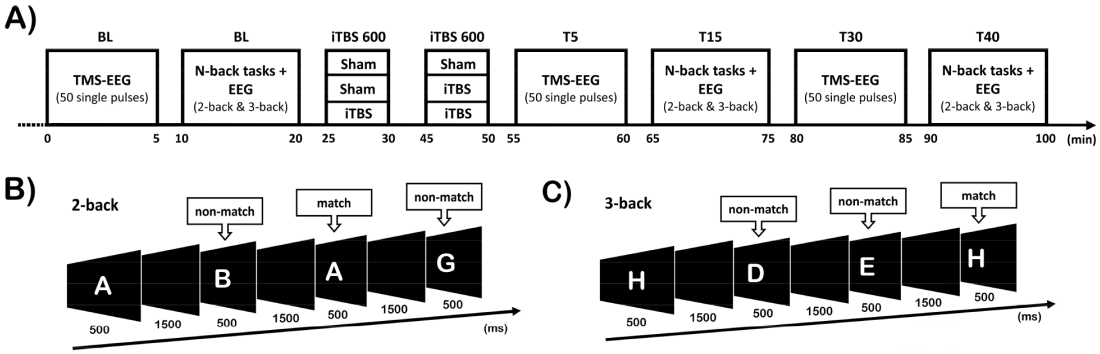
[15] Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59 Suppl 20:22-33;quiz 4-57.

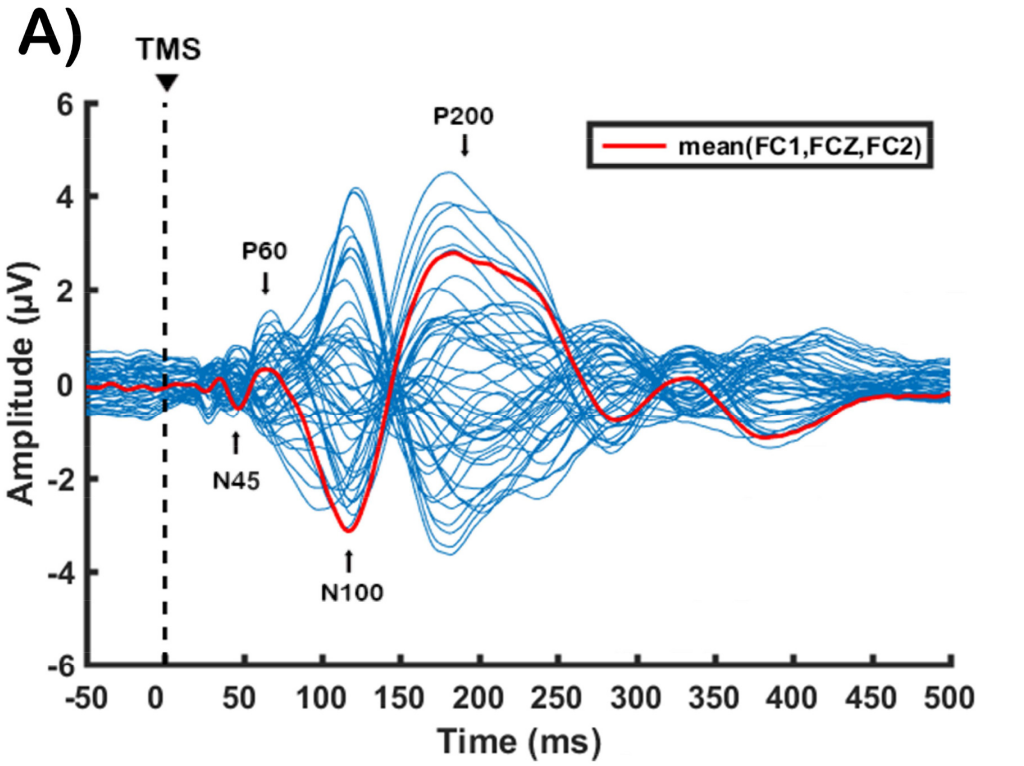
[16] Volz LJ, Benali A, Mix A, Neubacher U, Funke K. Dose-dependence of changes in cortical protein expression induced with repeated transcranial magnetic theta-burst stimulation in the rat. Brain Stimul 2013;6(4):598-606.

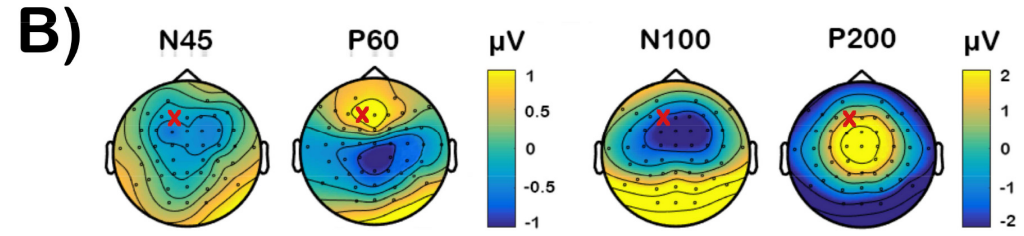
[17] Nyffeler T, Cazzoli D, Hess CW, Muri RM. One session of repeated parietal theta burst stimulation trains induces long-lasting improvement of visual neglect. Stroke 2009;40(8):2791-6.

411 [18] Conforto AB, Z'Graggen WJ, Kohl AS, Rosler KM, Kaelin-Lang A. Impact of coil position and
412 electrophysiological monitoring on determination of motor thresholds to transcranial magnetic
413 stimulation. Clin Neurophysiol 2004;115(4):812-9.
414 [19] Rogasch NC, Thomson RH, Daskalakis ZJ, Fitzgerald PB. Short-latency artifacts associated
415 with concurrent TMS-EEG. Brain Stimul 2013;6(6):868-76.
416 [20] Hill AT, Rogasch NC, Fitzgerald PB, Hoy KE. Effects of prefrontal bipolar and high-definition
417 transcranial direct current stimulation on cortical reactivity and working memory in healthy adults.
418 Neuroimage 2017;152:142-57.
419 [21] Haatveit BC, Sundet K, Hugdahl K, Ueland T, Melle I, Andreassen OA. The validity of d prime
420 as a working memory index: results from the "Bergen n-back task". J Clin Exp Neuropsychol
421 2010;32(8):871-80.
422 [22] Rogasch NC, Sullivan C, Thomson RH, Rose NS, Bailey NW, Fitzgerald PB, et al. Analysing
423 concurrent transcranial magnetic stimulation and electroencephalographic data: A review and
424 introduction to the open-source TESA software. Neuroimage 2017;147:934-51.
425 [23] Rogasch NC, Daskalakis ZJ, Fitzgerald PB. Cortical inhibition of distinct mechanisms in the
426 dorsolateral prefrontal cortex is related to working memory performance: a TMS-EEG study. Cortex
427 2015;64:68-77.
428 [24] Rogasch NC, Thomson RH, Farzan F, Fitzgibbon BM, Bailey NW, Hernandez-Pavon JC, et al.
429 Removing artefacts from TMS-EEG recordings using independent component analysis: importance
430 for assessing prefrontal and motor cortex network properties. Neuroimage 2014;101:425-39.
431 [25] Coull JT. Neural correlates of attention and arousal: insights from electrophysiology,
432 functional neuroimaging and psychopharmacology. Prog Neurobiol 1998;55(4):343-61.
433 [26] Kok A. On the utility of P3 amplitude as a measure of processing capacity. Psychophysiology
434 2001;38(3):557-77.
435 [27] Nasr S, Moeeny A, Esteky H. Neural correlate of filtering of irrelevant information from visual
436 working memory. PLoS One 2008;3(9):e3282.
437 [28] Tadel F, Baillet S, Mosher JC, Pantazis D, Leahy RM. Brainstorm: a user-friendly application
438 for MEG/EEG analysis. Comput Intell Neurosci 2011;2011:879716.
439 [29] Hsu YF, Liao KK, Lee PL, Tsai YA, Yeh CL, Lai KL, et al. Intermittent theta burst stimulation
440 over primary motor cortex enhances movement-related beta synchronisation. Clin Neurophysiol
441 2011;122(11):2260-7.
442 [30] Oostenveld R, Fries P, Maris E, Schoffelen JM. FieldTrip: Open source software for advanced
443 analysis of MEG, EEG, and invasive electrophysiological data. Comput Intell Neurosci
444 2011;2011:156869.
445 [31] Premoli I, Castellanos N, Rivolta D, Belardinelli P, Bajo R, Zipser C, et al. TMS-EEG signatures
446 of GABAergic neurotransmission in the human cortex. J Neurosci 2014;34(16):5603-12.
447 [32] Aron AR. The neural basis of inhibition in cognitive control. Neuroscientist 2007;13(3):214-28.
448 [33] Kopp B, Rist F, Mattler U. N200 in the flanker task as a neurobehavioral tool for investigating
449 executive control. Psychophysiology 1996;33(3):282-94.
450 [34] Harrington A, Hammond-Tooke GD. Theta Burst Stimulation of the Cerebellum Modifies the
451 TMS-Evoked N100 Potential, a Marker of GABA Inhibition. PLoS One 2015;10(11):e0141284.
452 [35] Huang G, Mouraux A. MEP Latencies Predict the Neuromodulatory Effect of cTBS Delivered
453 to the Ipsilateral and Contralateral Sensorimotor Cortex. PLoS One 2015;10(8):e0133893.
454 [36] Bonnard M, Spieser L, Meziane HB, de Graaf JB, Pailhous J. Prior intention can locally tune
455 inhibitory processes in the primary motor cortex: direct evidence from combined TMS-EEG. Eur J
456 Neurosci 2009;30(5):913-23.
457 [37] Premoli I, Rivolta D, Espenhahn S, Castellanos N, Belardinelli P, Ziemann U, et al.
458 Characterization of GABAB-receptor mediated neurotransmission in the human cortex by paired-
459 pulse TMS-EEG. Neuroimage 2014;103:152-62.

[38] Rogasch NC, Daskalakis ZJ, Fitzgerald PB. Mechanisms underlying long-interval cortical inhibition in the human motor cortex: a TMS-EEG study. J Neurophysiol 2013;109(1):89-98.
[39] Yamanaka K, Kadota H, Nozaki D. Long-latency TMS-evoked potentials during motor execution and inhibition. Front Hum Neurosci 2013;7:751.
[40] Folstein JR, Van Petten C. Influence of cognitive control and mismatch on the N2 component of the ERP: a review. Psychophysiology 2008;45(1):152-70.
[41] ter Braack EM, de Vos CC, van Putten MJ. Masking the Auditory Evoked Potential in TMS-EEG: A Comparison of Various Methods. Brain Topogr 2015;28(3):520-8.
[42] Brunoni AR, Vanderhasselt MA. Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: a systematic review and meta-analysis. Brain Cogn 2014;86:1-9.
[43] Gamboa OL, Antal A, Laczo B, Moliadze V, Nitsche MA, Paulus W. Impact of repetitive theta burst stimulation on motor cortex excitability. Brain Stimul 2011;4(3):145-51.
[44] Kramar EA, Babayan AH, Gavin CF, Cox CD, Jafari M, Gall CM, et al. Synaptic evidence for the efficacy of spaced learning. Proc Natl Acad Sci U S A 2012;109(13):5121-6.
[45] Monte-Silva K, Kuo MF, Hessenthaler S, Fresnoza S, Liebetanz D, Paulus W, et al. Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. Brain Stimul 2013;6(3):424-32.
[46] Mensen A, Khatami R. Advanced EEG analysis using threshold-free cluster-enhancement and non-parametric statistics. Neuroimage 2013;67:111-8.
[47] Lioumis P, Kicic D, Savolainen P, Makela JP, Kahkonen S. Reproducibility of TMS-Evoked EEG responses. Hum Brain Mapp 2009;30(4):1387-96.




A)
TMS
P200
mean(FC1,FCZ,FC2)
P60
N45
N100
Amplitude (μV)
6
4
2
0
-2
-4
-6
-50
0
50
100
150
200
250
300
350
400
450
500
Time (ms)


B)
N45
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P200
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1
0.5
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2
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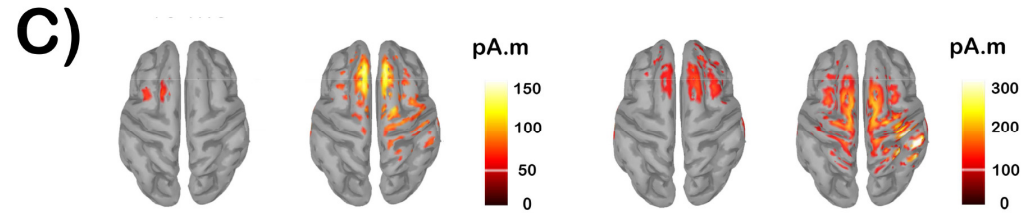
C)
pA.m
150
100
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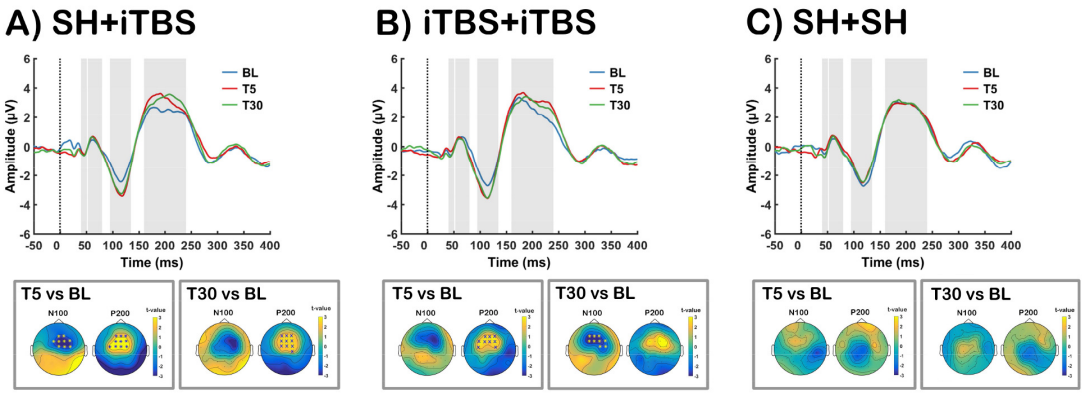

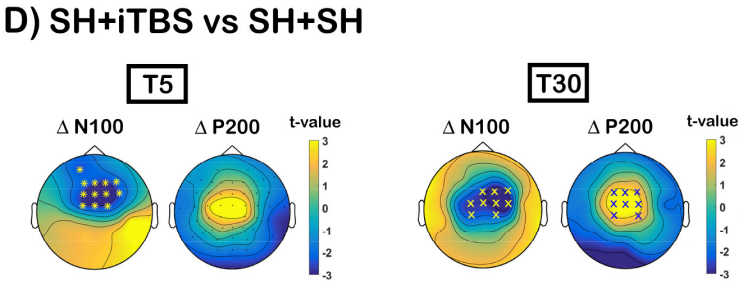

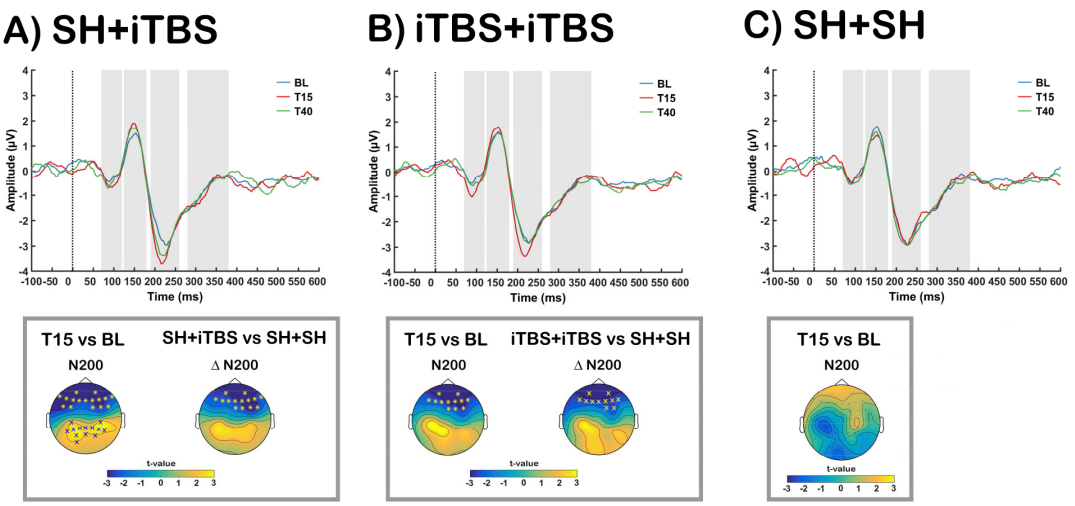

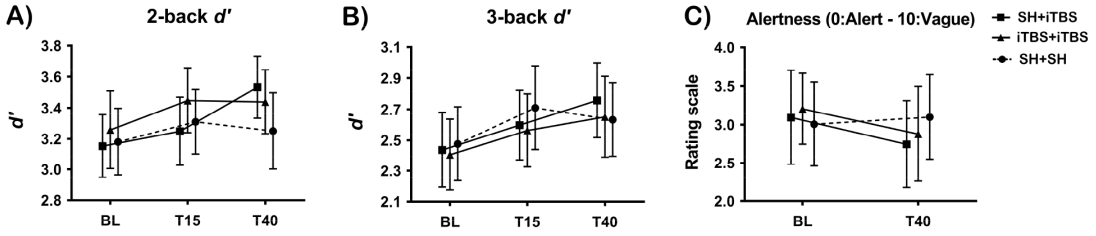

Figure 1. Experimental design of the study. (A) Combined transcranial magnetic stimulation and electroencephalography (TMS-EEG) and N-back tasks were obtained at baseline (BL) before intermittent theta burst stimulation (iTBS). Two blocks of sham and/or real iTBS was given at 15 min interval, and post-iTBS measures were obtained twice (TMS-EEG – T5 and T30; N-back – T15 and T40). (B-C) Schematic diagram of N-back tasks illustrating match trials for either 2-back or 3-back task. Letters were presented for 500 ms with 1500 ms interval in-between.

Figure 2. Transcranial magnetic stimulation (TMS)-evoked potentials following single-pulse stimulation over left prefrontal cortex (F1 electrode) before theta-burst stimulation (data combined for all stimulation conditions at baseline). (A) Butterfly plot of all electrodes with peaks of interest (N45, P60, N100, P200) shown in text. The red line indicates the waveform obtained from the average of three fronto-central electrodes (FC1, FCz, FC2) for graphical representation. (B) Voltage distribution and (C) Minimum Norm Estimates (MNEs) of the source level activity at the cortex for each peak. 'X' on topoplots represent the stimulation site.

Figure 3. Modulation of cortical activity assessed via transcranial magnetic stimulation (TMS)-evoked potentials (TEPs) following different intermittent theta burst stimulation (iTBS) conditions (A: SH+iTBS; B: iTBS+iTBS; C: SH+SH). Grand average TEP waveforms at BL (blue), T5 (red) and T30 (green) using the average 3 fronto-central electrodes (FC1, FCz and FC2). Scalp maps represent t-values for comparison between time points. (D) Comparison between iTBS-induced Δ N100 and Δ P200 between SH+iTBS and SH+SH conditions at T5 and T30. Asterisks and 'X's on topoplots indicate significant sensors between comparisons (cluster-based statistics, $^{*}p < 0.01$, $^{X}p < 0.025$).

Figure 4. Effects of different intermittent theta-burst stimulation (iTBS) conditions (A: SH+iTBS; B: iTBS+iTBS; C: SH+SH) on the event-related potentials during 3-back task. Grand average waveform of event-related potentials (ERPs) at BL (blue), T15 (red) and T40 (green) using the average 3 fronto-central electrodes (FC1, FCz and FC2), with scalp maps representing t-values for comparison between time points and/or conditions. Asterisks and 'X's on topoplots indicate significant sensors between comparisons (cluster-based statistics, $*p < 0.01$, $^{X}p < 0.025$).

Figure 5. Working memory performance assessed by *d*' at BL, T15 and T40 in different intermittent theta-burst stimulation (iTBS) conditions during (A) 2-back and (B) 3-back tasks, and (C) alertness level. Error bars indicate standard error of means (SEM).

- Effects of two blocks of prefrontal iTBS was compared to one block and sham
- Both active conditions resulted in significant changes in neurophysiology
- Active conditions failed to improve working memory performance relative to sham
- Two blocks of iTBS did not result in a linear accumulative effect

Supplementary Material

Methods

1. *EEG recording*

EEG was recorded using 48 TMS-compatible Ag/AgCl electrodes on a 64-channel EEG cap (AF3, AF4, F7, F5, F3, F1, Fz, F2, F4, F6, F8, FC5, FC3, FC1, FCz, FC2, FC4, FC6, T7, C5, C3, C1, Cz, C2, C4, C6, T8, CP5, CP3, CP1, CP2, CP4, CP6, P7, P5, P3, P1, Pz, P2, P4, P6, P8, PO3, POz, PO4, O1, Oz, O2), which were referenced to CPz and grounded to FPz. Electro-ocular activity was recorded by placing electrodes to left and right of each eye (outer canthus, referenced to each other), and one above and one below the left eye. EEG signals were amplified (1000 x) and low pass filtered (DC – 2000 Hz) using a high acquisition rate at 10,000 Hz (± 200 mV operating range) for TMS-EEG data, while EEG recordings during N-back task was filtered (0.05 – 200 Hz) and sampled at 1000 Hz with an operating window of ± 950 μV. Electrode impedance levels were regularly checked to maintain below 5 kΩ throughout the experiment. During single-pulse TMS, subjects listened to white noise through intra-auricular earphones (Etymotic Research, ER3-14A, USA) to minimise the influence of the auditory processing of the TMS click. The level of the sound was adjusted individually until TMS click was sufficiently blocked.

2. *EEG data preprocessing*

Offline analyses of EEG data were performed using EEGLAB (Delorme and Makeig, 2004), FieldTrip (Oostenveld et al., 2011), TESA (Rogasch et al., 2017) and custom scripts on the MATLAB platform (R2015b, The MathWorks, USA).

TMS-EEG data: Data were epoched around the TMS pulse (-1000 to 1000 ms) and baseline corrected (-500 to -50 ms). The large magnetic artefact from TMS pulse was removed and interpolated (-5 to 10 ms), and data were concatenated across epochs from three time points (BL, T5, T30) to avoid bias in component rejection. Data were downsampled to 1000 Hz and were visually inspected for removal of epochs containing bursts of muscle activity and/or disconnected electrodes. An average of 48.9 ± 1.2 (range: 45 – 50) trials were included in SH+SH condition, 49.2 ± 1.2 (range: 44 – 50) trials in the SH+iTBS condition and 48.6 ± 2.8 (range: 34 – 50) trials in the iTBS+iTBS condition across each time point. An initial round of independent component analysis (FastICA, 'tanh' contrast) was used to remove the remainder of large muscle artefacts using semi-automated component classification algorithm (classified if the component was 8 times larger than mean absolute

amplitude across the entire epoch; tesa_compselect function) (Rogasch et al., 2017). Data were bandpass filtered between 1 and 80 Hz (Butterworth, second-order, zero-phase) and bandstop filtered between 48 and 52 Hz to remove 50 Hz line noise. The second round of FastICA was applied to the data to remove non-neural signals using TESA toolbox (Rogasch et al., 2017) such as eye blinks and saccades (mean absolute z scores of two electrodes larger than 2.5), muscle activity (high frequency power above 60% of total power) and other noise-related signals (one or more electrode with an absolute z score of 4).

N-back EEG data: The use of appropriate high-pass filter (≤ 0.1 Hz) is important for slow components such as P300 in the ERP research (Duncan et al., 2009; Kappenman and Luck, 2010). It is also recommended that high-pass filter is applied to continuous EEG data (Tanner et al., 2015). However, the drift in 0.1 Hz filtered data is not favourable for ICA (Debener and De Vos, 2011). To address these issues, steps were taken for the analysis of EEG during the N-back task:

1) All data (continuous) were bandpass filtered between 0.1 Hz and 80 Hz (Butterworth, second-order, zero-phase), bandstop filtered between 48 and 52 Hz, epoched around the correctly encoded and maintained trials (-1450 to 1990 ms) and baseline corrected (-350 to -50 ms). Data were concatenated across epochs from three time points (BL, T15, T40) and two N-back tasks, and stored.

2) The original data (continuous) were bandpass filtered between 1 Hz and 80 Hz, bandstop filtered, epoched, baseline corrected and concatenated as described in step 1. The data then underwent preprocessing as described for TMS-EEG data (Rejection of epochs and/or channels with excessive noise, only one round of FastICA for the removal of non-neural artefact).

3) The ICA weight matrix and the information on the epoch and/or channel rejections from step 2 were then applied to the data in step 1.

The average number of trials included in each condition were: SH+SH = 68.7 ± 18.2 (range: 33 – 107) for 2-back, 74.8 ± 20.7 (range: 32 – 109) for 3-back; SH+iTBS = 70.8 ± 15.2 (range: 33 – 102) for 2-back, 73.2 ± 19.9 (range: 29 – 105) for 3-back; and iTBS+iTBS = 69.5 ± 16.7 (range: 30 – 101) for 2-back, 72.1 ± 20.8 (range: 31 – 110) for 3-back tasks. The large range is driven by four subjects, two of whom had below average performance while the other two subjects exhibited above average performance.

For all EEG data (both TMS-EEG and the N-back EEG), any removed channels were interpolated and data were re-referenced to common average reference. Concatenated data were split into time point blocks (BL, T5 or T15, T30 or T40), and/or tasks (2-back, 3-back). Split epochs were then averaged for each condition/time point.

3. Source estimation

To estimate the cortical sources underlying the peaks in the EEG sensor data, the depth-weighted minimum norm estimation (MNE) approach was applied using the Brainstorm software, which is documented and freely available for download online under the GNU general public licence (http://neuroimage.usc.edu/brainstorm/). Due to the unavailability of individual anatomical MRI scans, a template model (ICBM 152) from the software was used. The symmetric Boundary Element Method implemented in OpenMEEG software was used for the forward model, and dipole orientations were constrained to be normal to the cortex for the inverse model.

4. Individual's resting motor threshold

Table S1. Individual's resting motor threshold at each session (% maximum output of MagVentre stimulator)

Subjects	SH+SH	SH+iTBS	iTBS+iTBS	Average (within-subject)	SD
S01	58	58	59	58.33	0.58
S02	47	47	47	47	0
S03	67	68	68	67.67	0.58
S04	60	59	59	59.33	0.58
S05	48	49	47	48	1
S06	57	56	54	55.67	1.53
S07	63	64	64	63.67	0.58
S08	49	50	52	50.33	1.53
S09	48	48	46	47.33	1.15
S10	55	55	56	55.33	0.58
S11	50	50	50	50	0
S12	48	47	47	47.33	0.58
S13	62	62	62	62	0
S14	55	55	55	55	0
S15	52	54	54	53.33	1.15
S16	62	62	63	62.33	0.58
S17	47	47	47	47	0
S18	49	48	48	48.33	0.58
Average (within-session)	54.28	54.39	54.33		
SD	6.5	6.6	6.9		

Results

1. *SNR analysis*

Table S1 summarises the averaged SNR of single-pulse TMS included in the analyses. The values represent how many standard deviations each peak amplitude were above baseline. A value of 3 SDs (99.7% of the data) denotes a good SNR. Qualitatively N45 and P60 peaks displayed a moderate-to-good SNR, but N100 and P200 exhibited excellent SNR.

Table S1. Signal-to-noise ratio (SNR) of each peak at baseline (BL), 5-min post (T5) and 30-min post (T30) each stimulation condition (mean ± SD)

	SH+iTBS			**iTBS+iTBS**			**SH+SH**		
	BL	**T5**	**T30**	**BL**	**T5**	**T30**	**BL**	**T5**	**T30**
N45	2.33 (±1.44)	2.49 (±1.74)	2.42 (±1.68)	2.26 (±1.53)	1.98 (±1.01)	2.27 (±1.84)	2.46 (±1.60)	2.27 (±1.81)	2.50 (±2.05)
P60	3.35 (±2.69)	3.12 (±3.25)	3.17 (±2.51)	2.90 (±2.29)	3.46 (±3.23)	3.18 (±2.99)	3.11 (±3.97)	3.68 (±3.06)	3.11 (±3.97)
N100	6.20 (±2.93)	8.12 (±3.39)	7.84 (±3.52)	6.68 (±3.28)	8.15 (±4.07)	8.03 (±4.07)	6.89 (±3.14)	6.59 (±2.76)	6.42 (±4.09)
P200	7.32 (±3.64)	8.71 (±4.27)	8.52 (±4.67)	7.45 (±3.92)	8.39 (±5.46)	7.83 (±4.23)	7.88 (±4.25)	7.70 (±3.95)	7.91 (±4.15)

2. Power analysis of ΔN100 and ΔP200

A power analysis was performed on ΔN100 and ΔP200 to determine if the current study was powered to detect differences between stimulation conditions using G*Power software (Faul et al., 2007). A large effect size was required for the detection of differences, which was not present in the comparison between active conditions (Fig S1).

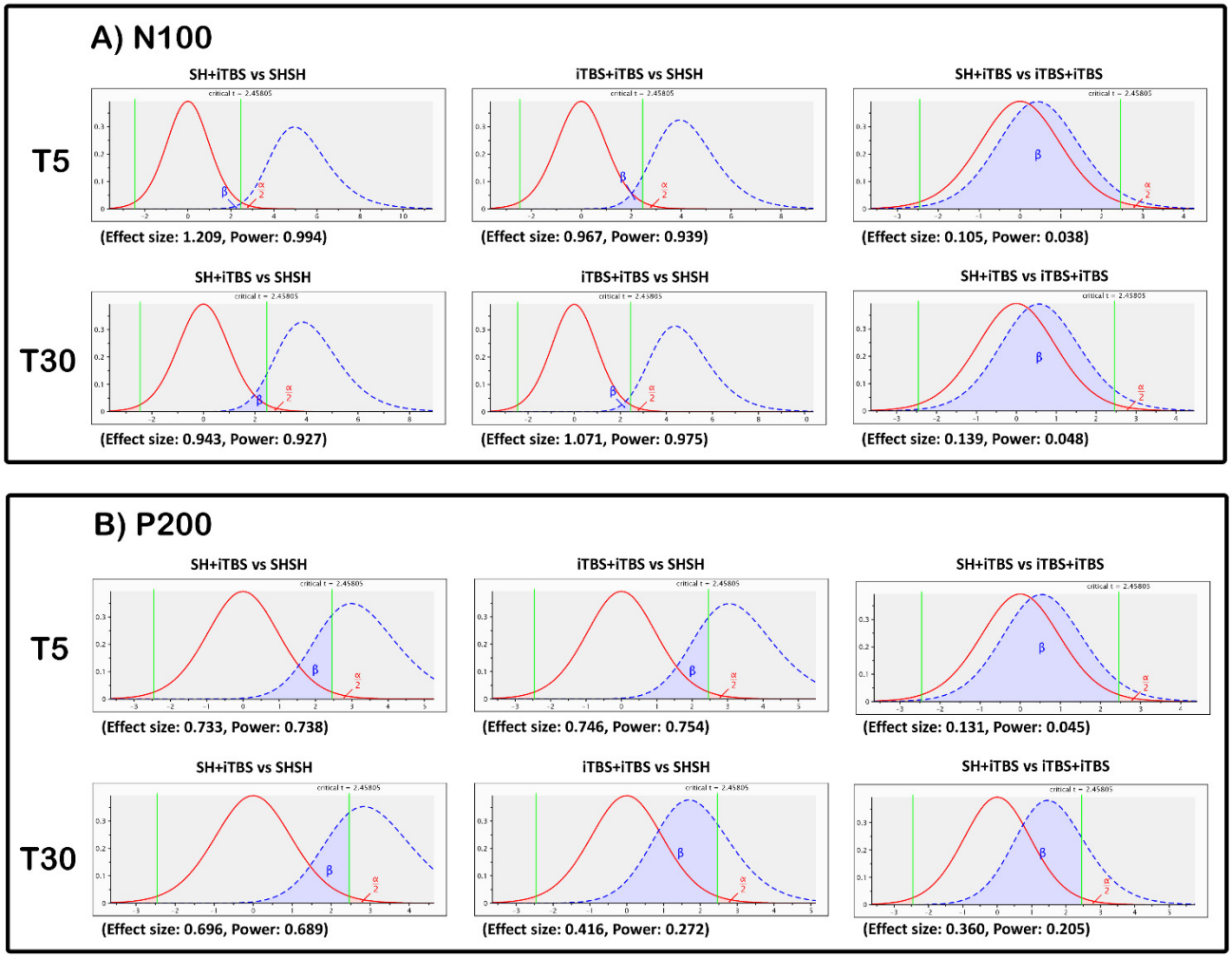

Figure S1. Power analysis on TMS-evoked (A) ΔN100 and (B) ΔP200 between intermittent theta-burst stimulation (iTBS) conditions (SH+iTBS, iTBS+iTBS and SH+SH) at T5 and T30. Graphs are plotted using the average 3 fronto-central electrodes (FC1, FCz and FC2).

3. TMS-evoked N100 and P200 for each subject

Figure S2 illustrates TEP N100 and P200 in each stimulation condition at each time point. TMS-evoked N100 and P200 were examined at a single-subject level to determine whether variability in response to stimulation had an impact on the TMS-EEG results.

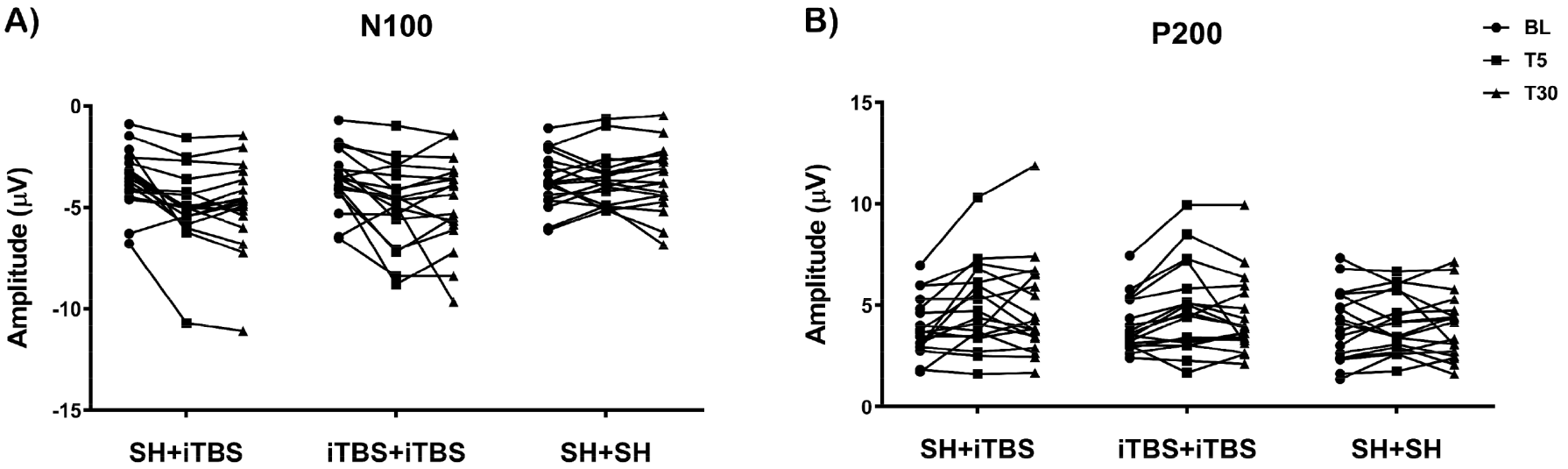

Figure S2. TMS-evoked (A) N100 and (B) P200 for each subject in each intermittent theta-burst stimulation (iTBS) condition (SH+iTBS, iTBS+iTBS and SH+SH) at each time point (BL, T5 and T30). Graphs are plotted using the average 3 fronto-central electrodes (FC1, FCz and FC2).

Figure S3 illustrates normalised data (Δ N100 and Δ P200) for each subject. The majority of the subjects responded in one direction (i.e. increased amplitude) following active iTBS conditions whereas such specific directional change was not present in sham condition (Table S3).

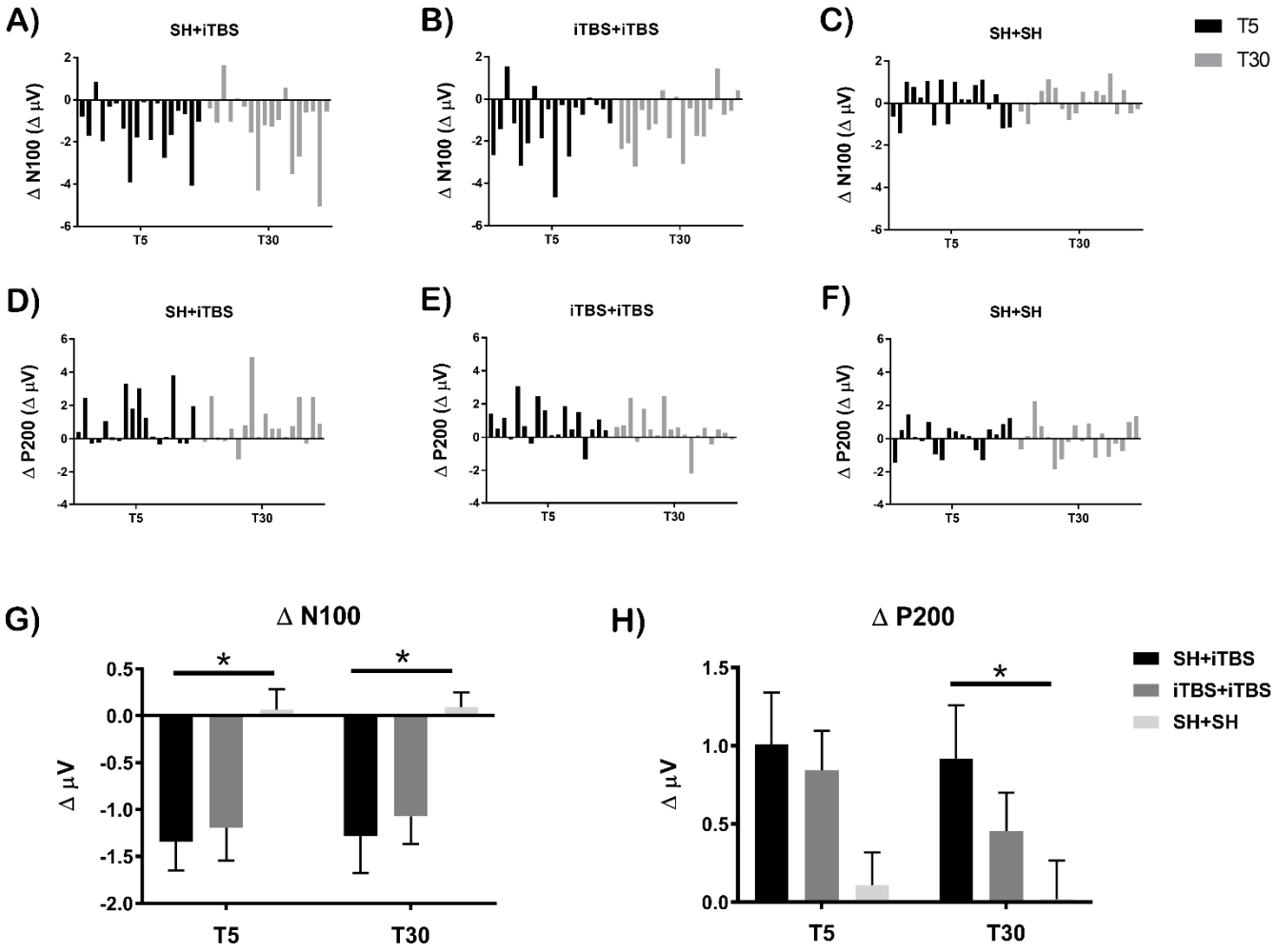

Figure S3. Normalised transcranial magnetic stimulation-evoked potential (TEPs) for each subject in each intermittent theta-burst stimulation (iTBS) condition (SH+iTBS, iTBS+iTBS and SH+SH) at T5 and T30. (A–C) Δ N100 and (D-F) Δ P200. Data averaged across subjects for (G) Δ N100 and (H) Δ P200. Error bars indicate standard error of the mean (SEM). Asterisks indicate significant differences (based on cluster-based permutation statistics described in Section 3.3). Graphs are plotted using the average 3 fronto-central electrodes (FC1, FCz and FC2).

Table S3. Number of subjects (out of 18) in which TEPs increased/decreased relative to baseline.

		N100			P200		
		SH+SH	SH+iTBS	iTBS+iTBS	SH+SH	SH+iTBS	iTBS+iTBS
T5	↑	7	**17**	16	12	**12**	**14**
	↓	11	1	2	6	6	4
T30	↑	9	16	**15**	8	**12**	14
	↓	9	2	3	10	6	4

*Significant changes from baseline highlighted in bold

4. *2-back event-related potentials (ERPs) following different iTBS conditions*

No significant differences were seen before and after different iTBS conditions at any time point (all $p > 0.025$).

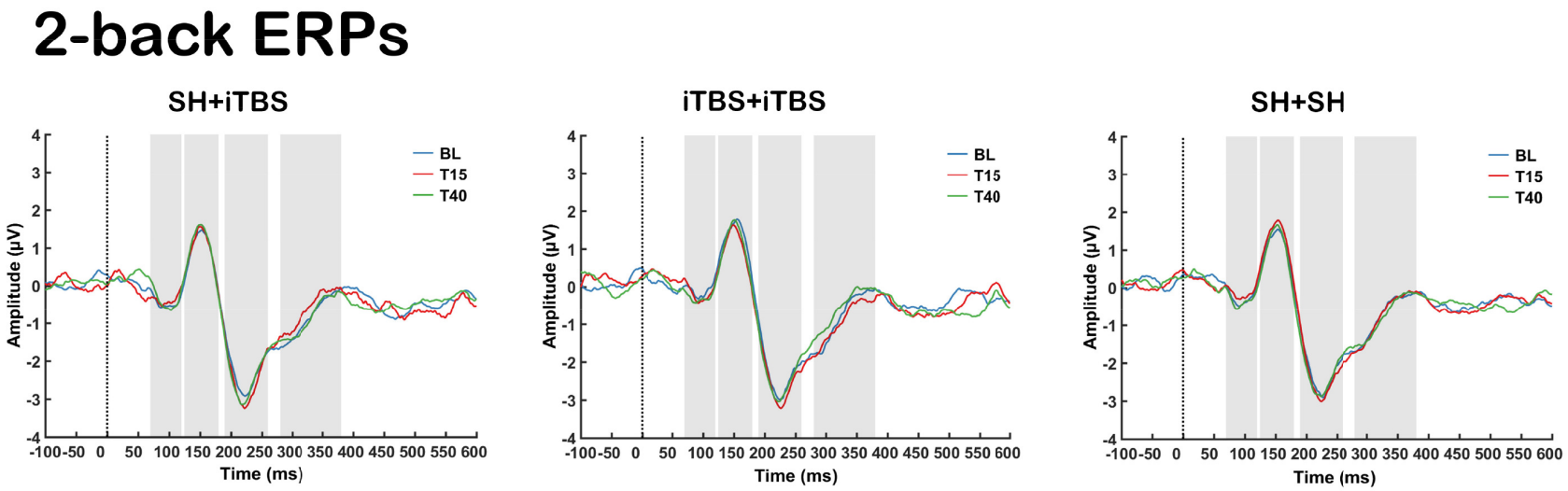

Figure S4. Effects of different intermittent theta-burst stimulation (iTBS) conditions (SH+iTBS; iTBS+iTBS; SH+SH) on the electrophysiology recordings during 2-back task, illustrated in grand average waveform of event-related potentials (ERPs) at BL (blue), T15 (red) and T40 (green) using the average 3 fronto-central electrodes (FC1, FCz and FC2).

5. Link between TMS-evoked activity and neurophysiology during the 3-back task

Studies indicate an involvement of inhibitory mechanism in the TMS-evoked N100 (Chung et al., 2017; Rogasch et al., 2015) and visual cognitive task-related N200 (Aron, 2007; Kopp et al., 1996; Sasaki et al., 1989), and therefore, correlation analysis was conducted between TMS-evoked Δ N100 and ERP Δ N200 during 3-back task using the average of 3 fronto-central electrodes (FC1, FCz and FC2). These electrodes were close to the site of stimulation and commonly showed significant iTBS-induced changes in two different measures. Pearson's correlation revealed significant correlations between TMS-evoked Δ N100 at and ERP Δ N200 during 3-back task in SH+iTBS condition at both time points (Post 1, T5 for TEP, T15 for ERP – r = 0.663, p = 0.003; Post 2, T30 for TEP, T40 for ERP – r = 0.607, p = 0.008; Fig S5A). Only a trend towards significance was observed following iTBS+iTBS condition at Post 1 time point (r = 0.430, p = 0.075; Fig S5B), and no correlations in sham stimulation (Fig S5C). Positive correlations suggest that these peaks share similar mechanism which can be modulated by iTBS.

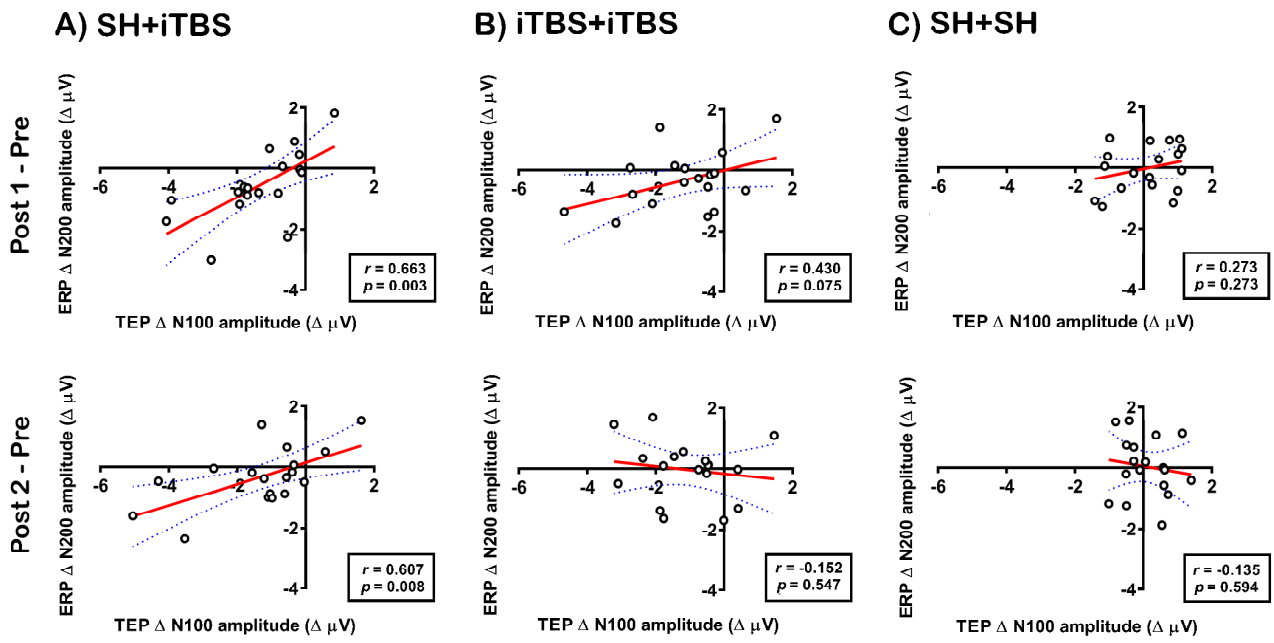

Figure S5. Correlations between iTBS-induced changes in TMS-evoked N100 amplitude (TEP Δ N100) and 3-back task related N200 amplitude (ERP Δ 200) in (A) SH+iTBS, (B) iTBS+iTBS and (C) SH+SH conditions. Top rows: early time point (T5 for TMS-EEG, T15 for 3-back task), bottom rows: late time point (T30 for TMS-EEG, T40 for 3-back task).

6. Working memory performance following iTBS

The effect of iTBS on working memory performance is shown in Table S4 measured via *d'* (accuracy) and accurate reaction time (in ms).

Table S4. Mean (SD) *d'* and accurate reaction time (ms) of 2-back and 3-back after different stimulation conditions, and statistical tests. Asterisks (*) represent significant main effect.

	2-back			**3-back**		
	BL	**T15**	**T40**	**BL**	**T15**	**T40**
d' (SD)						
SH+SH	3.18 (0.92)	3.31 (0.89)	3.25 (1.05)	2.48 (1.02)	2.71 (1.14)	2.63 (1.01)
SH+iTBS	3.15 (0.87)	3.24 (0.94)	3.53 (0.84)	2.44 (1.03)	2.60 (0.96)	2.76 (1.02)
iTBS+iTBS	3.26 (1.07)	3.45 (0.88)	3.44 (0.87)	2.41 (0.98)	2.56 (1.01)	2.65 (1.10)
Two-way ANOVA (3x3)	**Condition** $F_{2,34} = 0.648$, $p = 0.529$	**Time** $F_{2,34} = 4.100$, $p = 0.025$*	**Interaction** $F_{4,68} = 0.970$, $p = 0.430$	**Condition** $F_{2,34} = 0.263$, $p = 0.770$	**Time** $F_{2,34} = 5.375$, $p = 0.009$*	**Interaction** $F_{4,64} = 0.606$, $p = 0.659$
Reaction time (SD)						
SH+SH	473.07 (76.82)	459.75 (106.60)	482.16 (88.24)	514.95 (115.98)	530.93 (154.74)	515.02 (134.26)
SH+iTBS	477.84 (109.54)	463.47 (106.99)	465.55 (91.63)	514.07 (139.13)	522.27 (124.49)	526.23 (133.99)
iTBS+iTBS	473.45 (89.40)	466.43 (81.99)	477.02 (119.26)	506.74 (94.19)	543.04 (128.90)	515.93 (108.75)
Two-way ANOVA (3x3)	**Condition** $F_{2,34} = 0.025$, $p = 0.975$	**Time** $F_{2,32} = 0.762$, $p = 0.474$	**Interaction** $F_{4,64} = 0.351$, $p = 0.482$	**Condition** $F_{2,32} = 0.010$, $p = 0.990$	**Time** $F_{2,32} = 1.304$, $p = 0.285$	**Interaction** $F_{4,64} = 0.565$, $p = 0.689$

In light of recent meta-analysis of the working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex (Brunoni and Vanderhasselt, 2014), we calculated Hedges' *g* (Hedges, 1985) for the measure of effect size compared to sham stimulation in the change in *d*' (Δ *d')* in a similar manner to be comparable to the meta-analysis. We found a moderate size improvement in accuracy following SH+iTBS compared to sham stimulation only at T40 in both 2-back and 3-back tasks. iTBS+iTBS condition showed a small size improvement, again only at T40 in both 2-back and 3-back tasks (Table S5).

Table S5. Effect sizes from comparison between active iTBS vs sham stimulation in accuracy (*d'*)

	2-back Δ *d'*		**3-back Δ *d'***	
	T15	**T40**	**T15**	**T40**
SMD (95% CI)				
SH+iTBS vs SH+SH	-0.06 (-0.71 0.59)	0.48 (-0.18 1.15)	-0.11 (-0.76 0.55)	0.43 (-0.23 1.09)
iTBS+iTBS vs SH+SH	0.13 (-0.53 0.78)	0.25 (-0.41 0.90)	-0.11 (-0.76 0.55)	0.18 (-0.48 0.83)

7. Alertness level following iTBS

We also examined if iTBS had any effect on attention via alertness rating (0: Alert – 10: Vague) (Table S6). One-way repeated measures ANOVA showed no significant main effect of condition ($F_{2,34}$ = 0.056, p = 0.946), time ($F_{1,17}$ = 0.399, p = 0.536), nor interaction ($F_{2,34}$ = 0.764, p = 0.474). We next explored if the alertness level had any influence on the working memory performance using correlational analyses between Δ *d'* and Δ alertness. However, no relationship was observed in any condition at any time point (all p > 0.05).

Table S6. Effect sizes from comparison between active iTBS vs sham stimulation in accuracy (*d'*)

	0: Alert – 10: Vague	
	BL	**T40**
Alertness (SD)		
SH+SH	3.00 (2.32)	3.10 (2.33)
SH+iTBS	3.09 (2.60)	2.74 (2.42)
iTBS+iTBS	3.21 (1.96)	2.88 (2.63)

8. The link between physiological changes and behavioural outcome

To examine if above correlated physiological changes, namely iTBS-induced changes in TMS-evoked N100 (TEP Δ N100) and 3-back task related N200 (ERP Δ N200), had any influence in the improvement of accuracy during 3-back task, correlation analyses were performed against iTBS-induced change in 3-back *d'* with the same datasets used for TEP Δ N100 and ERP Δ N200 correlation (average of 3 fronto-central electrodes: FC1, FCz, FC2). Pearson's correlation revealed significant

correlations between TEP Δ N100 and 3-back Δ *d'* in the SH+iTBS condition at both time points (Post 1, T5 for TEP, T15 for *d'* – *r* = -0.495, *p* = 0.037; Post 2, T30 for TEP, T40 for *d'* – *r* = -0.607, *p* = 0.008; Fig S6A). However, such correlations were not present in the iTBS+iTBS and SH+SH conditions at any time point (all *p* > 0.05; Fig S6B & S6C). Significant correlations found in the SH+iTBS condition indicate that increased TEP N100 amplitude may relate to improved accuracy in working memory performance following a single application of iTBS.

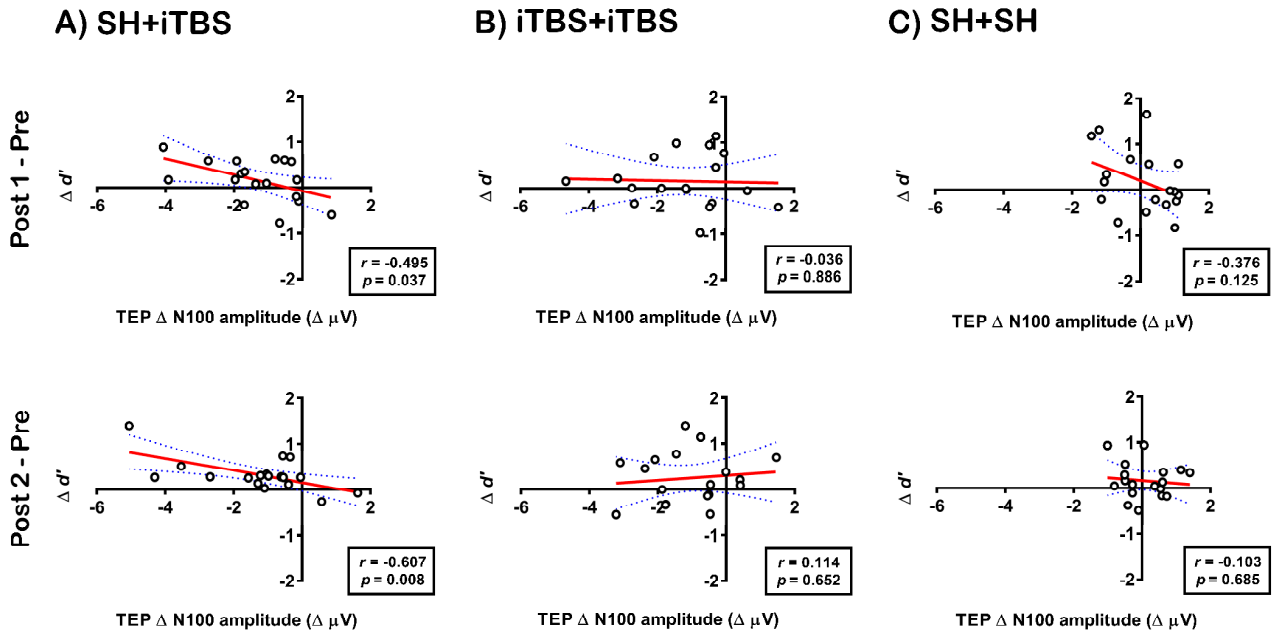

Figure S6. Correlations between intermittent theta burst stimulation (iTBS)-induced changes in transcranial magnetic stimulation (TMS)-evoked N100 amplitude (TEP Δ N100) and accuracy during 3-back task (Δ *d'*) in (A) SH+iTBS (B) iTBS+iTBS and (C) SH+SH conditions. Top rows: early time point (T5 for TEP, T15 for the 3-back task), bottom rows: late time point (T30 for TEP, T40 for the 3-back task).

Similar correlations were observed between ERP Δ N200 and 3-back Δ *d'* in these stimulation conditions. There were significant correlations in SH+iTBS condition at both time points (Post 1, T15 for ERP and *d'* – *r* = -0.591, *p* = 0.010; Post 2, T40 for ERP and *d'* – *r* = -0.515, *p* = 0.029; Fig S7A), but such correlations were absent in iTBS+iTBS or SH+SH condition (all *p* > 0.05; Fig S7B & S7C). Similarly, significant correlations found in SH+iTBS condition suggest that increased ERP N200 amplitude may predict improved accuracy in working memory performance following a single application of iTBS.

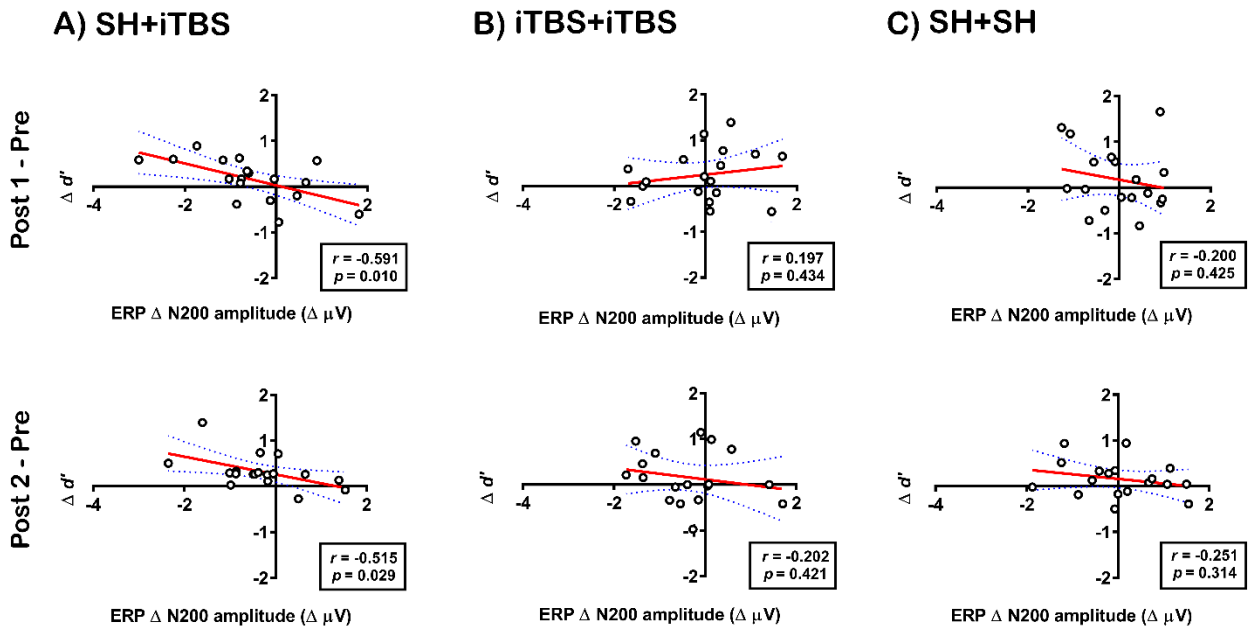

Figure S7. Correlations between intermittent theta burst stimulation (iTBS)-induced changes in 3-back task related N200 amplitude (ERP Δ 200) and accuracy during 3-back task (Δ *d'*) in (A) SH+iTBS (B) iTBS+iTBS and (C) SH+SH conditions. Top rows: early time point (T15), bottom rows: late time point (T40).

References

Aron, A.R., 2007. The neural basis of inhibition in cognitive control. Neuroscientist 13, 214-228.
Brunoni, A.R., Vanderhasselt, M.A., 2014. Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: a systematic review and meta-analysis. Brain Cogn 86, 1-9.
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. Clin Neurophysiol 128, 1117-1126.
Debener, S., De Vos, M., 2011. The benefits of simultaneous EEG-fMRI for EEG analysis. Clin Neurophysiol 122, 217-218.
Delorme, A., Makeig, S., 2004. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods 134, 9-21.
Duncan, C.C., Barry, R.J., Connolly, J.F., Fischer, C., Michie, P.T., Naatanen, R., Polich, J., Reinvang, I., Van Petten, C., 2009. Event-related potentials in clinical research: guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400. Clin Neurophysiol 120, 1883-1908.
Faul, F., Erdfelder, E., Lang, A.G., Buchner, A., 2007. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 39, 175-191.
Hedges, L.V., & Olkin, I., 1985. Statistical Methods for Meta-Analysis. Academic Press., Orlando, FL.
Kappenman, E.S., Luck, S.J., 2010. The effects of electrode impedance on data quality and statistical significance in ERP recordings. Psychophysiology 47, 888-904.
Kopp, B., Rist, F., Mattler, U., 1996. N200 in the flanker task as a neurobehavioral tool for investigating executive control. Psychophysiology 33, 282-294.
Oostenveld, R., Fries, P., Maris, E., Schoffelen, J.M., 2011. FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Comput Intell Neurosci 2011, 156869.
Rogasch, N.C., Daskalakis, Z.J., Fitzgerald, P.B., 2015. Cortical inhibition of distinct mechanisms in the dorsolateral prefrontal cortex is related to working memory performance: a TMS-EEG study. Cortex 64, 68-77.
Rogasch, N.C., Sullivan, C., Thomson, R.H., Rose, N.S., Bailey, N.W., Fitzgerald, P.B., Farzan, F., Hernandez-Pavon, J.C., 2017. Analysing concurrent transcranial magnetic stimulation and electroencephalographic data: A review and introduction to the open-source TESA software. Neuroimage 147, 934-951.
Sasaki, K., Gemba, H., Tsujimoto, T., 1989. Suppression of visually initiated hand movement by stimulation of the prefrontal cortex in the monkey. Brain Res 495, 100-107.
Tanner, D., Morgan-Short, K., Luck, S.J., 2015. How inappropriate high-pass filters can produce artifactual effects and incorrect conclusions in ERP studies of language and cognition. Psychophysiology 52, 997-1009.

CHAPTER ELEVEN

Effects of frequency of iTBS in the prefrontal cortex

Chung SW, Sullivan MC, Rogasch NC, Hoy KE, Bailey NW, Cash RFH, Fitzgerald PB. 2017. The effects of individualised intermittent theta burst stimulation in the prefrontal cortex: a TMS-EEG study.

Preamble to empirical paper

In Chapter 10, repeated application of iTBS in the prefrontal cortex did not result in a linear accumulative effect in either the electrophysiological or behavioural measures. In addition, active stimulation conditions failed to outperform sham stimulation in working memory performance. Previous chapters showed a reliable and replicable electrophysiological metric of iTBS-induced changes in the prefrontal cortex such as TMS-evoked N100, however, effects of iTBS on working memory performance remained elusive.

As shown in the meta-analysis of TBS in the motor cortex (Chapter 7), the most commonly used frequency setting for TBS is 50 Hz burst every 5 Hz, followed by a substantially smaller number of studies using 30 Hz burst at 5 – 6 Hz stimulation. While 30 Hz iTBS has shown a similar effect to 50 Hz stimulation in the motor cortex (Pedapati et al., 2015; Wu et al., 2012a), a direct comparison has not been made. One study reported superiority of 30 Hz stimulation in a comparison study, however, it was done so using cTBS in the motor cortex (Goldsworthy et al., 2012b). In addition, the 'one-size-fits-all' approach may not be most optimal in plasticity induction, and more tailored approach may improve the efficacy of

stimulation. As such, a new method for determining individual iTBS frequencies was developed by measuring theta-gamma coupling during a working memory task in participants prior to iTBS.

In the final empirical paper of this thesis, the effects of different frequency of iTBS (30/6 Hz, 50/5Hz and individualised Hz) were compared using TMS-EEG and its impact on mood and working memory performance were investigated. It was hypothesised that individualised iTBS would result in the greatest change in TMS-evoked P60 and N100 amplitude, followed by 30Hz and 50 Hz. Improvement in mood and working memory performance were also anticipated in the same order.

The effects of individualised intermittent theta burst stimulation in the prefrontal cortex: a TMS-EEG study

Sung Wook Chung[1]
Caley M. Sullivan[1]
Nigel C. Rogasch[2]
Kate E. Hoy[1]
Neil W. Bailey[1]
Robin F.H. Cash[1]
Paul B. Fitzgerald[1,3]

1. Monash Alfred Psychiatry Research Centre, Monash University, Central Clinical School and The Alfred, Melbourne, Australia

2. Brain and Mental Health Laboratory, School of Psychological Sciences and Monash Biomedical Imaging, Monash Institute of Cognitive and Clinical Neuroscience, Monash University, Melbourne, Australia

3. Epworth Clinic, Epworth Healthcare, Camberwell VIC, Australia

Correspondence: Sung Wook Chung
Monash Alfred Psychiatry Research Centre
[redacted]

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Abstract

Introduction: Recent studies have highlighted neurophysiological and behavioural variability in response to theta burst stimulation (TBS) in humans. The TBS paradigm was originally developed in rodents to mimic gamma bursts coupled with theta rhythms, and was shown to elicit long-term potentiation. The protocol was subsequently adapted for humans using a standardised frequency of stimulation. However, each individual has different rhythmic firing pattern. The present study sought to explore whether individualised intermittent TBS (Ind iTBS) could outperform the neurophysiological and behavioural (mood and working memory) effects of two other iTBS variants.

Methods: 20 healthy volunteers received iTBS over left prefrontal cortex using 30 Hz at 6 Hz, 50 Hz at 5 Hz, or individualised (Ind) frequency in separate sessions. Ind iTBS was determined using theta-gamma coupling during the 3-back task. Concurrent use of transcranial magnetic stimulation and electroencephalography (TMS-EEG) was used to track changes in cortical plasticity. We also utilised mood ratings using a visual analogue scale and assessed working memory via the 3-back task before and after stimulation.

Results: No group-level effect was observed following either 30 Hz or 50 Hz iTBS in TMS-EEG. Ind iTBS significantly increased the amplitude of the TMS-evoked P60, and decreased N100 and P200 amplitudes. A significant positive correlation between neurophysiological change and change in mood rating was also observed. Improved accuracy in the 3-back task was observed following both 50 Hz and Ind iTBS conditions.

Conclusions: These findings highlight the critical importance of frequency in the parameter space of iTBS. Tailored stimulation parameters appears more efficacious than standard paradigms in neurophysiological and mood changes. This novel approach presents a promising option and benefits may extend to clinical applications.

Keywords: Theta burst stimulation (TBS); theta-gamma coupling; TMS-EEG; prefrontal cortex; working memory; mood

Abbreviations: Ag/AgCl, silver-silver chloride; BL, baseline; EEG, electroencephalography; GABA, gamma-aminobutyric acid; ICA, independent component analysis; ICF, intracortical facilitation; Ind, individualised; LTD/LTP, long-term depression/potentiation; MEP, motor evoked potential; MNE, minimum norm estimation; (a/r) MT, (active/resting) motor threshold; PAC, phase-amplitude coupling; SAI, short-latency afferent inhibition; SICI, short-interval intracortical inhibition; tDCS, transcranial direct current stimulation; TGC, theta-gamma coupling; (c/i) TBS, (continuous/intermittent) theta burst stimulation; TEP, TMS-evoked potential; (r)TMS, (repetitive) transcranial magnetic stimulation

1. Introduction

Theta burst stimulation (TBS) is a modified form of repetitive transcranial magnetic stimulation (rTMS) which is able to modulate brain activity beyond the time of stimulation in humans (Huang et al., 2005). TBS was originally developed from the observation of patterned neuronal firing that occurred in rats during exploratory behaviour (Larson and Munkacsy, 2015). The stimulation pattern mimicking such bursts of neuronal firing, i.e. the combination of the complex-spike pattern (gamma frequency at 100 Hz) with a theta frequency (~5 Hz) repetition rate, resulted in robust long-term potentiation (LTP) in the hippocampal slices (Larson et al., 1986). This patterned stimulation protocol was adapted in humans using similar frequency parameters to animal models and has been widely used for over a decade. Typically, TBS in humans involves the application of high-frequency bursts (3 pulses at 50Hz) at low-frequency interval (5 Hz) using a total of 600 pulses at 70 – 80% of active/resting motor threshold (a/rMT). When applied continuously (cTBS) for 40 s, TBS has shown to decrease corticospinal excitability measured via motor-evoked potentials (MEPs) for up to 60 mins. When applied intermittently (iTBS; 2 s on, 8 s off) for 192 s, an opposite effect was observed up to 30 mins (Huang et al., 2005).

Despite early reports of robust changes in the size of MEPs beyond the stimulation duration (Di Lazzaro et al., 2008; Huang et al., 2005), studies of TBS have shown large variability in recent years. Studies with larger sample sizes have shown no overall effects of TBS (Hamada et al., 2013; Lopez-Alonso et al., 2014), and a recent meta-analysis has found evidence that the effect sizes in the literature may be overestimated (Chung et al., 2016). One possible reason for the large variability in responses to TBS may be due to the direct adaptation of the method used in the animal studies. The peak frequency of theta oscillations not only differs between rodents and humans (Jacobs, 2014; Watrous et al., 2013), but also between subjects and within subjects at different time points (Klimesch et al., 1996). Some studies have modified the frequency of TBS (30 Hz at 6 Hz) and found more robust effects in the motor region (Goldsworthy et al., 2012) and frontal eye fields (FEF)

(Nyffeler et al., 2006a, b). While it remains unknown which frequency is responsible for the enhanced outcome, targeting the centre frequency of the intrinsic rhythm, i.e. 6 Hz in theta (4 – 8 Hz), may have played an important role. More recently, Brownjohn and colleagues (Brownjohn et al., 2014) investigated whether applying TBS at individual theta peak would result in larger effects in the motor cortex, however, improved effects were not obtained compared to conventional TBS. It is possible that the interaction between modulating (theta) and modulated (gamma) signals is more important for improving the effect of TBS. The relationship between theta and gamma, also known as theta-gamma coupling (TGC), plays a key role in cognitive processing and communication between brain regions (Lisman, 2010; Lisman and Jensen, 2013; Schack et al., 2002; Tort et al., 2009). In humans, TGC has been observed during working memory tasks in hippocampal intracranial (Chaieb et al., 2015) and electroencephalography (EEG) recordings (Friese et al., 2013; Koster et al., 2014; Park et al., 2013). Given that the theta-gamma relationship is variable between subjects, TGC may hold the key to improving the effects of TBS using more physiologically derived parameters.

The optimisation of TBS by tailoring the protocol at individual level would have potential clinical importance as TBS is increasingly being investigated as an alternative to conventional rTMS in various clinical populations due to its short application time and low intensity requirement (Desmyter et al., 2016; Prasser et al., 2015; Turriziani et al., 2012). The variability in neurophysiological and behavioural outcomes present therapeutic limitations, an obstacle that needs to be addressed. In particular, research should address this issue examining clinically relevant areas such as the prefrontal cortex, the focus of investigation for psychiatric and cognitive disorders.

Advances in technology have facilitated the measurement of plastic changes following neuromodulation in non-motor regions using concurrent recording of TMS and EEG (TMS-EEG) (Casula et al., 2016; Chung et al., 2017a; Chung et al., 2015; Hill et al., 2017). Measuring TMS-evoked responses before and after neuromodulatory paradigms provides a metric of neural plasticity at the cortical level. For instance, a positive peak at a latency of 60 ms (P60) may provide a marker of

excitability in motor and prefrontal regions (Cash et al., 2017b; Hill et al., 2017), whereas a negative peak at a latency of 100 ms (N100) may be associated with inhibitory mechanisms [in motor regions (Bonnard et al., 2009; Premoli et al., 2014b; Rogasch et al., 2013a); in prefrontal regions (Chung et al., 2017a; Rogasch et al., 2015)]. Consequently, the balance in the relationship between the P60 and N100 has been proposed to relate to the balance of neural excitation and inhibition in humans (Noda et al., 2017c).

In the present study, we investigated the effects of different frequencies of iTBS (30 Hz at 6 Hz, 50 Hz at 5 Hz and individualised frequency) on neurophysiological measures using TMS-EEG. We also measured mood on a visual analogue scale (VAS) and working memory performance via 3-back task following iTBS to investigate relationship between the neurobiological effects of iTBS and the change in behaviour. We hypothesized that individualised iTBS would produce the strongest change in P60 and N100, followed by 30 Hz and 50 Hz stimulation.

1. Material and methods

1.1. Participants

Twenty right-handed healthy subjects (26.0 ± 9.2 years, 13 female) volunteered in the study. The average years of education were 16.5 ± 3.0 years. All participants were screened with Mini International Neuropsychiatric Interview to confirm no history of psychiatric illness (Sheehan et al., 1998) and written informed consent was obtained prior to the experiment. Ethics approval for the study was obtained from the Alfred Hospital and Monash University Human Research and Ethics Committee.

1.2. Procedure

Figure 1 depicts the overview of the experimental design. Each participant attended 3 sessions (pseudorandomised) with each session at least 72 hours apart to avoid any potential carry-over effects. The experimental procedures comprised concurrent recording of EEG during 75 single TMS pulses at baseline (BL), 5-min post (T5) and 30-min post (T30) iTBS over the left prefrontal cortex. Volunteers received iTBS at varying frequency; either (1) 30 Hz bursts repeated at 6 Hz (30 Hz iTBS), (2) 50 Hz bursts repeated at 5 Hz (50 Hz iTBS), or (3) individualised frequency (Ind iTBS) in each session. Subjects also performed the 3-back working memory task at BL, 20-min post (T20) and 45-min post (T45) iTBS while EEG was recording. Participants rated their current mood on visual analogue scales (VAS) at BL and 60-min post (T60) iTBS. During the resting period at BL, theta-gamma coupling (TGC) from the EEG data during the 3-back task was analysed off-line to determine individualised iTBS stimulation frequencies (see below for details).

Insert Figure 1 Here

1.3. EEG recordings

EEG recordings were obtained from 50 TMS-compatible Ag/AgCl electrodes on a 64-channel EEG cap (FP1, FP2, AF3, AF4, F7, F5, F3, F1, Fz, F2, F4, F6, F8, FC5, FC3, FC1, FCz, FC2, FC4, FC6, T7, C5, C3, C1, Cz, C2, C4, C6, T8, CP5, CP3, CP1, CP2, CP4, CP6, P7, P5, P3, P1, Pz, P2, P4, P6, P8, PO3, POz, PO4, O1, Oz, O2) via Synamps^2 amplifier onto Neuroscan Acquire software (Compumedics, Melbourne, Australia). Electrodes were on-line referenced to CPz and grounded to FPz. For TMS-EEG recordings, EEG signals were amplified (1,000 x) and low-pass filtered (DC – 2,000 Hz) with a high acquisition rate of 10,000 Hz using a large operating window (± 200 mV). For EEG recordings during the 3-back task, EEG signals were filtered (0.05 – 200 Hz) and sampled at 1,000 Hz with an operating range of ± 950 μV. During TMS-EEG recordings, participants listened to white noise through intra-auricular earphones (Etymotic Research, ER3-14A, USA) to limit the contamination of the EEG signals produced by the TMS click sound (Nikouline et al., 1999; Rogasch et al., 2014). The sound level was adjusted individually until single TMS pulses at 120% rMT were adequately blocked.

1.4. Transcranial magnetic stimulation

Both single-pulse TMS and iTBS were delivered using a figure-of-eight MagVenture B-65 fluid-cooled coil (MagVenture A/S, Denmark) in a biphasic mode. Stimuli were applied to the left hemisphere with the coil positioned at 45° angle relative to midline (handle pointing posterior). Resting motor threshold (rMT) was determined as the minimum stimulus intensity required to elicit at least 3 out of 6 motor evoked potentials (MEPs) > 0.05 mV in amplitude (Conforto et al., 2004) in the relaxed first dorsal interosseous muscles. Prefrontal TMS was administered over F1 electrode as previously described (Chung et al., 2017b). The edge of the coil was marked on the cap for consistent re-positioning of the coil. This has shown accuracy to within 5 mm when neuronavigation is not available (Rogasch et al., 2013b). A thin plastic template was mounted on the EEG cap to ensure 45° angle and tangential placement of coil to further improve the consistency within and between

sessions (Supplementary Material, Section 1). Subjects received 75 single pulses to left prefrontal at 120% rMT before and after different iTBS conditions; (1) 30 Hz bursts repeated at 6 Hz (Goldsworthy et al., 2012), (2) 50 Hz bursts repeated at 5 Hz (Huang et al., 2005), (3) individualised frequency. Each iTBS block consisted of a burst of 3 pulses repeated 10 times with an 8 s break for a total of 600 pulses. The intensity of stimulation was adjusted to 75% of individuals' rMT. This intensity was selected as our previous study demonstrated more robust cortical effects following iTBS compared to 50% or 100% rMT (Chung et al., 2017b). The average intensity for each condition was as follows (mean ± SD): 30 Hz iTBS = 51.6 ± 6.5 %; 50 Hz iTBS = 51.6 ± 6.4 %; Ind iTBS = 51.6 ± 6.4 %.

1.5. Working memory task

Each participant performed 5 mins of the 3-back task before (BL) and after (T20 & T45) iTBS. A randomised series of white letters (A to J) were presented consecutively on a black screen for 500 ms followed by 1500 ms of a blank screen. Participants were instructed to remember each stimulus and press a button when the presented letter corresponded to the one that appeared three letters earlier (3-back) (Fig 1B). The task contained 25% target trials out of 130 letters in total. Working memory performance was evaluated using the d prime sensitivity (*d'*; *z*-transformed values of hit-rate minus false-alarm rate) and accurate reaction time (Haatveit et al., 2010).

1.6. Mood rating

The mood rating was assessed via self-rated visual analogue scale (VAS) (Ahearn, 1997), which has been used to evaluate the mood state in both clinical (Le-Niculescu et al., 2009) and healthy populations (Robinson et al., 2010; Robinson and Sahakian, 2009). Subjects drew a line on a 100 mm VAS to indicate their current mood compared to saddest subject has ever felt (0) and happiest subject has ever felt (100) (Fig 1C).

1.7. Manipulation of the pulse intervals

For a flexible and rapid manipulation of pulse intervals for iTBS, the Arduino open-source microcontroller platform was used (https://www.arduino.cc/). The Arduino is an inexpensive, low-level microcontroller which has an excellent temporal resolution owing to its property of bypassing the hardware and software environments of modern operating systems (D'Ausilio, 2012). Several studies have shown that the Arduino is able to measure signals with less than 1 ms variability (D'Ausilio, 2012; Schubert et al., 2013; Schultz and van Vugt, 2016), making it an ideal low-cost lab equipment. A customised script allowed for an instantaneous manipulation of pulses at desired theta and gamma frequencies. This process reduced the waiting period for the manual programming of MagVenture machine and ensured subject blinding and consistent procedural steps across different conditions. A comparison example between the MagVenture and Arduino programmed stimuli (50 Hz iTBS) can be found in the Supplementary Material, which shows no difference between the two techniques in TBS trigger timing, Fig S2.

1.8. Selection of individualised frequencies of iTBS based on theta-gamma coupling

The individualised frequency for Ind iTBS was determined by the phase-amplitude cross-frequency coupling (PAC) between frontal theta (phase) and parietal gamma (amplitude) oscillations during the 3-back task. Detailed information can be found in Supplementary Material, Section 3. Briefly, ten correct trials were selected by randomly ordering the epochs and using the first 10 epochs after shuffling for TGC (45 s in length; Fig 2A). The raw signals were filtered at the respective frequencies; 3 – 9 Hz for theta (Fz electrode) and 20 – 70 Hz for gamma (Pz electrode). Data were subjected to Hilbert transform and theta-filtered gamma amplitude envelope was then extracted prior to PAC estimation (Fig 2B). Phase-amplitude coupling between theta and gamma was calculated using a general linear model (GLM) (Penny et al., 2008) and performed at every filter step to produce a comodulogram matrix. The peak of the comodulogram matrix was used to infer the specific

frequencies within the theta (4 – 8 Hz) and gamma (30 – 60 Hz) bands at which the highest coupling occurred, yielding individual theta and gamma frequencies for iTBS (Fig 2C shows examples from two participants, maximum value indicated by black asterisks). Participants' individualised frequency of stimulation are plotted in figure 2D, with an average of gamma frequency at 41.90 ± 7.7 Hz and theta frequency at 5.97 ± 1.0 Hz. This procedure was performed for every condition to be consistent across different sessions and thereby minimising any potential differences in total duration of the experiment.

Insert Figure 2 Here

1.9. EEG data preprocessing

TMS-EEG data were analysed offline using EEGLAB (Delorme and Makeig, 2004), TESA (Rogasch et al., 2017), FieldTrip (Oostenveld et al., 2011) toolboxes and custom scripts within the MATLAB platform (R2015b, The MathWorks, USA). Preprocessing steps of EEG data followed previously description (Chung et al., 2017a). Data were epoched around the TMS pulse (-1,000 to 1,000 ms), baseline corrected (-500 to -50 ms) and the large magnetic pulses were removed and interpolated (-5 to -15 ms). The epoched data were concatenated across three time points (BL, T5 and T30) to avoid bias in component rejection from the independent component analysis (ICA). Data were downsampled to 1,000 Hz and manual inspection was performed to remove epochs containing excessive noise (i.e. burst of muscle activity) and/or disconnected electrodes. The average number of epochs included in the analyses for each condition was as follows (mean ± SD): 30 Hz iTBS = 73.0 ± 3.2; 50 Hz iTBS = 72.4 ± 3.6; Ind iTBS = 73.5 ± 2.1. Two rounds of ICA (FastICA, 'tanh' contrast) were performed for the artefact rejection using semi-automated component classification algorithm

(tesa_compselect function (Rogasch et al., 2017)). The first ICA was used to remove the remaining tail of TMS-evoked muscle artefacts (Rogasch et al., 2014) which was identified if the component time course was 8 times larger than the mean absolute amplitude across the entire time course. All data were band-pass (Butterworth, second-order, zero-phase, 1 – 80 Hz) and band-stop filtered (line noise removal, 49 – 51 Hz), and epochs were visually inspected again to remove any anomalous activity in the EEG data. The second round of ICA was performed to remove other non-neural artefacts including eye blinks and saccadic movement (mean absolute *z* score of two frontal electrodes FP1 and FP2 > 2.5), persistent muscle activity (high frequency power > 60% of total power), decay artefact and electrode noises (absolute *z* score of an electrode(s) > 4. Removed channels were interpolated and FP1 and FP2 were removed from all the datasets as these channels were generally contaminated by artefacts. Finally, data were re-referenced to common average and were segregated into original time point blocks (BL, T5 and T30) and epochs averaged.

For the EEG data during the 3-back task, continuous EEG data were band-pass (Butterworth, second-order, zero-phase, 0.1 – 80 Hz) and band-stop (49 – 51 Hz) filtered. Data were then epoched around the correctly responded trial (-7,000 ms to 1,000 ms) which contained a correct probe (e.g. first 'H' in Fig 2A), correct holds (correctly not responded; e.g. 'D' and 'E' in Fig 2A), and a correct response (e.g. 'H' with an arrow above in Fig 2A). This epoch was chosen for having all sequence of items leading to a correct response. Data were baseline corrected to the entire trial, visually inspected to remove any epochs containing a burst of muscle activity and underwent one round of ICA. The same component rejection was performed as the second round of ICA of TMS-EEG data. Any removed channels were then interpolated, FP1 and FP2 removed as mentioned above, and data were re-referenced to common average.

1.10. TMS-evoked potentials (TEPs)

Graphical representation of the waveforms was produced using the average of three fronto-central electrodes (FC1, FCz and FC2) for the close proximity of the stimulation site (F1 electrode), while F1 was omitted to avoid introducing TMS coil contact related noise to the waveform (Rogasch et al., 2013a). Statistical analyses were conducted on TEPs using cluster-based permutation tests at a global scalp level. Comparisons were made using the averaged amplitude values of pre-defined time windows for the peaks of interest; N45 (40 – 55 ms), P60 (55 – 85 ms), N100 (95 – 135 ms) and P200 (160 – 240 ms). These peaks are commonly observed following prefrontal stimulation (Chung et al., 2017a; Hill et al., 2017; Rogasch et al., 2014). Extraction of TEP values (for graphical representation and statistical / correlational analyses) was performed using the averaged signal ± 5 ms of maximum (for positive peaks) and minimum (for negative peaks) values within the range window as above, consistent with previous studies (Chung et al., 2017a; Hill et al., 2017; Opie et al., 2017). Exploratory analyses were performed regarding the relationship between iTBS-induced change in P60 and N100 amplitudes in order to examine whether significant differences in any of the iTBS conditions could reflect altered inhibitory / excitatory balances (Noda et al., 2017c).

1.11. Source estimation

All estimation of the cortical source was performed using Brainstorm (Tadel et al., 2011) which is documented and freely available for download online under the GNU general public licence (http://neuroimage.usc.edu/brainstorm/). Individual magnetic resonance imaging scans were unavailable, and hence EEG data were co-registered with the template model (ICBM 152). The forward model used the Symmetric Boundary Element Method implemented in OpenMEEG software (Gramfort et al., 2010) and the inverse model used the computation of minimum norm estimations (MNEs) with dipole orientations constrained to be normal to the cortex (Lin et al., 2006). Differences in estimation were calculated using absolute subtraction.

1.12. Statistical analyses

All statistical analyses were performed in SPSS (IBM Corp, Armonk, Ny; Version 22), MATLAB, and Fieldtrip. Analyses of TEPs were conducted using non-parametric cluster-based permutation statistics which provides a model-free method that does not run the risk of violating the assumptions of parametric tests and is an effective method of controlling for multiple comparisons across space (EEG channels) and time (Oostenveld et al., 2011). It is therefore commonly used in the analysis of TMS-EEG, EEG, MEG and MRI research (Casula et al., 2016; Maris and Oostenveld, 2007; Opie et al., 2017; Premoli et al., 2017). Comparisons were first made across time point for each iTBS condition (within-comparison; between BL and T5 / T30). Between-condition comparisons were performed using change-from-baseline scores (post – pre; Δ). Monte Carlo p-values were calculated on 2,500 random permutations and clusters were defined as more than 2 neighbouring electrodes with a *p*-value of < 0.05, controlling for multiple comparisons across space ($p < 0.025$; two-tailed test).

For mood rating, one-way repeated measure analysis of variance (ANOVAs) were computed between conditions using Δ values (post-pre). For the 3-back task, two-way repeated measure analysis of variance (ANOVAs) was used to investigate working memory performance 3 [stimulation conditions (30 Hz, 50 Hz and Ind iTBS)] x3 [time (BL, T20 and T45)]. Post-hoc pairwise comparisons were performed using Bonferroni corrections to further explore the significant main effects, while significant interactions were examined using one-way ANOVAs and paired *t-tests*.

For variability and correlational analyses, data were extracted from the average of 6 prefrontal electrodes (F1, Fz, F2, FC1, FCz and FC2). The TEP peaks were detected within the pre-defined time window as stated in Section 2.10 [N45 (40 – 55 ms), P60 (55 – 85 ms), N100 (95 – 135 ms) and P200 (160 – 240 ms)] and the amplitude was calculated by averaging the signal between ± 5 ms of the selected peak latency as previously described (Chung et al., 2017a). Pearson's correlations were used to examine the relationship between the change in physiological measures (e.g. Δ N100) and the

change in behavioural outcome (e.g. Δ mood). The ratio between Δ N100 and Δ P60 resulted in extreme outliers. The data were tested for normality (Shapiro-Wilk test) and outliers were winsorised by setting extreme values to the corresponding adjacent 5th and 95th percentile value (Wilcox, 1997).

2. Results

2.1. Baseline single-pulse TMS

Single-pulse TMS over left prefrontal cortex resulted in a series of negative and positive peaks including N45, P60, N100 and P200 (Fig 3A). Consistent with other TMS-EEG studies in the prefrontal cortex (Chung et al., 2017a; Hill et al., 2017; Rogasch et al., 2014), each peak showed a distinctive pattern in scalp topography (Fig 3B) and source estimation (Fig 3C).

Insert Figure 3 Here

2.2. Plastic effects of iTBS on TMS-evoked potentials (TEPs)

We first performed comparisons on the amplitude of TEPs between stimulation conditions at BL, and found no significant differences (all $p > 0.025$; two-tailed test). We next assessed the iTBS-induced effects on the amplitude of TEPs within each stimulation condition over time (T5 vs BL and T30 vs BL). Testing for an effect in each peak of interest in pre-defined latency range (refer to Section 2.8), the cluster-based permutation tests revealed no significant differences between baseline (BL) and any of post-iTBS (T5 and T30) following both 30 Hz (Fig 4A) and 50 Hz (Fig 4B) iTBS at any peak (all $p > 0.025$).

However, Ind iTBS showed significant differences between BL and T5 for the P60 (increase, p = 0.021, frontal), N100 (decrease, p = 0.014, fronto-central) and P200 (decrease, p = 0.012, fronto-central; p = 0.009, posterior), and between T30 and BL for the P60 (increase, p = 0.020, posterior) and N100 (decrease, p = 0.008, fronto-central) (Fig 4C).

Insert Figure 4 Here

Examination of the response to each iTBS condition in TEPs demonstrated large inter-individual variability following both 30 Hz and 50 Hz iTBS (see Table 1). More in-depth exploration of inter-individual variability can be found in Supplementary Material, Section 5.

Table 1. Percentage of subjects in which TEPs increased/decreased relative to baseline.

		P60			N100			P200		
		30Hz	**50Hz**	**Ind**	**30Hz**	**50Hz**	**Ind**	**30Hz**	**50Hz**	**Ind**
T5	↑	50 %	45 %	**80 %**	60 %	45 %	50 %	55 %	50 %	35 %
	↓	50 %	55 %	20 %	40 %	55 %	**50 %**	45 %	50 %	**65 %**
T30	↑	55 %	40 %	**75 %**	45 %	45 %	30 %	55 %	45 %	45 %
	↓	45 %	60 %	25 %	55 %	55 %	**70 %**	45 %	55 %	55 %

*Significant changes highlighted in bold (based on cluster-based statistics)

We next conducted across-condition comparisons using the change-from-baseline scores (Δ) obtained from subtracting pre-signals (BL) from post-signals (T5 and T30). We found that Δ P60 was significantly larger following Ind iTBS compared to 30 Hz iTBS at T30 (p = 0.018, frontal) (Fig 5D), and compared to 50 Hz iTBS at T5 (p = 0.021, frontal; p = 0.015, posterior) and T30 (p = 0.022, posterior) (Fig 5E). Source estimation of P60 largely corroborated the results of the sensor-level analysis whereby Ind iTBS showed increased current density at the site of stimulation (Fig 5A) while minimal changes were seen following 30 Hz (Fig 5B) or 50 Hz (Fig 5C) iTBS. iTBS-induced change in other peaks (Δ N45, Δ N100 and Δ P200) yielded in no significant differences in these comparisons (all p >

0.025). In addition, no significant differences in iTBS-induced change were found between 30 Hz and 50 Hz iTBS in any peak at any time point (all $p > 0.025$).

To validate the statistical method used for the comparison of TEPs in this study (nonparametric cluster-based permutation statistics), 3 (iTBS condition) x 3 (time) repeated measures ANOVA was performed using the data extracted from 6 frontal electrodes (F1, Fz, F2, FC1, FCz and FC2) as described in section 2.12. The results corroborated the outcomes following cluster-based statistics (Supplementary Materials, Section 6).

Insert Figure 5 Here

2.3. Effects of iTBS on the relationship between P60 and N100

Previous research has demonstrated relationship between P60 and N100 (Noda et al., 2017c). We explored whether there was an association in changes in the amplitude of these peaks following iTBS. For this analysis, electrodes were chosen to ensure that changes in P60 and N100 were captured across individuals and comprised F1, Fz, F2, FC1, FCz and FC2 electrodes. While Pearson's correlations revealed no significant correlations following 30 Hz iTBS at any time point (T5 – r = -0.371, p = 0.108; T30 – r = 0.298, p = 202) (Fig 6A), strong negative correlations were found following 50 Hz iTBS at both time points (T5 – r = -0.700, p = 0.001; T30 – r = -0.615, p = 0.004) (Fig 6B) indicating that increased P60 amplitude (more positive) was related to increased N100 amplitude (more negative) following iTBS. Even though this correlation was absent at T5 following Ind iTBS (r = 0.072, p = 0.763), it was present at T30 (r = -0.710, p = 0.001) (Fig 6C).

Insert Figure 6 Here

2.4. The effect of different frequency of iTBS on mood rating

We examined the effects of different iTBS conditions on mood and the relationship between neurophysiological changes and mood changes. The average mood rating before and after each stimulation condition was as follows (BL & T60; mean ± SD; rating out of 100 on VAS, see methods): 30 Hz iTBS = 77.3 ± 13.3 & 78.2 ± 13.7; 50 Hz iTBS = 76.4 ± 12.6 & 77.4 ± 14.9; Ind iTBS = 75.6 ± 13.0 & 81.4 ± 11.6. There were no significant differences between conditions at baseline. One-way repeated measures ANOVA for Δ mood rating yielded a significant main effect of condition ($F_{2,38}$ = 5.495, p = 0.008). Post-hoc pairwise comparison revealed that Δ mood was significantly larger following Ind iTBS compared to both 30 Hz (p = 0.024) and 50 Hz (p = 0.046) iTBS (Fig 7A). No significant difference was found between 30 Hz and 50 Hz iTBS (p = 1.000).

We next explored which neurophysiological changes, namely P60, N100 and P200, corresponded to the changes in mood using the combined dataset (n = 60). Using the same data from above correlations (average of 6 fronto-central electrodes), Pearson's correlations revealed a significant positive correlation between Δ mood and Δ P60 at T5 (r = 0.293, p = 0.023) (Fig 7B) but not at T30 (r = 0.055, p = 0.674). No significant correlation was found between Δ mood and Δ N100 at T5 (r = 0.203, p = 0.119), but showed a significant positive correlation at T30 (r = 350, p = 0.006) (Fig 7C). No significant correlation was found between Δ mood and Δ P200 (r = -0.049, p = 0.713) (Fig 7D). A significant positive correlation indicates increased P60 (more positive) / decreased N100 (less negative) corresponds to higher mood rating.

Insert Figure 7 Here

2.5. The effect of different frequency of iTBS on working memory performance

Order effect analysis was first conducted on the working memory performance at baseline across different stimulation conditions. One-way repeated measures ANOVA resulted in no significant session order effect in either accuracy ($F_{2,38}$ = 0.146, p = 0.865) or accurate reaction time ($F_{2,38}$ = 0.563, p = 0.574), confirming the effectiveness of the counter balancing.

Figure 8 illustrates working memory performance assessed via accuracy (*d*') and accurate reaction time (in ms) in different stimulation conditions over time. Two-way repeated measures ANOVA for *d*' demonstrated a significant interaction between Condition and Time ($F_{4,76}$ = 4.534, p = 0.002). A series of one-way ANOVAs was performed to further explore the interaction effect. Within condition comparisons resulted no significant main effect of time in the 30 Hz iTBS condition ($F_{2,38}$ = 0.138, p = 0.871), but a significant main effect of time in the 50 Hz iTBS condition ($F_{2,38}$ = 5.905, p = 0.006), and a significant main effect of time in the Ind iTBS condition ($F_{2,38}$ = 7.173, p = 0.002). Post-hoc pairwise comparisons in 50 Hz iTBS condition revealed that *d*' was significantly higher at T20 compared to BL (p = 0.028) and T45 (p = 0.044). No significant difference was found between BL and T45 (p = 0.100). For Ind iTBS condition, *d*' was significantly higher at T45 compared to both BL (p = 0.029) and T20 (p = 0.039). No significant difference was found between T0 and T20 (p = 0.100).

Between condition comparisons showed no significant main effect at BL ($F_{2,38}$ = 0.407, p = 0.669), but a significant main effect at T20 ($F_{2,38}$ = 4.360, p = 0.020) and a trend toward significance at T45 ($F_{2,38}$ = 2.688, p = 0.081). Post-hoc pairwise comparisons in the main effect at T20 revealed that *d*' was significantly higher following 50 Hz iTBS compared to Ind iTBS (p = 0.015), and non-significantly higher compared to 30 Hz iTBS (p = 0.079). No significant differences were found between Ind iTBS and 30 Hz iTBS (p = 1.000).

For accurate reaction time, two-way repeated measures ANOVA yielded no significant main effect of condition ($F_{2,38}$ = 0.783, p = 0.464) and no significant interaction effect ($F_{2,38}$ = 0.493, p = 0.741), but a significant main effect of time ($F_{2,38}$ = 4.299, p = 0.021).

Insert Figure 8 Here

We also explored if iTBS-induced changes in *d*' (Δ *d*') had any association with Δ P60 and Δ N100, but no significant correlations were found ($p > 0.05$). We sought to determine if the ratio between Δ N100 and Δ P60 (Δ N100/Δ P60) had any influence on the improvement in *d*'. The ratio resulted in outliers which were winsorised to fit normal distribution (2 data points each for 30 Hz iTBS T5 and T30, and Ind iTBS T30). Pearson's correlations revealed no significant correlations in 30 Hz iTBS condition either at early ($r = 0.197$, $p = 0.405$) or late time point ($r = -0.150$, $p = 0.541$) (Fig 9A). In 50 Hz iTBS condition, a significant correlation was observed at early time point ($r = 0.512$, $p = 0.021$), but not at late time point ($r = 0.280$, $p = 0.232$) (Fig 9B). For Ind iTBS, a significant correlation was found at late time point ($r = 0.610$, $p = 0.004$) but not at early time point ($r = 0.364$, $p = 0.115$) (Fig 9C).

Insert Figure 9 Here

2.6. Secondary analyses of sham condition

Secondary analyses of sham condition (data collected from a previous study) revealed no significant changes in TEPs, mood or working memory performance over time (Details in Supplementary Material, Section 7).

3. Discussion

In this study, we examined the neurophysiological effects of iTBS applied at varying frequency in the prefrontal cortex and the association to LTP-like plasticity. We also investigated whether there was a relationship between iTBS-induced changes in neurophysiology and mood and working memory performance. The data indicate large variability in response to iTBS following both 30 Hz and 50 Hz iTBS. However, individualised iTBS resulted in more robust changes in neurophysiology and mood compared to standard paradigms. We also demonstrated that working memory may provide a possible behavioural marker of neurophysiological changes following iTBS. The data suggest the frequency of stimulation is an important parameter of iTBS, and a more tailored stimulation protocol may increase the efficacy, and hence could have implications for its therapeutic application.

3.1. Effect of individualised iTBS on plastic effects in the prefrontal cortex

Individualised iTBS modulated the amplitude of P60, N100 and P200. The increased P60 amplitude was initially localised around the stimulated area, and later also detected at parieto-occipital sensors. This may represent the propagation of activity across interconnected regions of the cortex over time, a conjecture which is supported by the source localisation (Fig 5C). Such an increase in network level of activity following iTBS has been described during working memory performance (Hoy et al., 2016) and TMS-EEG (Chung et al., 2017b). A similar increase in fronto-parietal P60 has also been observed following a facilitatory neuromodulatory technique, anodal transcranial direct current stimulation (tDCS), in the prefrontal cortex (Hill et al., 2017). A growing body of evidence suggests P60 may provide a marker of cortical excitability. In the motor cortex, P60 amplitude positively correlated with MEP amplitude (Rogasch et al., 2013a), and the amplitude was reduced following short-latency afferent inhibition (SAI), an MEP suppression paradigm (Ferreri et al., 2012). In addition, P60 amplitude was attenuated with short-interval intracortical inhibition (SICI) and increased with intracortical facilitation (ICF) in motor cortex (Cash et al., 2017b), concurrent with

changes in MEPs. In the prefrontal cortex, SAI resulted in a reduction of this component (Noda et al., 2017b). SICI reduced and ICF increased the amplitude of P60 (Cash et al., 2017b), supporting the findings from the motor cortex. Therefore, it is possible that increased P60 amplitude following Ind iTBS reflects enhanced cortical excitability in the prefrontal cortex. The Δ P60 following Ind iTBS was larger compared to either 30 Hz or 50 Hz iTBS, particularly around the stimulated region, supported by the cortical activation map.

Individualised stimulation decreased the amplitude of both N100 and P200. While the origin of TMS-evoked P200 is still largely unknown, the physiological property of N100 is more well-defined than other TEPs. The N100 is regarded as the most robust component in TMS-EEG recordings (Noda et al., 2016) with excellent reproducibility (Lioumis et al., 2009) and signal to noise ratio (Chung et al., 2017a). In addition, the N100 deflection is considered to have a high sensitivity to small changes in cortical excitability compared to other TEPs (Nikulin et al., 2003), making it an ideal candidate for tracking neuromodulatory paradigms. Studies have reported N100 to be associated with $GABA_B$-mediated inhibitory mechanisms in both motor (Bonnard et al., 2009; Farzan et al., 2013; Premoli et al., 2014b; Rogasch et al., 2013a) and prefrontal cortex (Chung et al., 2017a; Rogasch et al., 2015). The amplitude of N100 increased following SAI both in motor and prefrontal cortex (Noda et al., 2016; Noda et al., 2017b), but decreased following cerebellar iTBS (Casula et al., 2016), which are in line with the change observed in N100 following Ind iTBS. However, our previous study showed increased N100 following prefrontal iTBS (Chung et al., 2017a), and the discrepancy of the outcome is not yet clear. Again, it is likely that the inter-individual variability contributed to the differences between the studies. Overall, by mimicking the original animal study where application of patterned stimulation resembling spike discharge patterns of hippocampal neurons during exploratory behaviours that led to a robust LTP (Larson et al., 1986), it is possible that tailoring the temporal dynamics of pulses to target the individual's disinhibition window (Cash et al., 2010; Cash et al., 2011) yielded a robust LTP-like effect following Ind iTBS. A similar modified approach of stimulation

(known as disinhibition stimulation) by individualising the intra and inter-burst frequencies have also shown success in LTP-like plasticity induction in the motor cortex (Cash et al., 2016).

3.2. Relationship between iTBS-induced P60 and N100

On the surface, the observation of no overall effects following both 30 Hz and 50 Hz iTBS may imply that the two stimulation conditions are indistinguishable. However, the correlation analyses between Δ P60 and Δ N100 demonstrated a close relationship between the peaks following 50 Hz iTBS which lasted up to 35 mins (See Fig 6B). This pattern was not present in 30 Hz stimulation (See Fig 6A). In addition, 50Hz but not 30Hz stimulation produced changes in working memory performance. On the other hand, Ind iTBS temporarily altered this association at T5 with an overall increase in P60 amplitude, which was balanced by larger changes in N100 at T30, indicating a prolonged elevation of the balance between the two peaks (See Fig 6C). In the human motor cortex, a pharmacological study demonstrated that $GABA_A$ agonists decreased while $GABA_B$ agonists increased the amplitude of N100 (Premoli et al., 2014a). In the instance of the balance between P60 and N100 in this study, a shift in N100 could reflect either an increase in the ratio (reduced $GABA_B$) or a shift to maintain the ratio (increased $GABA_A$ signalling). It is likely to be the latter in this study, and such adaptation of inhibition has also been described in an animal model (Elfant et al., 2008; Heiss et al., 2008). These findings are a suggestive reflection of potential metric for LTP (above 0) or long-term depression (LTD; below 0) with respect to maintenance of the balance between P60 and N100, at least following iTBS.

3.3. Relationship between neurophysiological changes and the change in mood and working memory performance

In line with the neurophysiological effects of iTBS, minimal changes were observed in mood rating following both 30 Hz and 50 Hz iTBS, whereas Ind iTBS resulted in a higher mood rating. Positive correlations were observed only between mood and neurophysiological measures that showed the greatest change (i.e. Δ P60 at T5, Δ N100 at T30), suggesting robust physiological changes are required to translate into a behavioural outcome. Another possible explanation is that the mood ratings were re-assessed 60 mins after iTBS (T60), at which time the effect of iTBS on the P60 may have been washed out. Alternatively, the early changes in neurophysiology and later changes in mood may be both related to another variable such as a change in connectivity or a delayed onset change in TEPs which was not measured at T60 in this study. The correlations were specific to Δ P60 and Δ N100, and not with Δ P200. Characterisation of P200 is needed to better understand its role, as the changes in this component are often observed following neuromodulation (Casula et al., 2016; Chung et al., 2017a; Noda et al., 2016) or in clinical populations (Noda et al., 2017a).

Studies have demonstrated increased or decreased performance of medium-load (2-back) working memory following left prefrontal iTBS (Hoy et al., 2016) and cTBS (Schicktanz et al., 2015), respectively, using the conventional 50 Hz protocol (Huang et al., 2005). In the current study, the 3-back task was used and demonstrated to be a potential behavioural marker of neurophysiological changes following iTBS. The balanced and dynamic regulation of inhibitory and excitatory activity plays an important role in working memory (Knight et al., 1999; Lim and Goldman, 2013), which is a critical aspect of animal (Xue et al., 2014) and human functional neural circuitry (Cash et al., 2017c; Dehghani et al., 2016). While excitatory plasticity provides a mechanism for learning and memory formation (Froemke, 2015), inhibitory plasticity is essential in maintaining the balance for efficient information processing in cortical networks (Deneve and Machens, 2016; Vogels et al., 2011). The origin of TEPs (P60 and N100) are still largely unknown and no consensus has been reached on what each peak represents. While it is speculative, the correlations between working memory performance and the ratio of P60 and N100 may partially be explained by the well-maintained modulation of potential inhibition (N100) and excitation (P60) (Noda et al., 2017c). When both Δ P60

and Δ N100 showed well-balanced changes (50 Hz iTBS at T5, Ind iTBS at T30), the accuracy increased (50 Hz iTBS at T20, Ind iTBS at T45). The physiological changes, namely Δ P60 and Δ N100, did not correlate with the performance change by themselves, but rather the ratio between the changes in these peaks corresponded with the change in performance. This finding indicates that well-balanced change is more important for working memory than changes in either excitation or inhibition in isolation, as increased excitation alone (as shown in TMS-EEG at T5 in Ind iTBS condition) was not able to enhance the accuracy (*d'* at T20 in Ind iTBS condition). Such balance is thought to play an important role in cortical processing and working memory (Kirkwood, 2015; Legon et al., 2016; Lim and Goldman, 2013) and alteration in the balance may lead to cognitive impairment (Cline, 2005; Vogels and Abbott, 2009). However, although 50 Hz iTBS showed significant correlations between Δ P60 and Δ N100 at T30, no sustained improvement was seen in the accuracy of the 3-back task. It is possible that the effect of stimulation was short-lived and may have diminished by T45 when the 3-back task was performed again. In general, the effect of 50 Hz iTBS in the motor cortex lasts up to 30 minutes (Chung et al., 2016). It is unknown if the effects of Ind iTBS would persist longer than T45, and needs to be addressed in the future. However, the elevated mood level at T60 suggests the effect may have been sustained.

3.4. Inter-individual variability in the response to conventional iTBS

A group-level modulation in TEPs was observed following Ind iTBS, but not following 30 Hz nor 50 Hz iTBS. This is in contrast with our previous study in the prefrontal cortex where we observed robust changes following 50 Hz iTBS, particularly in N100 amplitude (Chung et al., 2017a). In addition, there was substantial inter-individual variability in response to iTBS in the current sample (See Table 1). The variability was larger following 30 Hz iTBS, which showed a large varied response in the direction of change in TEPs (increase or decrease at each time point). A notable amount of opposite directional change was also observed between T5 and T30 (Supplementary Material, Section 5). The

reason for such within-subject variability over time (T5 vs T30) following 30 Hz iTBS remains unclear. One possible explanation for this phenomenon is that the effects of 30 Hz iTBS was short-lived and regulatory homeostatic mechanisms were at play. It was interesting to observe that while 50 Hz iTBS also resulted in a large inter-individual variability in the change in TEPs, peaks were in the same direction for both T5 and T30 in the majority of subjects. Subtle modifications of the rTMS protocols can influence the effect of stimulation (Cash et al., 2017a; Cash et al., 2016; Ridding and Ziemann, 2010), and the data suggest frequency of iTBS is an important parameter that can contribute to inter-individual variability.

To our knowledge, 30 Hz iTBS had not been tested in the prefrontal cortex to date, and our data demonstrate no superiority, and probably inferiority, over 50 Hz iTBS. It is interesting to note that cerebellar iTBS resulted in the opposite changes in N100 in two separate studies using 50 Hz (Casula et al., 2016) and 30 Hz stimulation (Harrington and Hammond-Tooke, 2015). However, it is unclear whether the outcome was due to varying frequency of stimulation, or a result of inter-individual variability, and more studies are needed to address this discrepancy. In the motor cortex, 30 Hz cTBS resulted in a larger and more consistent decrease in MEP amplitude than 50 Hz cTBS (Goldsworthy et al., 2012). Although such a trend was not evident in our data, the differences could be explained by the differences in TBS paradigm (cTBS vs iTBS), differences in the stimulated region (M1 vs DLPFC) or the differences in outcome measure (MEPs vs TEPs). Beyond the motor cortex, Nyffeler and colleagues targeted the FEF, which is in close proximity to the prefrontal cortex, and found prolonged saccadic delay following 30 Hz cTBS (Nyffeler et al., 2006b). Saccadic delay has also been reported following 50 Hz cTBS over the FEF, however, involvement of executive control of saccades were found following prefrontal stimulation (Cameron et al., 2015), suggesting the effect of TBS may be distinct in different brain regions. As there has been no other study using 30 Hz iTBS in the prefrontal cortex or FEF, future studies are required to confirm and expand these findings. Having no overall effect on neurophysiology, mood and working memory performance following 30 Hz iTBS in the current study indicates this protocol may not be suitable in the prefrontal cortex. It is critical to

note that the carrying frequency was 6 Hz in 30 Hz iTBS, and future studies should employ more systematic comparison. We adopted this frequency to be comparable to the direct comparison study in the motor cortex (Goldsworthy et al., 2012), which resulted in a robust decrease in MEPs following 30 Hz / 6 Hz cTBS.

Taken together, these findings suggest that prefrontal iTBS using the conventional parameters of stimulation also suffers from inter-individual variability as observed from studies with larger sample sizes in the motor cortex (Hamada et al., 2013; Hinder et al., 2014).

Repetitive TMS of the prefrontal cortex is one therapeutic option for treatment-resistant depression and it is being investigated for use in various mood and cognitive disorders. In order to reduce treatment time, clinics have been exploring the use of short protocols such as TBS (Cash et al., 2017d; Desmyter et al., 2016; Duprat et al., 2016; Li et al., 2014), however limited clinical efficacy has also been reported (Prasser et al., 2015). The present data provide the first evidence that using conventional iTBS may not be optimal for neuromodulation, and indicate the need for a more individualised approach of stimulation. Further research is required to explore whether the present method extends to clinical efficacy.

3.5. Limitations

There are several limitations of the present study. Our study design did not include a primary sham condition, however, the main intention of this study was to compare the effects between the two most commonly used paradigms as well as a novel method of application. Although secondary analyses of data comparing responses to a sham condition demonstrated no significant changes following sham stimulation, it should be noted that volunteers were different from the main analyses, however, were aged and gender-ratio matched and had similar years of education. In

addition, a control for single-pulse TMS was not included in the study. TMS click sound was masked by white noise but any sound via bone conduction could not be avoided. TMS pulse may induce N100-P200 component in the EEG trace (ter Braack et al., 2015), however, it is unlikely that the elicited response is purely auditory-related effect. Any auditory response should be consistent across time, and sham condition did not show any change in these components. In regards to somatosensory input, baseline and post sampling parameters were equivalent across all conditions, including sham (e.g. equal intensity and stimulation site). Therefore, the differences between conditions are likely to be driven by cortical plasticity, in accordance with the *a priori* hypothesis. It should be noted that iTBS-induced changes in TEPs correlated with the changes in mood rating and working memory performance, which suggest TEPs exhibit functional relevance. The selection of iTBS parameters (50 / 5 Hz and 30 / 6 Hz) was based on similar parameters used in motor cortex studies. The motor cortex is one region where a measurable output (i.e. MEPs) is obtained following TMS administration. As a result, most studies have used stimulation protocols based on the outcome of motor cortex studies. Future studies would benefit from improving the effect of stimulation tailored to the specific brain region of interest. Due to time constraints, TEPs were not measured at T60 which may have limited more temporally accurate onset of neurophysiological changes to the mood changes. The consistency of the stimulation site could be improved by using MRI-guided neuronavigation, however, this was not feasible in this study. We have taken extra steps to ensure more accurate positioning of the coil. In addition, the TEP waveforms in this study are consistent with other TMS-EEG studies in the prefrontal cortex (Chung et al., 2017a; Hill et al., 2017; Rogasch et al., 2014), and EEG-guided (Chung et al., 2017a; Hill et al., 2017; Rogasch et al., 2014) and MRI-guided (Lioumis et al., 2009) methods have shown comparable results.

4. Conclusions

In conclusion, the current study indicates that the individualised iTBS in the prefrontal cortex is able to exert LTP-like plasticity at a group level. These findings provide support for the use of more tailored stimulation approach in order to obtain a more efficacious outcome, and potentially be beneficial in clinical trials.

5. References

Ahearn, E.P., 1997. The use of visual analog scales in mood disorders: a critical review. J Psychiatr Res 31, 569-579.
Bonnard, M., Spieser, L., Meziane, H.B., de Graaf, J.B., Pailhous, J., 2009. Prior intention can locally tune inhibitory processes in the primary motor cortex: direct evidence from combined TMS-EEG. Eur J Neurosci 30, 913-923.
Brownjohn, P.W., Reynolds, J.N., Matheson, N., Fox, J., Shemmell, J.B., 2014. The effects of individualized theta burst stimulation on the excitability of the human motor system. Brain Stimul 7, 260-268.
Cameron, I.G., Riddle, J.M., D'Esposito, M., 2015. Dissociable Roles of Dorsolateral Prefrontal Cortex and Frontal Eye Fields During Saccadic Eye Movements. Front Hum Neurosci 9, 613.
Cash, R.F., Jegatheeswaran, G., Ni, Z., Chen, R., 2017a. Modulation of the Direction and Magnitude of Hebbian Plasticity in Human Motor Cortex by Stimulus Intensity and Concurrent Inhibition. Brain Stimul 10, 83-90.
Cash, R.F., Murakami, T., Chen, R., Thickbroom, G.W., Ziemann, U., 2016. Augmenting Plasticity Induction in Human Motor Cortex by Disinhibition Stimulation. Cereb Cortex 26, 58-69.
Cash, R.F., Noda, Y., Zomorrodi, R., Radhu, N., Farzan, F., Rajji, T.K., Fitzgerald, P.B., Chen, R., Daskalakis, Z.J., Blumberger, D.M., 2017b. Characterization of Glutamatergic and GABAA-Mediated Neurotransmission in Motor and Dorsolateral Prefrontal Cortex Using Paired-Pulse TMS-EEG. Neuropsychopharmacology 42, 502-511.
Cash, R.F., Udupa, K., Mazzella, F., Daskalakis, Z.J., Wong, A.H., Kennedy, J.L., Fitzgerald, P.B., Chen, R., 2017c. Influence of the BDNF Val66Met polymorphism on the balance of excitatory and inhibitory neurotransmission and relationship to plasticity in human cortex., Brain Stimulation, p. 502.
Cash, R.F., Ziemann, U., Murray, K., Thickbroom, G.W., 2010. Late cortical disinhibition in human motor cortex: a triple-pulse transcranial magnetic stimulation study. J Neurophysiol 103, 511-518.
Cash, R.F., Ziemann, U., Thickbroom, G.W., 2011. Inhibitory and disinhibitory effects on I-wave facilitation in motor cortex. J Neurophysiol 105, 100-106.
Cash, R.F.H., Dar, A., Hui, J., De Ruiter, L., Baarbe, J., Fettes, P., Peters, S., Fitzgerald, P.B., Downar, J., Chen, R., 2017d. Influence of inter-train interval on the plastic effects of rTMS. Brain Stimul 10, 630-636.
Casula, E.P., Pellicciari, M.C., Ponzo, V., Stampanoni Bassi, M., Veniero, D., Caltagirone, C., Koch, G., 2016. Cerebellar theta burst stimulation modulates the neural activity of interconnected parietal and motor areas. Sci Rep 6, 36191.
Chaieb, L., Leszczynski, M., Axmacher, N., Hohne, M., Elger, C.E., Fell, J., 2015. Theta-gamma phase-phase coupling during working memory maintenance in the human hippocampus. Cogn Neurosci 6, 149-157.
Chung, S.W., Hill, A.T., Rogasch, N.C., Hoy, K.E., Fitzgerald, P.B., 2016. Use of theta-burst stimulation in changing excitability of motor cortex: A systematic review and meta-analysis. Neurosci Biobehav Rev 63, 43-64.
Chung, S.W., Lewis, B.P., Rogasch, N.C., Saeki, T., Thomson, R.H., Hoy, K.E., Bailey, N.W., Fitzgerald, P.B., 2017a. Demonstration of short-term plasticity in the dorsolateral prefrontal cortex with theta burst stimulation: A TMS-EEG study. Clin Neurophysiol 128, 1117-1126.
Chung, S.W., Rogasch, N.C., Hoy, K.E., Fitzgerald, P.B., 2015. Measuring Brain Stimulation Induced Changes in Cortical Properties Using TMS-EEG. Brain Stimul 8, 1010-1020.
Chung, S.W., Rogasch, N.C., Hoy, K.E., Sullivan, C.M., Cash, R.F.H., Fitzgerald, P.B., 2017b. Impact of different intensities of intermittent theta burst stimulation on the cortical properties during TMS-EEG and working memory performance. Hum Brain Mapp.
Cline, H., 2005. Synaptogenesis: a balancing act between excitation and inhibition. Curr Biol 15, R203-205.

Conforto, A.B., Z'Graggen, W.J., Kohl, A.S., Rosler, K.M., Kaelin-Lang, A., 2004. Impact of coil position and electrophysiological monitoring on determination of motor thresholds to transcranial magnetic stimulation. Clin Neurophysiol 115, 812-819.
D'Ausilio, A., 2012. Arduino: a low-cost multipurpose lab equipment. Behav Res Methods 44, 305-313.
Dehghani, N., Peyrache, A., Telenczuk, B., Le Van Quyen, M., Halgren, E., Cash, S.S., Hatsopoulos, N.G., Destexhe, A., 2016. Dynamic Balance of Excitation and Inhibition in Human and Monkey Neocortex. Sci Rep 6, 23176.
Delorme, A., Makeig, S., 2004. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods 134, 9-21.
Deneve, S., Machens, C.K., 2016. Efficient codes and balanced networks. Nat Neurosci 19, 375-382.
Desmyter, S., Duprat, R., Baeken, C., Van Autreve, S., Audenaert, K., van Heeringen, K., 2016. Accelerated Intermittent Theta Burst Stimulation for Suicide Risk in Therapy-Resistant Depressed Patients: A Randomized, Sham-Controlled Trial. Front Hum Neurosci 10, 480.
Di Lazzaro, V., Pilato, F., Dileone, M., Profice, P., Oliviero, A., Mazzone, P., Insola, A., Ranieri, F., Meglio, M., Tonali, P.A., Rothwell, J.C., 2008. The physiological basis of the effects of intermittent theta burst stimulation of the human motor cortex. J Physiol 586, 3871-3879.
Duprat, R., Desmyter, S., Rudi de, R., van Heeringen, K., Van den Abbeele, D., Tandt, H., Bakic, J., Pourtois, G., Dedoncker, J., Vervaet, M., Van Autreve, S., Lemmens, G.M., Baeken, C., 2016. Accelerated intermittent theta burst stimulation treatment in medication-resistant major depression: A fast road to remission? J Affect Disord 200, 6-14.
Elfant, D., Pal, B.Z., Emptage, N., Capogna, M., 2008. Specific inhibitory synapses shift the balance from feedforward to feedback inhibition of hippocampal CA1 pyramidal cells. Eur J Neurosci 27, 104-113.
Farzan, F., Barr, M.S., Hoppenbrouwers, S.S., Fitzgerald, P.B., Chen, R., Pascual-Leone, A., Daskalakis, Z.J., 2013. The EEG correlates of the TMS-induced EMG silent period in humans. Neuroimage 83, 120-134.
Ferreri, F., Ponzo, D., Hukkanen, T., Mervaala, E., Kononen, M., Pasqualetti, P., Vecchio, F., Rossini, P.M., Maatta, S., 2012. Human brain cortical correlates of short-latency afferent inhibition: a combined EEG-TMS study. J Neurophysiol 108, 314-323.
Friese, U., Koster, M., Hassler, U., Martens, U., Trujillo-Barreto, N., Gruber, T., 2013. Successful memory encoding is associated with increased cross-frequency coupling between frontal theta and posterior gamma oscillations in human scalp-recorded EEG. Neuroimage 66, 642-647.
Froemke, R.C., 2015. Plasticity of cortical excitatory-inhibitory balance. Annu Rev Neurosci 38, 195-219.
Goldsworthy, M.R., Pitcher, J.B., Ridding, M.C., 2012. A comparison of two different continuous theta burst stimulation paradigms applied to the human primary motor cortex. Clin Neurophysiol 123, 2256-2263.
Gramfort, A., Papadopoulo, T., Olivi, E., Clerc, M., 2010. OpenMEEG: opensource software for quasistatic bioelectromagnetics. Biomed Eng Online 9, 45.
Haatveit, B.C., Sundet, K., Hugdahl, K., Ueland, T., Melle, I., Andreassen, O.A., 2010. The validity of d prime as a working memory index: results from the "Bergen n-back task". J Clin Exp Neuropsychol 32, 871-880.
Hamada, M., Murase, N., Hasan, A., Balaratnam, M., Rothwell, J.C., 2013. The role of interneuron networks in driving human motor cortical plasticity. Cereb Cortex 23, 1593-1605.
Harrington, A., Hammond-Tooke, G.D., 2015. Theta Burst Stimulation of the Cerebellum Modifies the TMS-Evoked N100 Potential, a Marker of GABA Inhibition. PLoS One 10, e0141284.
Heiss, J.E., Katz, Y., Ganmor, E., Lampl, I., 2008. Shift in the balance between excitation and inhibition during sensory adaptation of S1 neurons. J Neurosci 28, 13320-13330.

Hill, A.T., Rogasch, N.C., Fitzgerald, P.B., Hoy, K.E., 2017. Effects of prefrontal bipolar and high-definition transcranial direct current stimulation on cortical reactivity and working memory in healthy adults. Neuroimage 152, 142-157.
Hinder, M.R., Goss, E.L., Fujiyama, H., Canty, A.J., Garry, M.I., Rodger, J., Summers, J.J., 2014. Inter- and Intra-individual variability following intermittent theta burst stimulation: implications for rehabilitation and recovery. Brain Stimul 7, 365-371.
Hoy, K.E., Bailey, N., Michael, M., Fitzgibbon, B., Rogasch, N.C., Saeki, T., Fitzgerald, P.B., 2016. Enhancement of Working Memory and Task-Related Oscillatory Activity Following Intermittent Theta Burst Stimulation in Healthy Controls. Cereb Cortex 26, 4563-4573.
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, 201-206.
Jacobs, J., 2014. Hippocampal theta oscillations are slower in humans than in rodents: implications for models of spatial navigation and memory. Philos Trans R Soc Lond B Biol Sci 369, 20130304.
Kirkwood, A., 2015. Balancing excitation and inhibition. Neuron 86, 348-350.
Klimesch, W., Doppelmayr, M., Russegger, H., Pachinger, T., 1996. Theta band power in the human scalp EEG and the encoding of new information. Neuroreport 7, 1235-1240.
Knight, R.T., Staines, W.R., Swick, D., Chao, L.L., 1999. Prefrontal cortex regulates inhibition and excitation in distributed neural networks. Acta Psychol (Amst) 101, 159-178.
Koster, M., Friese, U., Schone, B., Trujillo-Barreto, N., Gruber, T., 2014. Theta-gamma coupling during episodic retrieval in the human EEG. Brain Res 1577, 57-68.
Larson, J., Munkacsy, E., 2015. Theta-burst LTP. Brain Res 1621, 38-50.
Larson, J., Wong, D., Lynch, G., 1986. Patterned stimulation at the theta frequency is optimal for the induction of hippocampal long-term potentiation. Brain Res 368, 347-350.
Le-Niculescu, H., Kurian, S.M., Yehyawi, N., Dike, C., Patel, S.D., Edenberg, H.J., Tsuang, M.T., Salomon, D.R., Nurnberger, J.I., Jr., Niculescu, A.B., 2009. Identifying blood biomarkers for mood disorders using convergent functional genomics. Mol Psychiatry 14, 156-174.
Legon, W., Punzell, S., Dowlati, E., Adams, S.E., Stiles, A.B., Moran, R.J., 2016. Altered Prefrontal Excitation/Inhibition Balance and Prefrontal Output: Markers of Aging in Human Memory Networks. Cereb Cortex 26, 4315-4326.
Li, C.T., Chen, M.H., Juan, C.H., Huang, H.H., Chen, L.F., Hsieh, J.C., Tu, P.C., Bai, Y.M., Tsai, S.J., Lee, Y.C., Su, T.P., 2014. Efficacy of prefrontal theta-burst stimulation in refractory depression: a randomized sham-controlled study. Brain 137, 2088-2098.
Lim, S., Goldman, M.S., 2013. Balanced cortical microcircuitry for maintaining information in working memory. Nat Neurosci 16, 1306-1314.
Lin, F.H., Belliveau, J.W., Dale, A.M., Hamalainen, M.S., 2006. Distributed current estimates using cortical orientation constraints. Hum Brain Mapp 27, 1-13.
Lioumis, P., Kicic, D., Savolainen, P., Makela, J.P., Kahkonen, S., 2009. Reproducibility of TMS-Evoked EEG responses. Hum Brain Mapp 30, 1387-1396.
Lisman, J., 2010. Working memory: the importance of theta and gamma oscillations. Curr Biol 20, R490-492.
Lisman, J.E., Jensen, O., 2013. The theta-gamma neural code. Neuron 77, 1002-1016.
Lopez-Alonso, V., Cheeran, B., Rio-Rodriguez, D., Fernandez-Del-Olmo, M., 2014. Inter-individual variability in response to non-invasive brain stimulation paradigms. Brain Stimul 7, 372-380.
Maris, E., Oostenveld, R., 2007. Nonparametric statistical testing of EEG- and MEG-data. J Neurosci Methods 164, 177-190.
Nikouline, V., Ruohonen, J., Ilmoniemi, R.J., 1999. The role of the coil click in TMS assessed with simultaneous EEG. Clin Neurophysiol 110, 1325-1328.
Nikulin, V.V., Kicic, D., Kahkonen, S., Ilmoniemi, R.J., 2003. Modulation of electroencephalographic responses to transcranial magnetic stimulation: evidence for changes in cortical excitability related to movement. Eur J Neurosci 18, 1206-1212.

Noda, Y., Barr, M.S., Zomorrodi, R., Cash, R.F., Rajji, T.K., Farzan, F., Chen, R., George, T.P., Daskalakis, Z.J., Blumberger, D.M., 2017a. Reduced Short-latency Afferent Inhibition in Prefrontal but not Motor Cortex and its Association With Executive Function in Schizophrenia: A Combined TMS-EEG Study. Schizophr Bull.
Noda, Y., Cash, R.F., Zomorrodi, R., Dominguez, L.G., Farzan, F., Rajji, T.K., Barr, M.S., Chen, R., Daskalakis, Z.J., Blumberger, D.M., 2016. A combined TMS-EEG study of short-latency afferent inhibition in the motor and dorsolateral prefrontal cortex. J Neurophysiol 116, 938-948.
Noda, Y., Zomorrodi, R., Backhouse, F., Cash, R.F.H., Barr, M.S., Rajji, T.K., Chen, R., Daskalakis, Z.J., Blumberger, D.M., 2017b. Reduced Prefrontal Short-Latency Afferent Inhibition in Older Adults and Its Relation to Executive Function: A TMS-EEG Study. Front Aging Neurosci 9, 119.
Noda, Y., Zomorrodi, R., Cash, R.F., Barr, M.S., Farzan, F., Rajji, T.K., Chen, R., Daskalakis, Z.J., Blumberger, D.M., 2017c. Characterization of the influence of age on GABAA and glutamatergic mediated functions in the dorsolateral prefrontal cortex using paired-pulse TMS-EEG. Aging (Albany NY) 9, 556-572.
Nyffeler, T., Wurtz, P., Luscher, H.R., Hess, C.W., Senn, W., Pflugshaupt, T., von Wartburg, R., Luthi, M., Muri, R.M., 2006a. Extending lifetime of plastic changes in the human brain. Eur J Neurosci 24, 2961-2966.
Nyffeler, T., Wurtz, P., Luscher, H.R., Hess, C.W., Senn, W., Pflugshaupt, T., von Wartburg, R., Luthi, M., Muri, R.M., 2006b. Repetitive TMS over the human oculomotor cortex: comparison of 1-Hz and theta burst stimulation. Neurosci Lett 409, 57-60.
Oostenveld, R., Fries, P., Maris, E., Schoffelen, J.M., 2011. FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Comput Intell Neurosci 2011, 156869.
Opie, G.M., Rogasch, N.C., Goldsworthy, M.R., Ridding, M.C., Semmler, J.G., 2017. Investigating TMS-EEG Indices of Long-Interval Intracortical Inhibition at Different Interstimulus Intervals. Brain Stimul 10, 65-74.
Park, J.Y., Jhung, K., Lee, J., An, S.K., 2013. Theta-gamma coupling during a working memory task as compared to a simple vigilance task. Neurosci Lett 532, 39-43.
Penny, W.D., Duzel, E., Miller, K.J., Ojemann, J.G., 2008. Testing for nested oscillation. J Neurosci Methods 174, 50-61.
Prasser, J., Schecklmann, M., Poeppl, T.B., Frank, E., Kreuzer, P.M., Hajak, G., Rupprecht, R., Landgrebe, M., Langguth, B., 2015. Bilateral prefrontal rTMS and theta burst TMS as an add-on treatment for depression: a randomized placebo controlled trial. World J Biol Psychiatry 16, 57-65.
Premoli, I., Bergmann, T.O., Fecchio, M., Rosanova, M., Biondi, A., Belardinelli, P., Ziemann, U., 2017. The impact of GABAergic drugs on TMS-induced brain oscillations in human motor cortex. Neuroimage 163, 1-12.
Premoli, I., Castellanos, N., Rivolta, D., Belardinelli, P., Bajo, R., Zipser, C., Espenhahn, S., Heidegger, T., Muller-Dahlhaus, F., Ziemann, U., 2014a. TMS-EEG signatures of GABAergic neurotransmission in the human cortex. J Neurosci 34, 5603-5612.
Premoli, I., Rivolta, D., Espenhahn, S., Castellanos, N., Belardinelli, P., Ziemann, U., Muller-Dahlhaus, F., 2014b. Characterization of GABAB-receptor mediated neurotransmission in the human cortex by paired-pulse TMS-EEG. Neuroimage 103, 152-162.
Ridding, M.C., Ziemann, U., 2010. Determinants of the induction of cortical plasticity by non-invasive brain stimulation in healthy subjects. J Physiol 588, 2291-2304.
Robinson, O.J., Cools, R., Crockett, M.J., Sahakian, B.J., 2010. Mood state moderates the role of serotonin in cognitive biases. J Psychopharmacol 24, 573-583.
Robinson, O.J., Sahakian, B.J., 2009. A double dissociation in the roles of serotonin and mood in healthy subjects. Biol Psychiatry 65, 89-92.
Rogasch, N.C., Daskalakis, Z.J., Fitzgerald, P.B., 2013a. Mechanisms underlying long-interval cortical inhibition in the human motor cortex: a TMS-EEG study. J Neurophysiol 109, 89-98.

Rogasch, N.C., Daskalakis, Z.J., Fitzgerald, P.B., 2015. Cortical inhibition of distinct mechanisms in the dorsolateral prefrontal cortex is related to working memory performance: a TMS-EEG study. Cortex 64, 68-77.
Rogasch, N.C., Sullivan, C., Thomson, R.H., Rose, N.S., Bailey, N.W., Fitzgerald, P.B., Farzan, F., Hernandez-Pavon, J.C., 2017. Analysing concurrent transcranial magnetic stimulation and electroencephalographic data: A review and introduction to the open-source TESA software. Neuroimage 147, 934-951.
Rogasch, N.C., Thomson, R.H., Daskalakis, Z.J., Fitzgerald, P.B., 2013b. Short-latency artifacts associated with concurrent TMS-EEG. Brain Stimul 6, 868-876.
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.
Schack, B., Vath, N., Petsche, H., Geissler, H.G., Moller, E., 2002. Phase-coupling of theta-gamma EEG rhythms during short-term memory processing. Int J Psychophysiol 44, 143-163.
Schicktanz, N., Fastenrath, M., Milnik, A., Spalek, K., Auschra, B., Nyffeler, T., Papassotiropoulos, A., de Quervain, D.J., Schwegler, K., 2015. Continuous theta burst stimulation over the left dorsolateral prefrontal cortex decreases medium load working memory performance in healthy humans. PLoS One 10, e0120640.
Schubert, T.W., D'Ausilio, A., Canto, R., 2013. Using Arduino microcontroller boards to measure response latencies. Behav Res Methods 45, 1332-1346.
Schultz, B.G., van Vugt, F.T., 2016. Tap Arduino: An Arduino microcontroller for low-latency auditory feedback in sensorimotor synchronization experiments. Behav Res Methods 48, 1591-1607.
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. J Clin Psychiatry 59 Suppl 20, 22-33;quiz 34-57.
Tadel, F., Baillet, S., Mosher, J.C., Pantazis, D., Leahy, R.M., 2011. Brainstorm: a user-friendly application for MEG/EEG analysis. Comput Intell Neurosci 2011, 879716.
ter Braack, E.M., de Vos, C.C., van Putten, M.J., 2015. Masking the Auditory Evoked Potential in TMS-EEG: A Comparison of Various Methods. Brain Topogr 28, 520-528.
Tort, A.B., Komorowski, R.W., Manns, J.R., Kopell, N.J., Eichenbaum, H., 2009. Theta-gamma coupling increases during the learning of item-context associations. Proc Natl Acad Sci U S A 106, 20942-20947.
Turriziani, P., Smirni, D., Zappala, G., Mangano, G.R., Oliveri, M., Cipolotti, L., 2012. Enhancing memory performance with rTMS in healthy subjects and individuals with Mild Cognitive Impairment: the role of the right dorsolateral prefrontal cortex. Front Hum Neurosci 6, 62.
Vogels, T.P., Abbott, L.F., 2009. Gating multiple signals through detailed balance of excitation and inhibition in spiking networks. Nat Neurosci 12, 483-491.
Vogels, T.P., Sprekeler, H., Zenke, F., Clopath, C., Gerstner, W., 2011. Inhibitory plasticity balances excitation and inhibition in sensory pathways and memory networks. Science 334, 1569-1573.
Watrous, A.J., Lee, D.J., Izadi, A., Gurkoff, G.G., Shahlaie, K., Ekstrom, A.D., 2013. A comparative study of human and rat hippocampal low-frequency oscillations during spatial navigation. Hippocampus 23, 656-661.
Wilcox, R.R., 1997. Introduction to robust estimation and hypothesis testing. Academic Press, San Diego, CA.
Xue, M., Atallah, B.V., Scanziani, M., 2014. Equalizing excitation-inhibition ratios across visual cortical neurons. Nature 511, 596-600.

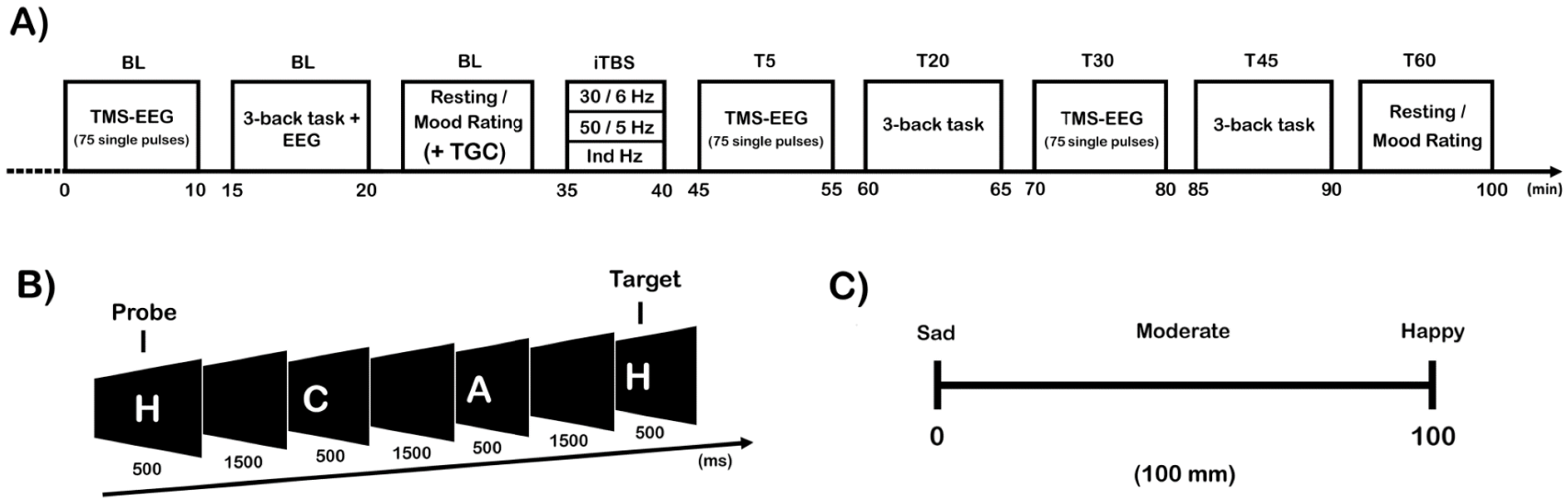

Figure 1. Schematic diagram of the experimental design of the study. (A) Combined transcranial magnetic stimulation and electroencephalography (TMS-EEG), 3-back task and mood rating were completed at baseline (BL). Theta-gamma coupling (TGC) was analysed off-line using the EEG data from the 3-back task. Intermittent theta burst stimulation (iTBS) was administered at one of three frequency patterns (30 Hz every 6 Hz, 50 Hz every 5 Hz and individualised Hz). TMS-EEG was repeated at T5 and T30, the 3-back task at T20 and T50 and mood rating at T60. (B) An example of a correctly responded trial for the 3-back task. Subjects were instructed to remember each stimulus and respond with a button press when the presented letter corresponded to the one that appeared 3 letters before. (C) Visual analogue scale (VAS) rating. Subjects drew a line on a 100 mm VAS to indicate their current mood, from sad (0) to happy (100).

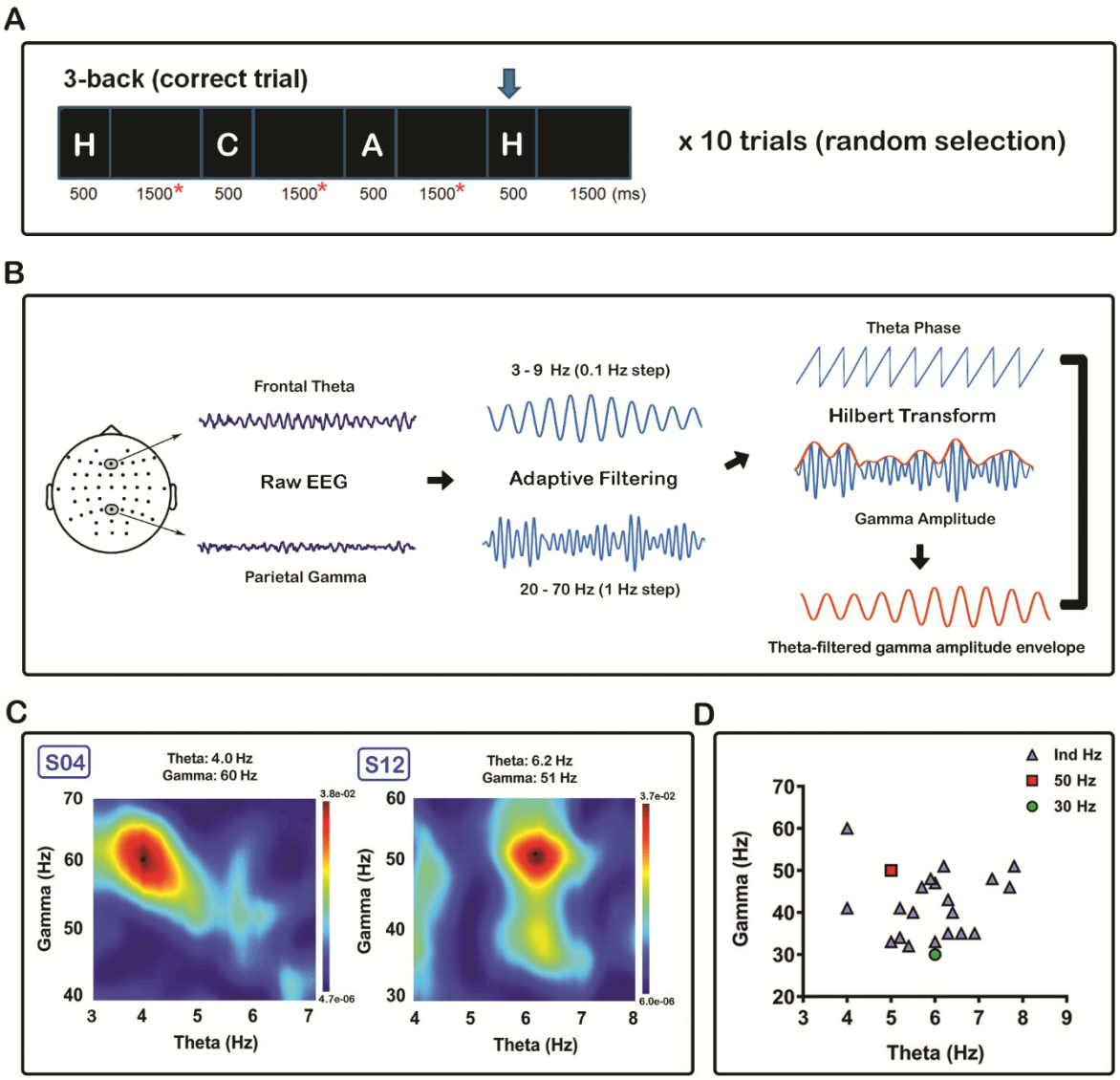

Figure 2. Procedures involved in the selection of the individualised frequency of iTBS. (A) Ten random correct trials selected for theta-gamma coupling (TGC). Only data from the maintenance period of each epoch (red asterisks) were included in the calculation to avoid spurious coupling resulting from the visual-evoked response and edge effects. (B) Raw data from Fz electrode was chosen as the modulating frequency (theta), and Pz electrode as the modulated frequency (gamma). Data were filtered (adaptive) in the frequency range in multiple steps and Hilbert transform was applied to obtain phase (theta) and amplitude (gamma). Theta-filtered gamma amplitude envelope was extracted prior to phase-amplitude coupling estimation using general linear model. (C) Comodulogram illustrated for two subjects (S04 and S12). Peak was detected using the maximum value in the frequency ranges of interest (4 – 8 Hz for theta, 30 – 60 Hz for gamma). (D) Values used for individualised iTBS in blue triangle, 50 Hz iTBS in red rectangle, and 30 Hz iTBS in green circle

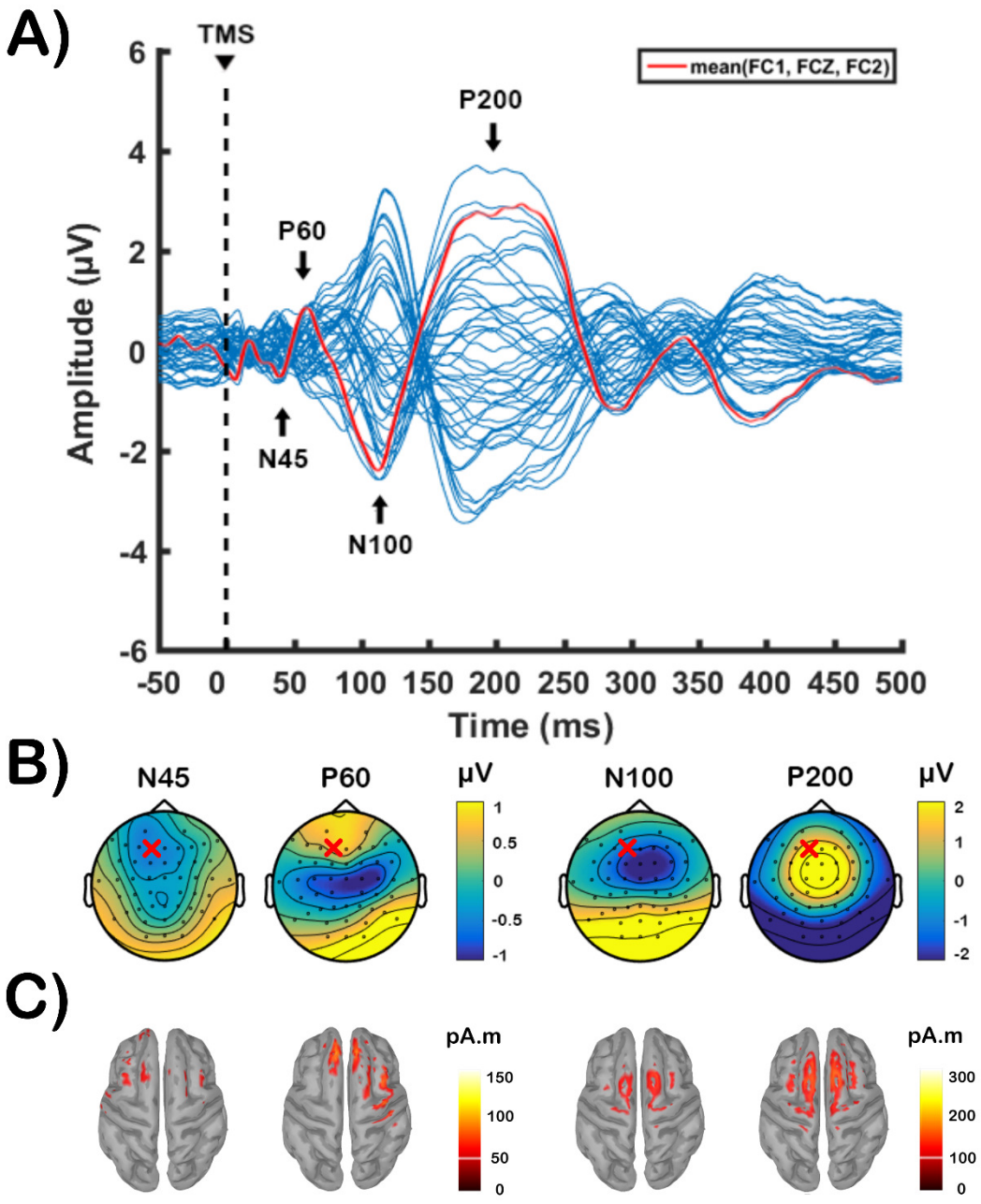

Figure 3. Transcranial magnetic stimulation (TMS)-evoked potentials following single-pulse TMS over left prefrontal cortex (F1 electrode) before the application of theta burst stimulation. Data were combined across three different stimulation conditions at baseline. (A) Butterfly plot of all electrodes with peaks of interest indicated in the text. The waveform in red line is formed using the average of three fronto-central electrodes (FC1, FCz, FC2) for graphical representation of prefrontal activity. Topographical distribution of (B) voltage and (C) source activity (Minimum Norm Estimates (MNEs)) at the level of cortex for each peak. 'X' on topoplots indicate stimulation site (F1 electrode).

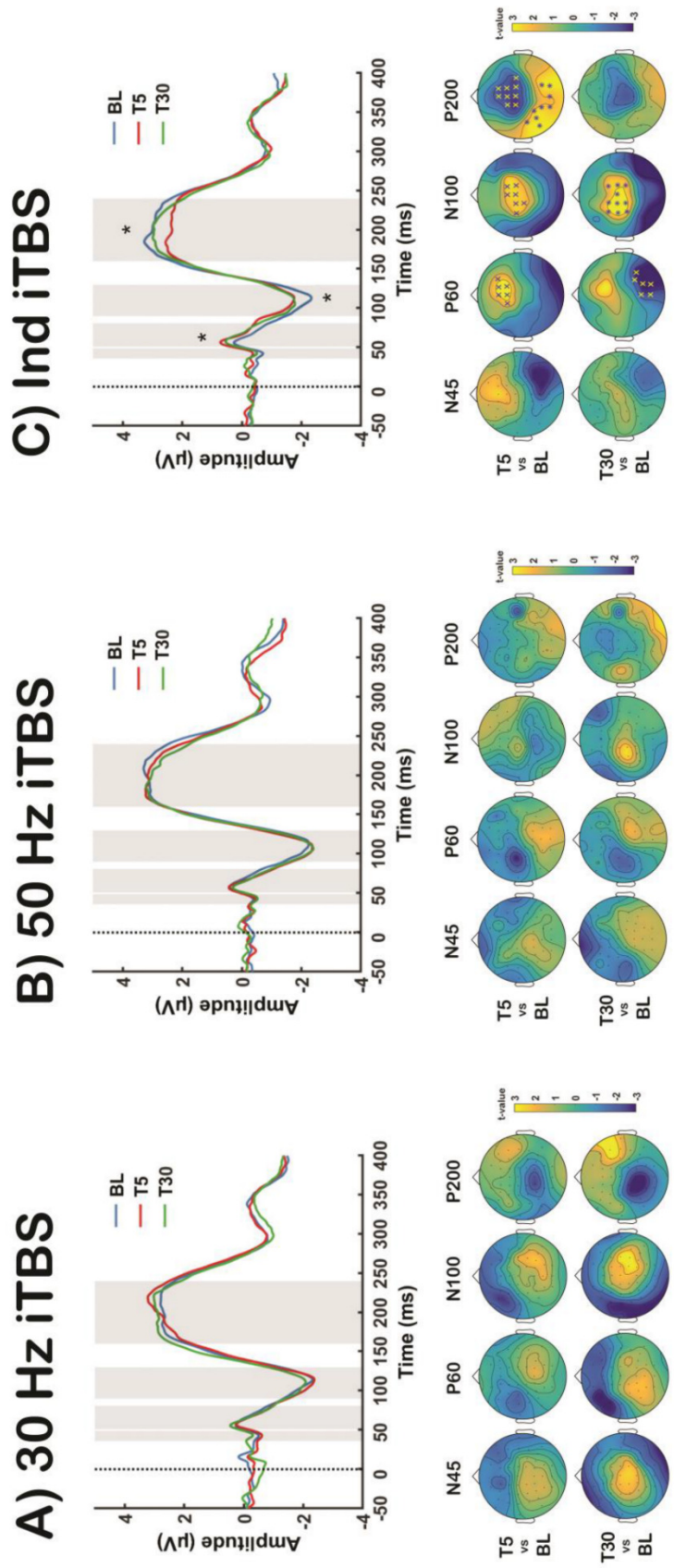

Figure 4. Assessment of transcranial magnetic stimulation (TMS)-evoked potentials (TEPs) following different intermittent theta burst stimulation (iTBS) conditions (A: 30 Hz iTBS, B: 50 Hz iTBS, C: Ind iTBS). Grand average TEP waveforms at baseline (BL: blue), 5-min post (T5: red) and 30-min post (T30: green) using 3 fronto-central electrodes (FC1, FCz and FC2). Topoplots represent t-values for comparison between time points. Asterisks and 'X's on scalp maps indicate significant sensors between comparisons (cluster-based statistics, $^{*}p < 0.01$, $^{x}p < 0.025$). For visualisation purposes, asterisks have been added to the TEP plots at deflections that were found to be significant in the cluster-based statistics.

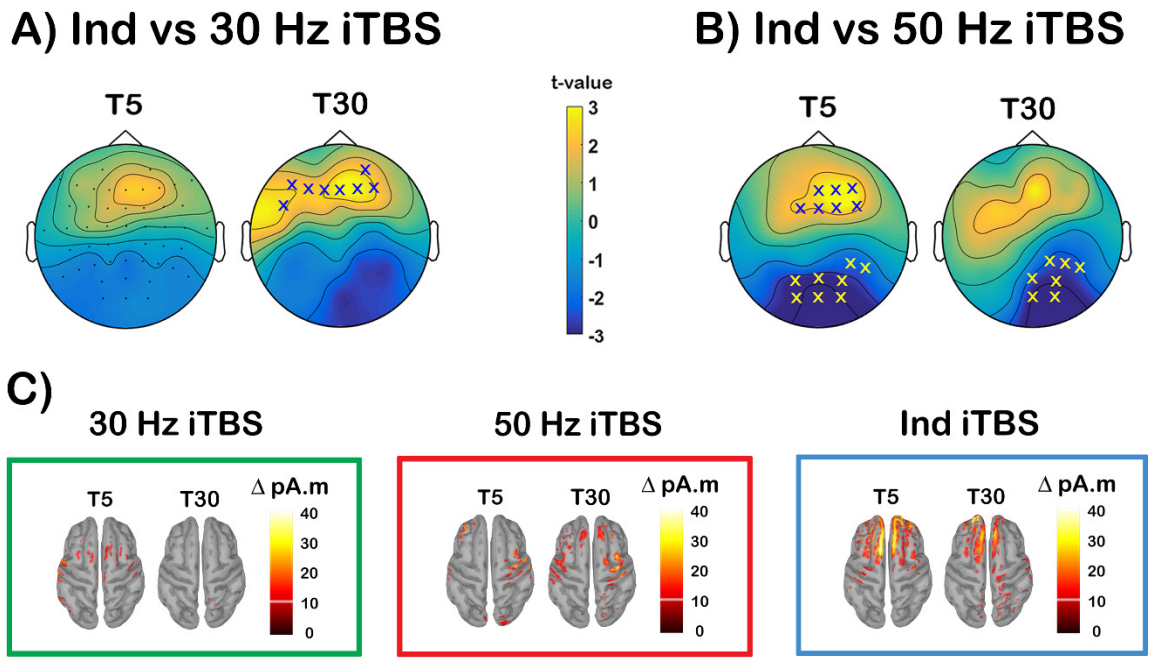

Figure 5. Comparison of the change in transcranial magnetic stimulation (TMS)-evoked P60 amplitude between different intermittent theta burst stimulation (iTBS) conditions. Scalp maps represent t-values for comparison of Δ P60 between (A) Ind iTBS and 30 Hz iTBS and (B) Ind iTBS and 50 Hz iTBS. (C) Minimum Norm Estimates (MNEs) of the source level activity at the cortex for the Δ P60 peak in different stimulation conditions. 'X's on scalp maps indicate significant sensors between comparisons (cluster-based statistics, $^{X}p < 0.025$).

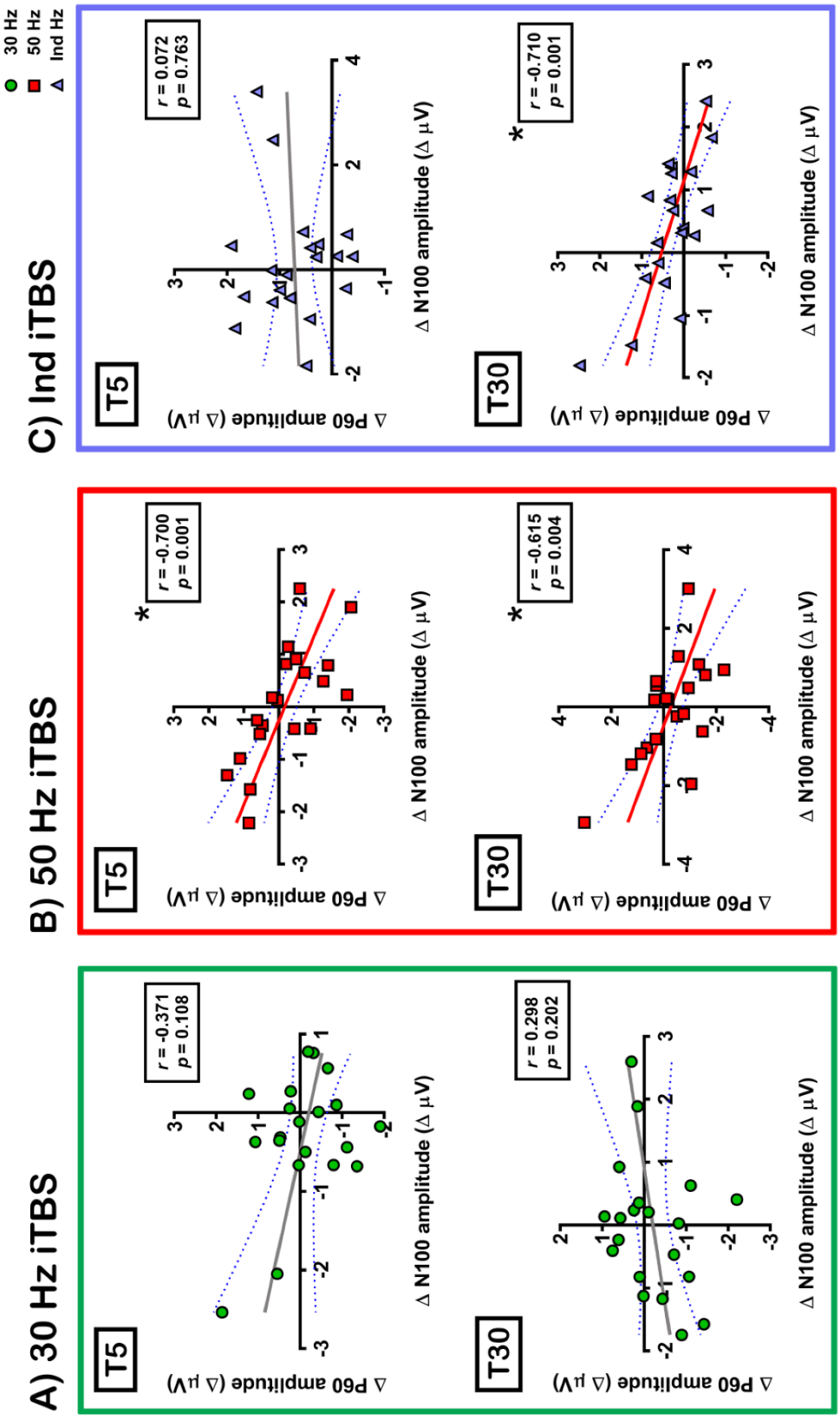

Figure 6. Correlations between intermittent theta burst stimulation (iTBS)-induced changes in the amplitude of transcranial magnetic stimulation (TMS)-evoked P60 (Δ P60) and TMS-evoked N100 (Δ N100) in (A) 30 Hz iTBS, (B) 50 Hz iTBS and (C) Ind iTBS. Asterisks indicate significant correlations ($p < 0.05$).

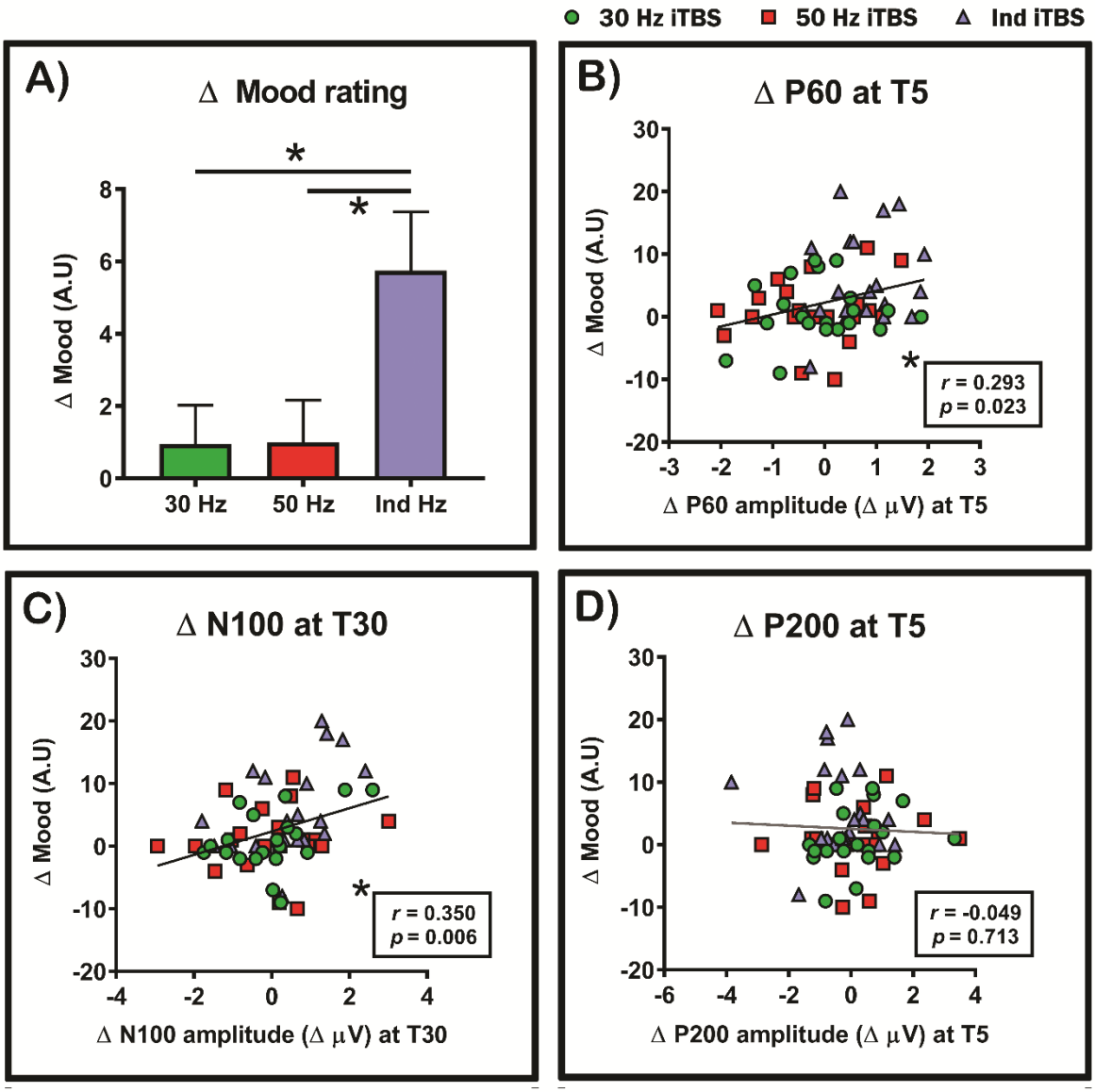

Figure 7. Impact of different intermittent theta burst stimulation (iTBS) condition on mood. (A) Significant differences between Ind iTBS and 30 / 50 Hz iTBS in mood. Correlations between iTBS-induced changes in mood (Δ mood) and the amplitude of transcranial magnetic stimulation (TMS)-evoked (B) Δ P60, (C) Δ N100 and (D) Δ P200. Asterisks indicate significant differences / correlations ($p < 0.05$) and error bars in (A) indicate standard error of means (SEM).

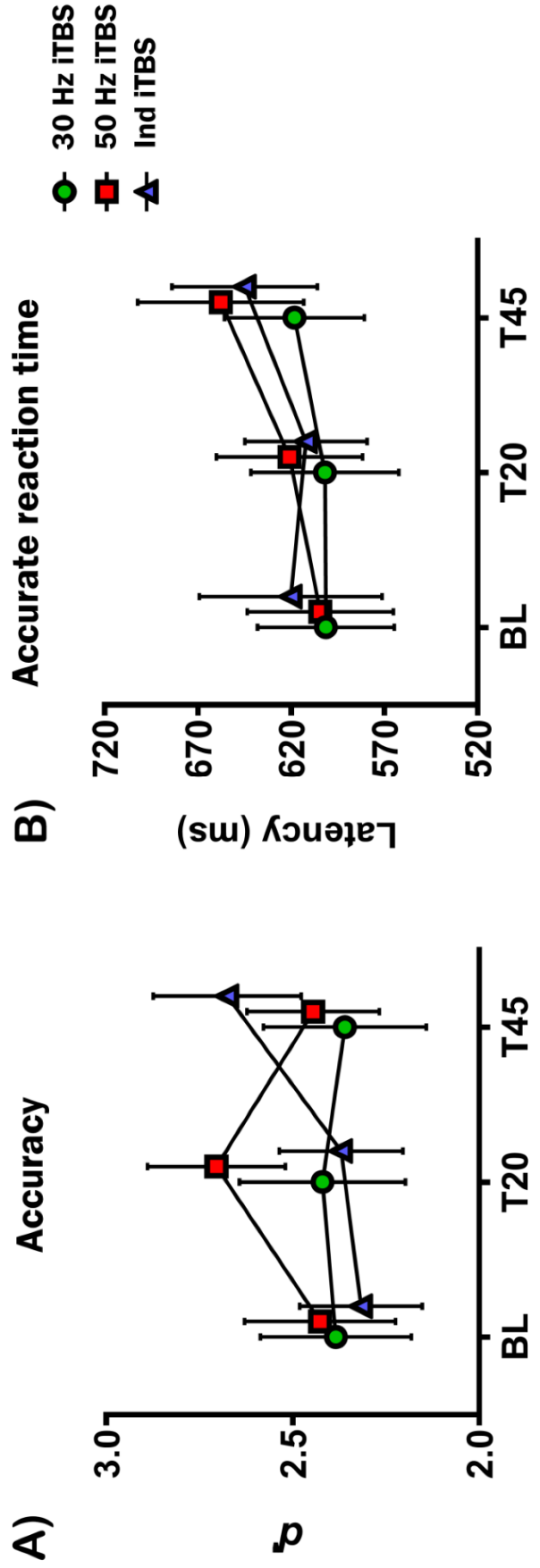

Figure 8. Working memory performance (3-back task) assessed via (A) accuracy (*d'*) and (B) accurate reaction time (in ms) at BL, T20 and T40 in different intermittent theta burst stimulation condition. Error bars indicate standard error of means (SEM).

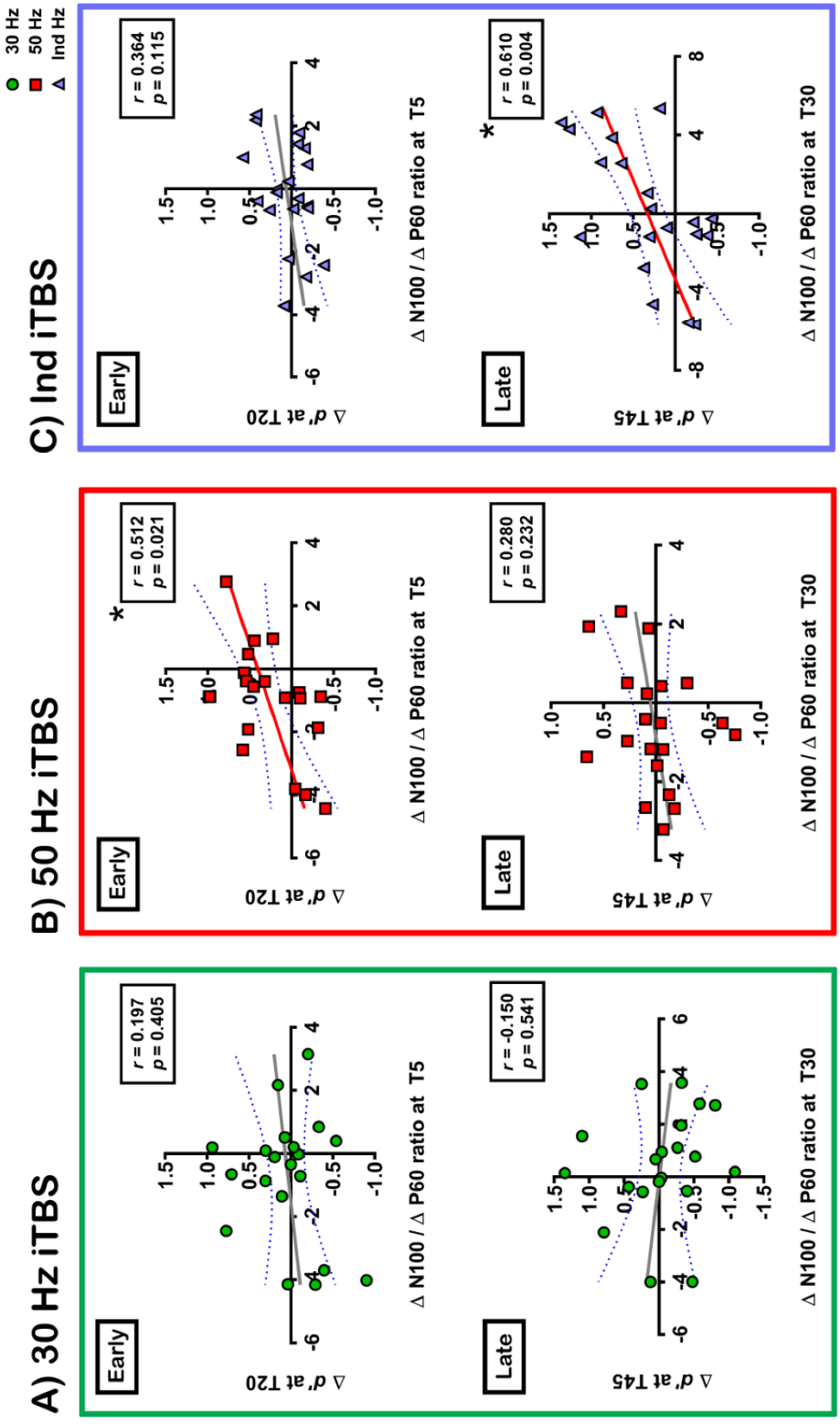

Figure 9. Correlations between working memory performance (accuracy; *d'*) and the ratio of intermittent theta burst stimulation (iTBS)-induced changes in the amplitude of transcranial magnetic stimulation (TMS)-evoked N100 and P60 (Δ N100 / Δ P60) in (A) 30 Hz iTBS, (B) 50 Hz iTBS and (C) Ind iTBS. Asterisks indicate significant correlations ($p < 0.05$).

Supplementary Material

1. *Coil re-positioning*

The concurrent use of transcranial magnetic stimulation (TMS) and electroencephalogram (EEG) allows non-invasive investigation of excitability, functional connectivity and oscillatory dynamics of the cortex. A growing body of research is using this technique (TMS-EEG) to explore the current state of the neural network, particularly outside of the motor cortex. In motor cortex, relatively accurate functional targeting has been possible without the use of neuronavigation by adjusting the coil to produce maximal motor response (i.e. motor evoked potentials (MEPs)). However, targeting behaviourally silent cortical areas requires navigation techniques for precise coil positioning. It has been demonstrated TMS-evoked response in the EEG trace has a degree of sensitivity to the small changes (~1 cm) in the stimulus site (Komssi et al., 2002) and the angle of the coil (Casarotto et al., 2010). This becomes a major problem for researchers when neuronavigation system is not readily available, and often be criticized on a potentially important finding. Additionally, failure in adherence to a strict rule of coil positioning can lead to inaccurate coil position, adding more variability across similar studies.

Here, we suggest a simple method that can be adapted in an experimental setting to minimize error in coil positioning / re-positioning.

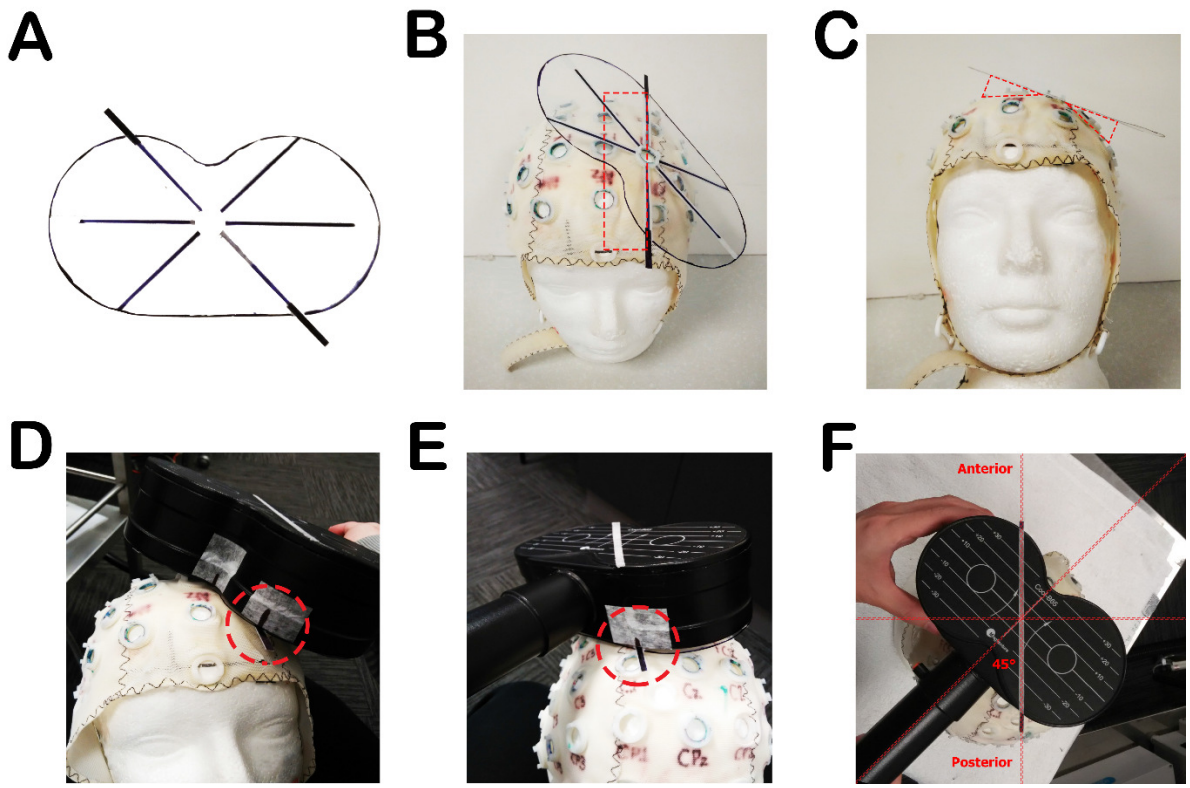

Figure S1. Use of coil template for accurate coil positioning / re-positioning based on the 10-20 system. (A) Transparent coil template customized for MagVenture B-65 fluid-cooled coil. (B) The template can be mounted on EEG cap. Red dotted rectangle indicates parallel positioning of the template to the mid-line. (C) The template provides a guide to tangential surface. TMS coil is marked to align with the template at anterior (D) and posterior (E) position. (F) Top view with coil in position.

A template of TMS coil (MagVenture B-65 fluid-cooled coil; MagVenture A/S, Denmark) was made using a transparent plastic sheet (a laminate), and lines were drawn at 45° angle (Fig S1A). The template can be secured into the rim of plastic electrode holder (i.e. F1 electrode) without increasing the distance between the cap and the coil (Fig S1B). The longer line provides a guide to 45° angle when positioned parallel to the mid-line of the EEG cap. In addition, the placement of the template is tangential to the head surface (Fig S1C). The TMS-coil is marked to align with the template at anterior (Fig S1D) and posterior (Fig S1E) site, allowing for an accurate 45° angle (Fig S1F). This method provides an accurate positioning of the coil based on the 10-20 system. More importantly, within – session reproducibility can be improved as the margin for error in re-positioning of the coil (i.e. before and after intervention) is minimized.

While this method does not provide an accurate site for individualised targets of interest (i.e. dorsolateral prefrontal cortex), placement of the coil follows strictly to the international 10-20 system. Investigative studies using an EEG cap as a guide can therefore benefit from using this method when neuronavigation is not available.

2. Comparison between MagVenture and Arduino programmed stimuli

Stimuli triggered using the Arduino microcontroller were identical to the ones programmed by MagVenture (Fig S2). The EEG were recorded during iTBS using 50 Hz / 5 Hz protocol (Huang et al., 2005).

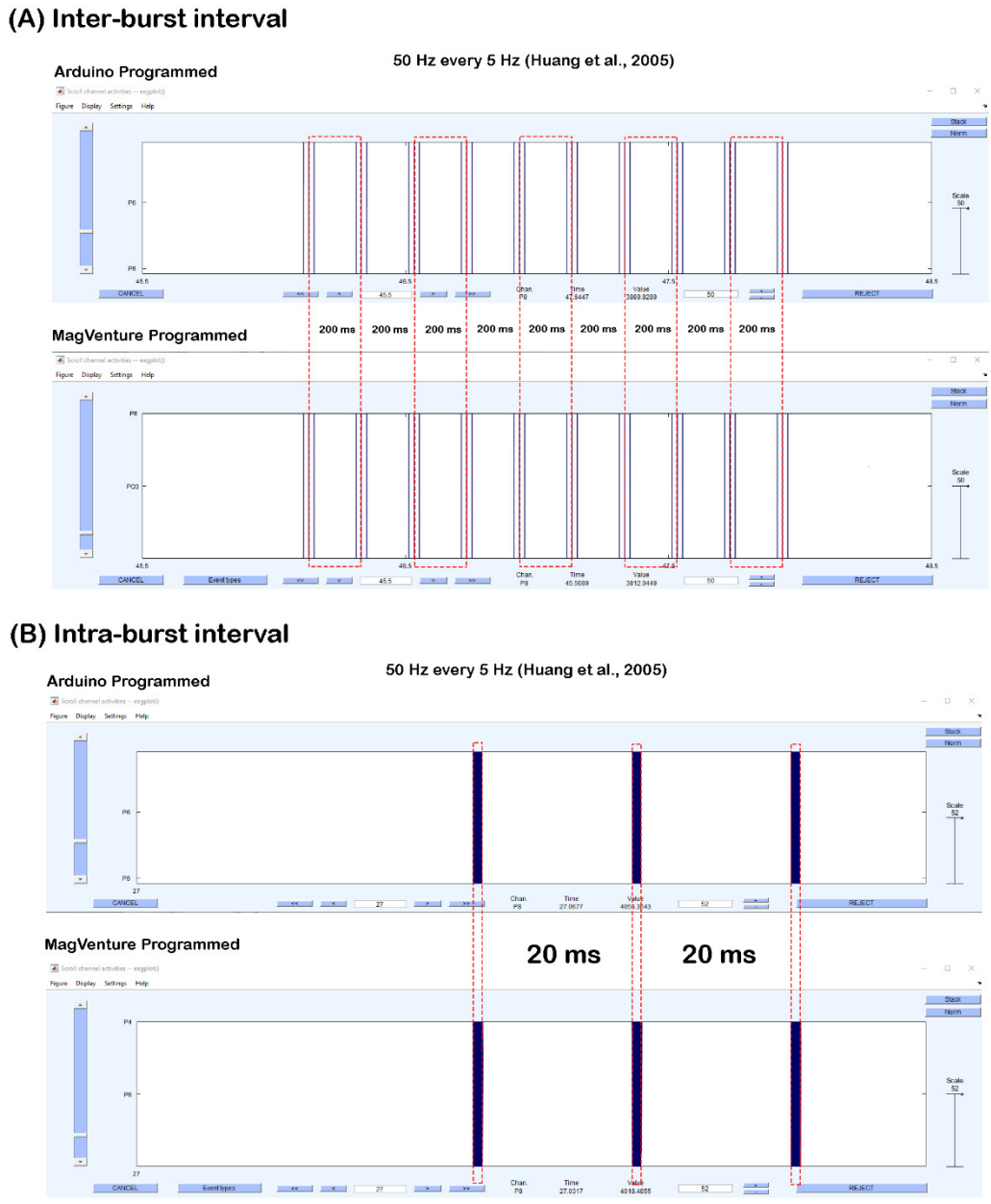

Figure S2. Comparison between MagVenture and Arduino programmed stimuli in electroencephalography (EEG) recording. (A) Inter-burst interval (5 Hz / 200 ms) and (B) Intra-burst interval (50 Hz / 20 ms). Red dotted boxes were drawn to illustrate how precisely pulses match.

3. Selection of individualised frequencies of iTBS based on theta-gamma coupling

The individualised frequency for Ind iTBS was determined by the phase-amplitude cross-frequency coupling (PAC) between frontal theta (phase) and parietal gamma (amplitude) oscillations during the 3-back task. The reasons for choosing between-channel TGC instead of within channel TGC include the observation of cross-frequency coupling between frontal theta and posterior gamma oscillations during working memory in human (Friese et al., 2013; Koster et al., 2014), increased fronto-parietal connectivity in theta and elevated parietal gamma power during working memory task following iTBS (Hoy et al., 2016), and increased frontal theta and parietal gamma power during TMS-EEG following iTBS (Chung et al., 2017). In addition, within-channel PAC is more likely to result in positive coupling due to a common driver which influences both neuronal generators instead of a direct interaction between them (Aru et al., 2015).

3-back EEG data were preprocessed off-line as described in Section 2.9. Several steps were taken to minimize common errors and to enhance the specificity of TGC using the recommendations of (Aru et al., 2015): (1) presence of a clear theta peak was verified; (2) adaptive filtering was used for the selection of bandwidths; (3) only the maintenance period of each epoch (indicated with red asterisks in Fig 2A) were included in the final calculation of TGC to avoid spurious coupling due to visual-evoked responses. As such, the beginning and end of each epoch (500 ms on each side) were discarded to prevent edge effects of filtering (for example, 'H's in Fig 2A); (4) between-channel TGC was used as cross-channel coupling is less likely to occur by a driving input to a single area.

Ten correct trials were selected by randomly ordering the epochs and using the first 10 epochs after shuffling for TGC (Fig 2A). This was to ensure that same amount of data were used for all participants while maintaining enough data length for a reliable estimation (10 cycles of the slowest oscillation (4 Hz); 10 x 0.25 = 2.5 s). Total length of data used in PAC estimation was 10 (epochs) x 4.5 (red asterisks in Fig 2A) = 45 s. The raw signals were zero-padded, concatenated and filtered (Butterworth, second-order, zero-phase) at the respective frequencies; 3 – 9 Hz for theta (Fz electrode) and 20 – 70 Hz for gamma (Pz electrode). Broader windows than traditional bandwidths were used to prevent any influence from the boundaries of filtering for the comodulogram matrix. For theta frequency, filters were applied in steps of 0.1 Hz with the bandwidth of 2 Hz. For gamma frequency, adaptive bandwidth filters were applied in steps of 1 Hz as accurate PAC estimation requires amplitude (gamma) filters with a bandwidth at least twice the centre frequency of the modulatory frequency (theta) (Dvorak and Fenton, 2014). Data were then subjected to Hilbert transform to obtain instantaneous phase and amplitude of the oscillatory signal components. Theta-filtered gamma amplitude envelope was then extracted prior to PAC estimation (Fig 2B). Phase-

amplitude coupling between theta and gamma was calculated using a general linear model (GLM) (Penny et al., 2008) and performed at every filter step to produce a comodulogram matrix. The comodulogram matrix was thresholded to display only significant values, and the *p*-values generated during the GLM calculation were collected and used to generate a significant mask. The masking threshold was adjusted for the number of multiple comparisons (61 theta bins * 51 gamma bins = 3,111; p_{thresh} = 0.05 * 3,111). Bins with a *p*-value greater than p_{thresh} were removed from the final comodulogram (white areas in Supplementary Material, Fig S3) such that only significant PAC values were considered in the final frequency estimates. The peak of the comodulogram matrix was used to infer the specific frequencies within the theta (4 – 8 Hz) and gamma (30 – 60 Hz) bands at which the highest coupling occurred. This maximum value was automatically selected, yielding individual theta and gamma frequencies for iTBS (Fig 2C shows examples from two participants, the maximum value indicated by black asterisks). These windows of frequency bands were chosen to be comparable to other stimulation conditions and for safety reasons (not exceeding 60 Hz as high-frequency bursts may pose a greater risk of seizure (Oberman et al., 2011)). Due to time constraints, PAC was performed three times using different 10 random epochs to ensure consistent TGC. Frequencies were selected using the PAC estimation closest to the mean of the three trials. Additional PAC estimations were performed post-hoc to verify the stability of the PAC and yielded stable results across trials (Supplementary Material, Fig S3). Participants' individualised frequency of stimulation are plotted in figure 2D, with an average of gamma frequency at 41.90 ± 7.7 Hz and theta frequency at 5.97 ± 1.0 Hz. This procedure was performed for every condition to be consistent across different sessions and thereby minimising any potential differences in total duration of the experiment.

4. Stability of TGC across different trials

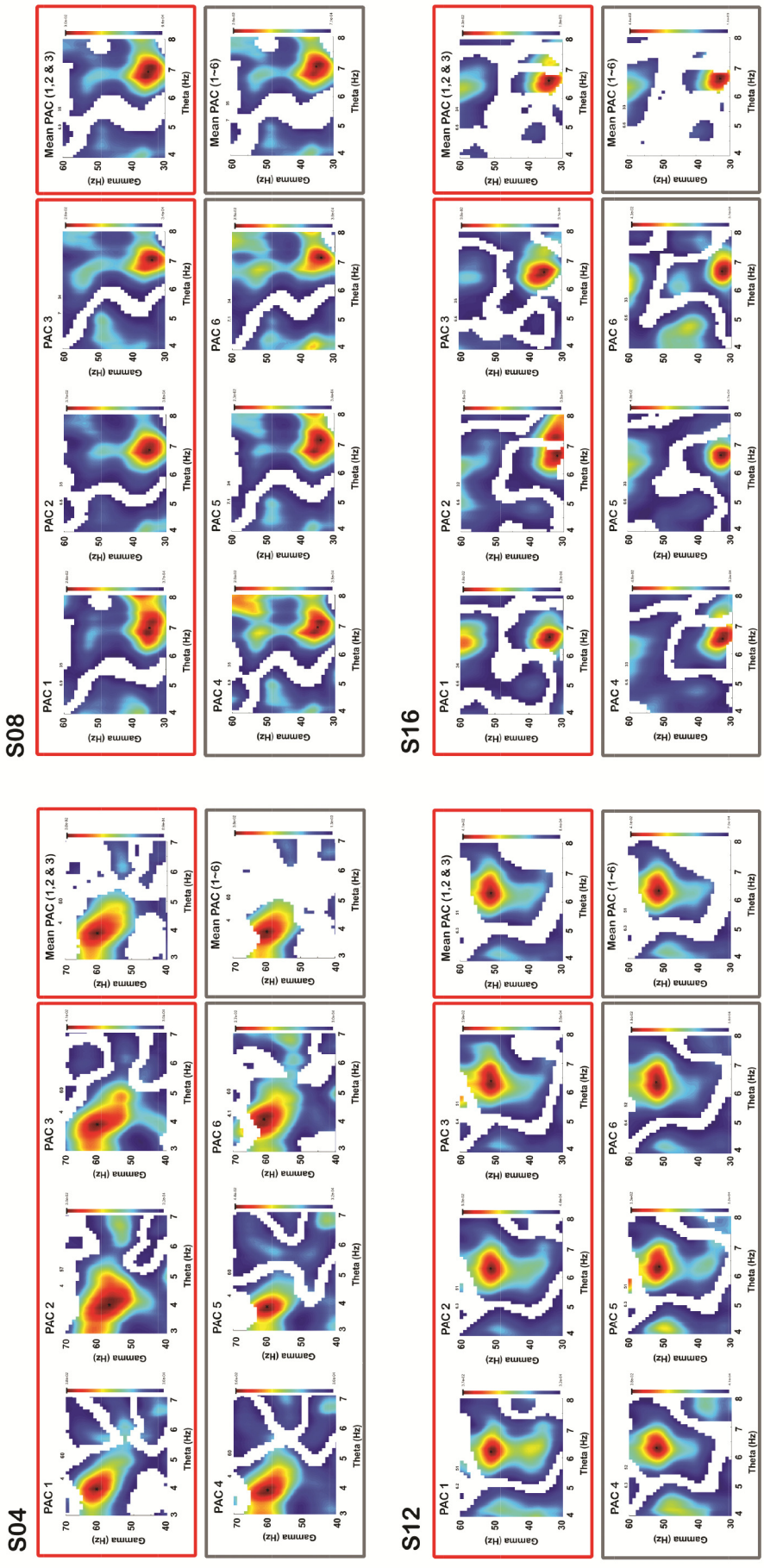

Figure S3. Stability of TGC across different trials illustrated using 4 subjects. Red boxes indicate estimation during experiment and gray boxes post-experiment for validation. Mean PAC was used as a guide for the selection of stimulation parameter and for verification. White patches indicate non-significant coupling with the threshold adjusted for the number of multiple comparisons (61 theta bins * 51 gamma bins = 3,111; p_{thresh} = 0.05 * 3,111).

5. Inter-individual variability in response to iTBS conditions

Figure S4 illustrates inter-individual variability in response to different iTBS conditions for Δ P60 and Δ N100 at T5 (black bar / left arrow) and T30 (gray bar / right arrow). There was a large variability in the number of subjects responding to 30 Hz iTBS both in the directions of iTBS-induced change [e.g. Δ P60 – T5: ↑ (09) ↓ (11); T30: ↑ (10) ↓ (10)] and over time (↑↓ & ↓↑) (Fig S4A & B). Even though 50 Hz iTBS showed a large variability in the direction of the change [e.g. Δ P60 – T5: ↑ (08) ↓ (12); T30: ↑ (08) ↓ (12)], only small number of volunteers responded differently over time (↑↓ & ↓↑) (Fig S4C & D). For Ind iTBS, both variability in the direction of the change and over time were relatively small (Fig S4E & F).

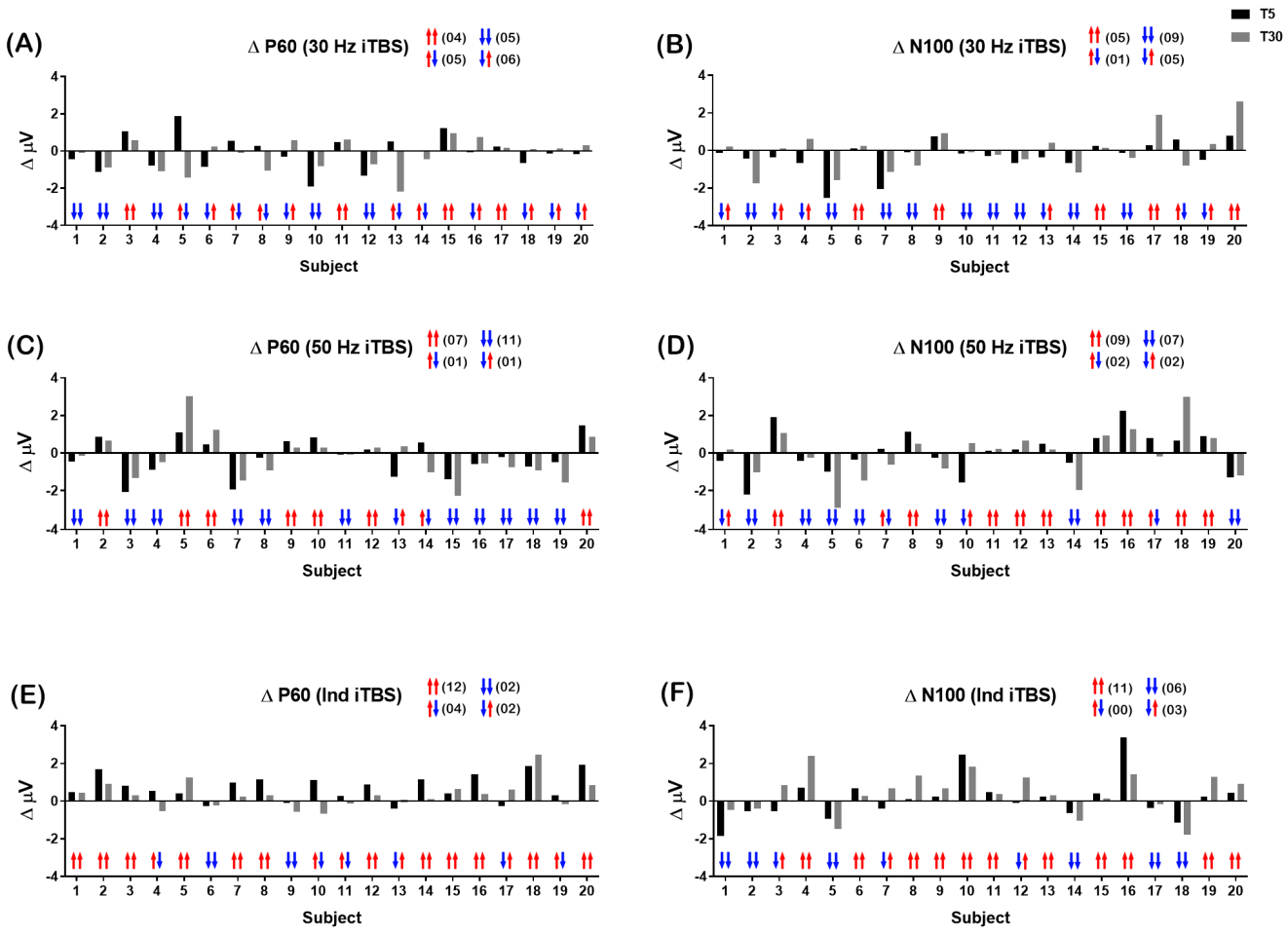

Figure S4. Inter-individual variability in response to different intermittent theta-burst stimulation (iTBS) conditions [(A-B) 30 Hz iTBS; (C-D) 50 Hz iTBS; and (E-F) Ind iTBS] in Δ P60 and Δ N100. Arrows indicate increase (↑) or decrease (↓) in the amplitude from baseline. First arrow indicates T5 and second arrow indicates T30.

6. Control analysis

To validate the statistical method used for the comparison of TEPs in this study (nonparametric cluster-based permutation statistics), 3 (iTBS condition) x 3 (time) repeated measures ANOVA was performed using the data extracted from 6 frontal electrodes (F1, Fz, F2, FC1, FCz and FC2) as described in section 2.12.

For P60 amplitude, a significant main effect of condition ($F_{2,38}$ = 7.433, p = 0.002) and a significant interaction ($F_{4,76}$ = 4.680, p = 0.002) were observed, however, no significant main effect of time was found ($F_{2,38}$ = 1.545, p = 0.227). In order to investigate the interaction effect, a series of one-way ANOVAs was performed. Within condition comparisons yielded a significant main effect of time in Ind iTBS condition ($F_{2,38}$ = 7.419, p = 0.002). Post-hoc pairwise comparisons (Bonferroni corrected) revealed that P60 amplitude was significantly higher at T5 (p = 0.003) and T30 (p = 0.027) compared to BL. No significant main effect of time was found in 30 Hz ($F_{2,38}$ = 0.775, p = 0.468) and 50 Hz iTBS conditions ($F_{2,38}$ = 2.020, p = 0.147). Across conditions, a significant main effect was found at T5 ($F_{2,38}$ = 8.762, p = 0.001) and at T30 ($F_{2,38}$ = 5.526, p = 0.008). Post-hoc pairwise comparisons revealed that P60 amplitude was significantly higher following Ind iTBS compared to both 30 Hz (T5 – p = 0.024; T30 – p = 0.046) and 50 Hz iTBS (T5 – p = 0.001; T30 – p = 0.031). No significant main effect was found at BL ($F_{2,38}$ = 0.055, p = 0.946).

For N100 amplitude, no significant main effects of condition ($F_{2,38}$ = 1.004, p = 0.376) or time ($F_{2,38}$ = 0.876, p = 0.425) were found. However, a significant interaction was observed ($F_{4,76}$ = 2.662, p = 0.039). Within condition comparisons using one-way ANOVAs yielded a significant main effect of time in Ind iTBS condition ($F_{2,38}$ = 8.621, p = 0.001). Post-hoc pairwise comparisons (Bonferroni corrected) revealed that N100 amplitude was smaller at T5 (p = 0.064) and T30 (p = 0.008) compared to BL. No significant main effect of time was found in 30 Hz ($F_{2,38}$ = 0.032, p = 0.969) and 50 Hz iTBS conditions ($F_{2,38}$ = 1.516, p = 0.232). Across conditions, no significant main effect was found at T5 ($F_{2,38}$ = 1.142, p = 0.330) and at T30 (a trend; $F_{2,38}$ = 2.690, p = 0.081). No significant main effect was found at BL ($F_{2,38}$ = 0.552, p = 0.580).

For P200 amplitude, no significant main effects or interaction were observed [Condition – ($F_{2,38}$ = 0.600, p = 0.554); Time – ($F_{2,38}$ = 0.315, p = 0.732); Interaction – ($F_{4,76}$ = 1.430, p = 0.232)].

7. Secondary analyses of sham condition

Twelve age and gender-ratio matched volunteers (4 female, 26.0 ± 6.2 years of age, 16.0 ± 2.26 years of formal education) were included in the study as a control condition for a secondary analysis where application of active stimulation was absent. The analyses were performed on data which were collected in a previous study (https://doi.org/10.1016/j.brs.2018.01.002). The protocols were very similar to the current study, with the same time frame for single-pulse TMS measurement (T5 & T30) followed by working memory performance. Sham iTBS (50 Hz at 5 Hz) was applied at 90° tilt with bottom of the TMS coil facing away from the scalp.

For mood and working memory performance, simple independent t-tests were used to compare active conditions to sham using change-from-baseline values (Δ) rather than absolute values because of; a) differences in the number of samples (20 vs 12) and population (repeated vs independent) and b) differences in baseline values as a result of different population.

TMS-EEG

No significant differences in TEPs were found following sham stimulation (Fig S5A). For comparison across conditions (using independent t-tests), significant differences were found between Ind iTBS and Sham condition [N45 (T5: $p = 0.005$), P60 (T5: $p = 0.001$; T30: $p = 0.019$), N100 (T30: $p = 0.016$), P200 (T5: $p = 0.021$)] (Fig S5B). No significant differences were found between sham condition and 30 / 50 Hz iTBS (all $p > 0.025$).

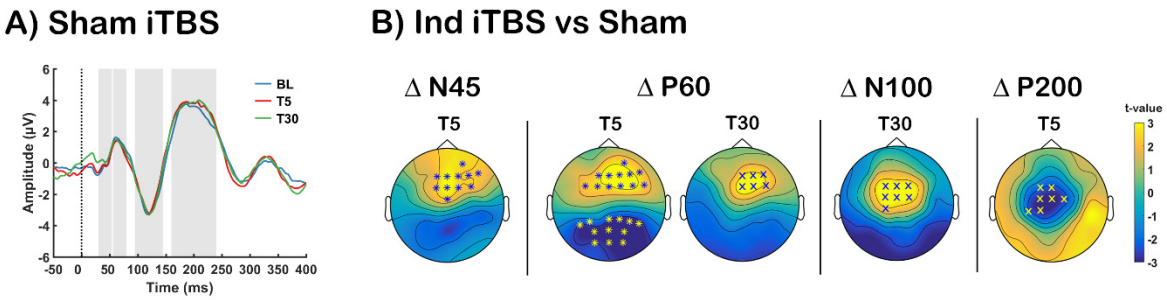

Figure S5. Assessment of transcranial magnetic stimulation (TMS)-evoked potentials (TEPs) following sham stimulation. Grand average TEP waveforms at baseline (BL: blue), 5-min post (T5: red) and 30-min post (T30: green) using 3 fronto-central electrodes (FC1, FCz and FC2). (B) Topoplots represent t-values for comparison between Ind iTBS and sham stimulation (cluster-based statistics, $*p < 0.01$, $^{X}p < 0.025$).

Mood rating

No overall change in mood was visible following sham stimulation (Fig S6). Independent samples t-tests revealed significant differences between Ind iTBS and sham stimulation (p = 0.006). No significant differences were found between sham stimulation and 30 Hz (p = 0.506) or 50 Hz iTBS (p = 0.509).

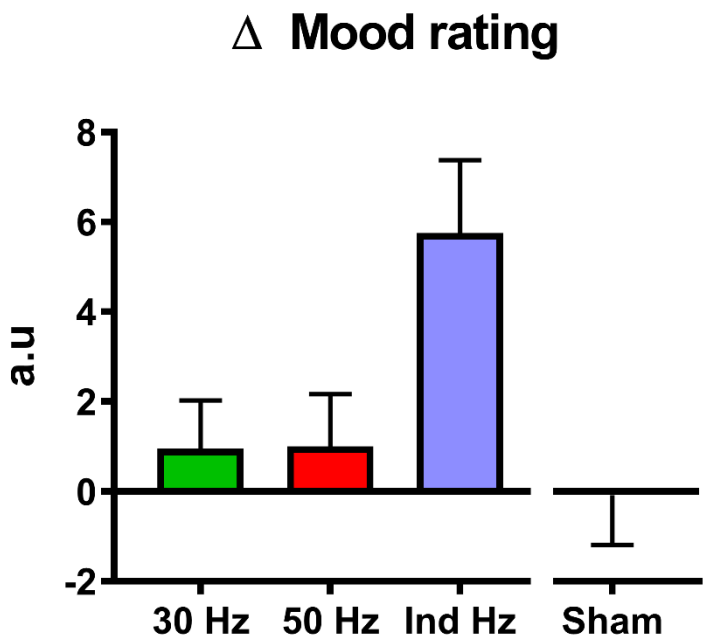

Figure S6. Visualisation for the effect of sham stimulation on the change in mood rating. Error bars indicate standard error of means (SEM).

3-back task

Figure S7 depcits the change-from-baseline scores of working memory performance following different iTBS conditions, separated by sham condition for visualisation purposes. No significant changes in working memory performance (*d'* and accurate reaction time) were found following sham stimulation over time (all $p > 0.05$). Independent samples t-tests revealed significant differences in *d'* between Ind iTBS and sham stimulation at T30 ($p = 0.005$). No other significant differences were seen between active conditions and sham stimulation in either *d'* or accurate reaction time (all $p > 0.05$).

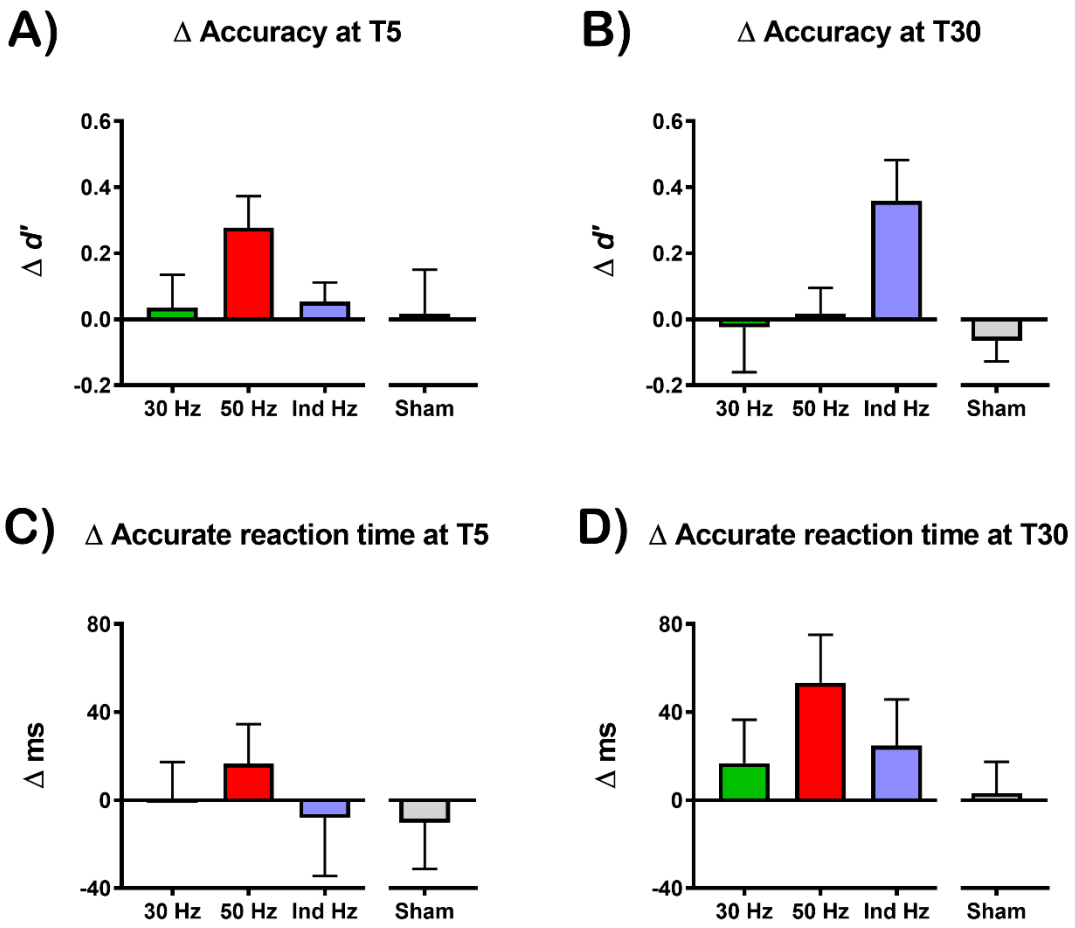

Figure S7. Change in working memory performance across different stimulation conditions. Error bars indicate standard error of means (SEM).

References

Aru, J., Aru, J., Priesemann, V., Wibral, M., Lana, L., Pipa, G., Singer, W., Vicente, R., 2015. Untangling cross-frequency coupling in neuroscience. Curr Opin Neurobiol 31, 51-61.
Casarotto, S., Romero Lauro, L.J., 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, e10281.
Chung, S.W., Rogasch, N.C., Hoy, K.E., Fitzgerald, P.B., 2017. More is not always better: impact of different intensities of intermittent theta burst stimulation in prefrontal cortex using TMS-EEG. Poster session presented at the 2nd International Brain Stimulation Conference, Barcelona, Spain, p. 0231.
Dvorak, D., Fenton, A.A., 2014. Toward a proper estimation of phase-amplitude coupling in neural oscillations. J Neurosci Methods 225, 42-56.
Friese, U., Koster, M., Hassler, U., Martens, U., Trujillo-Barreto, N., Gruber, T., 2013. Successful memory encoding is associated with increased cross-frequency coupling between frontal theta and posterior gamma oscillations in human scalp-recorded EEG. Neuroimage 66, 642-647.
Hoy, K.E., Bailey, N., Michael, M., Fitzgibbon, B., Rogasch, N.C., Saeki, T., Fitzgerald, P.B., 2016. Enhancement of Working Memory and Task-Related Oscillatory Activity Following Intermittent Theta Burst Stimulation in Healthy Controls. Cereb Cortex 26, 4563-4573.
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, 201-206.
Komssi, S., Aronen, H.J., Huttunen, J., Kesaniemi, M., Soinne, L., Nikouline, V.V., Ollikainen, M., Roine, R.O., Karhu, J., Savolainen, S., Ilmoniemi, R.J., 2002. Ipsi- and contralateral EEG reactions to transcranial magnetic stimulation. Clin Neurophysiol 113, 175-184.
Koster, M., Friese, U., Schone, B., Trujillo-Barreto, N., Gruber, T., 2014. Theta-gamma coupling during episodic retrieval in the human EEG. Brain Res 1577, 57-68.
Oberman, L., Edwards, D., Eldaief, M., Pascual-Leone, A., 2011. Safety of theta burst transcranial magnetic stimulation: a systematic review of the literature. J Clin Neurophysiol 28, 67-74.
Penny, W.D., Duzel, E., Miller, K.J., Ojemann, J.G., 2008. Testing for nested oscillation. J Neurosci Methods 174, 50-61.

CHAPTER TWELVE

Discussion and conclusions

This thesis examined the neurobiological response to different stimulation parameters of the motor and prefrontal TBS, utilising TMS-EEG and working memory measures in experimental studies in order to identify optimal methods of prefrontal TBS application. The main findings from the meta-analysis and empirical studies that make up the thesis are summarised below, followed by a discussion of the implications of these findings. Limitations of the research and future directions are also presented.

Summary of main findings

Study one (Chapter 7): Use of theta-burst stimulation in changing excitability of motor cortex: A systematic review and meta-analysis

In Chapter 7, the efficacy of iTBS and cTBS in modulating corticospinal excitability and factors affecting the outcome of stimulation were investigated. There were three main findings in this study. First, both iTBS and cTBS were shown to effectively modulate corticospinal excitability in healthy individuals, increasing the size of MEPs up to 30 minutes and decreasing up to 60 minutes, respectively. The overall effect size of iTBS was smaller than cTBS due to variability in response (larger standard deviation), and the presence of publication bias suggests overestimation of true effect size for both iTBS and cTBS. Second, repeated applications (600 pulses x 2 with an interval) resulted in larger after-effects produced by TBS than single trains (600 pulses). It is interesting to note that continuous stimulation with a break (i.e. 1200 pulses) can flip the direction of the excitability change. In

addition, 30 Hz TBS produced a larger change in MEPs than 50 Hz TBS. The effects of TBS were also influenced by BDNF polymorphism where individuals with Val/Val showed greater effect sizes while Met carriers demonstrated more variability. Third, only cTBS was able to suppress SICI, and no other intracortical circuits were affected by either iTBS or cTBS.

The significance of this study is the systematic demonstration of efficacy of TBS over the motor cortex in a meta-analytic design. Despite early reports of robust effects following TBS, more recent studies with larger sample sizes have shown large variability in response to TBS, which is supported by the strong presence of publication bias in this study. Yet overall, there appear to be modulatory effects. The results also indicate factors affecting the outcome of stimulation which may be useful in optimising the way TBS is applied, namely number of pulses / repeated applications and frequency of stimulation. It remains to be determined what effect TBS has in the prefrontal cortex and whether same factors would impact the stimulation outcome in this cortical region.

Study two (Chapter 8): Demonstration of short-term plasticity in the dorsolateral prefrontal cortex with theta burst stimulation: A TMS-EEG study

In the study described in Chapter 8, the utility of TMS-EEG was explored for tracking the changes in cortical activity in the left prefrontal cortex following iTBS, cTBS and sham. There were three main findings. First, TMS-EEG was able to probe TBS-induced changes in the prefrontal cortex via TMS-evoked potentials (TEPs) and TMS-evoked oscillations. This validated TMS-EEG as a method for tracking plasticity following TBS in the prefrontal cortex and enabled its use in subsequent studies. Second, iTBS resulted in more robust changes

compared to cTBS, with significant increases in TEP N100 amplitude, TMS-evoked theta power and long-interval intracortical inhibition (LICI) of theta power following iTBS. On the other hand, cTBS showed significantly decreased theta power. Third, TBS-induced change in LICI of theta frequency correlated with change in N100 amplitude, suggesting N100 in the prefrontal cortex may be associated with cortical inhibition.

The significance of this study is the demonstration that TBS modulates cortical reactivity and cortical inhibition in the prefrontal cortex, measures that were probed by TMS-EEG for the first time. By identifying markers of response to TBS, i.e. N100 amplitude, it was then possible to investigate the neurobiological effects of different TBS stimulation parameters as was explored in the subsequent studies. In addition, this study highlights the potential difference between motor and prefrontal cortex in response to TBS as findings from Chapter 7 displayed greater plastic effects following cTBS than iTBS whereas the opposite was true over the prefrontal cortex.

Several challenges associated with study two led to improvement in subsequent experimental procedures. For example, the stimulation site was adjusted to F1 electrode from F3 in order to minimise muscle activation. Additional measurements were performed such as TMS-EEG recording at T30 for the assessment of delayed effect and working memory task for the behavioural correlate of neurophysiological changes.

Study three (Chapter 9): Impact of different intensities of intermittent theta burst stimulation on the cortical properties during TMS-EEG and working memory performance

Chapter 9 describes the first optimisation study which examined the impact of different intensities of iTBS (50, 75 and 100% rMT) on prefrontal plasticity using the methods established in Chapter 8. As prefrontal cortex is involved in cognitive and memory processes, a working memory task was also performed as a behavioural outcome measure. There were three main findings. First, neurophysiological changes probed via TMS-EEG following iTBS, particularly TMS-evoked N100 and theta power, were maximal at the intermediate intensity of 75% rMT, and these changes were almost absent at the higher intensity of 100% rMT. Second, this inverse U-shaped effect of iTBS intensity was also observed in the neurophysiology of working memory performance, with increases in ERP N200 amplitude also largest at 75% rMT. These changes in ERPs were related to changes in TEPs (e.g. TEP N100 and ERP N200), suggesting similar or shared mechanisms. Third, iTBS-induced change in alpha power during the 3-back task demonstrated a close relationship with the change in reaction time, however, no significant differences were observed between active iTBS conditions in the working memory performances which may have been limited by the ceiling effect in healthy individuals.

The significance of this study is the impact of intensity on the effects of iTBS in the prefrontal cortex. This is the first empirical evidence to demonstrate an inverse U-shape effect of iTBS in this brain region. Recent studies have reported substantial variability in response to iTBS and a growing number of studies are addressing this problem. This study adds another dimension to the factors affecting the outcome of stimulation and

demonstrates that increasing the intensity may in fact reduce the after-effect of iTBS in the prefrontal cortex. From the clinical perspective, recent studies assessing iTBS in the prefrontal cortex for therapeutic intervention have varied substantially in the intensities used for administration, often using intensities higher than the originally described methods being investigated. This could potentially have a negative impact on the clinical outcome, and therefore, the findings from study 3 encourage the investigation of iTBS intensity in clinical populations.

Study four (Chapter 10): The effect of single and repeated prefrontal intermittent theta burst stimulation on cortical reactivity and working memory

In Chapter 10, the second optimisation study investigated the effect of repeated iTBS in the prefrontal cortex. Using the optimal intensity from Chapter 9, the cortical activity via TMS-EEG and working memory were compared following a single iTBS, repeated iTBS with 15-min interval and sham stimulation. There were three main findings. First, both single and repeated iTBS increased the amplitude of TMS-evoked N100 and P200, and 3-back task related N200. Even though no significant differences were found between the active conditions, only single iTBS-induced changes were significantly different from sham stimulation. Second, working memory performance improved regardless of stimulation condition and active conditions did not differ from sham stimulation, indicating learning effects only. Third, neurophysiological changes (i.e. TEP Δ N100 and ERP Δ N200 which may be linked to cortical inhibition) were associated with improved accuracy following single iTBS, suggesting that when iTBS-induced change is of adequate strength, it may translate into behavioural outcomes.

This study demonstrated that repeating the application of prefrontal iTBS after a short interval (15 mins) did not result in greater changes in cortical neurophysiology or working memory performance compared to a single iTBS train. In addition, these findings corroborate previous studies of iTBS in the prefrontal cortex and provide greater insight into the cortical mechanism underlying iTBS.

Although a small number of studies have shown no beneficial effect of repeated application in the motor cortex, the majority of studies have reported more robust and longer-lasting effects. The findings of this study are therefore in contrast with the majority of the motor cortex studies, and highlight the importance of detailed investigations in specific brain regions of interest rather than adopting the established method from the motor cortex. In clinical trials, repeated application of iTBS is often utilised particularly under accelerated treatment regimes. Findings from this study suggest a single application may be sufficient in modulating cortical activity in the prefrontal cortex. It remains to be determined if repeating its application for more than twice is necessary in order to achieve a superior outcome, as has been observed in the motor cortex (Nettekoven et al., 2014).

Study five (Chapter 11): The effect of individualised intermittent theta burst stimulation in the prefrontal cortex: a TMS-EEG study

In Chapter 11, the final optimisation of prefrontal iTBS examined the effect of different frequency of stimulation. Based on the findings of Chapter 7, a comparison was made between 30 Hz and 50 Hz iTBS in the prefrontal cortex, and the effect of individualised iTBS. These frequency conditions were investigated and the effects of stimulation were assessed

via TMS-EEG, mood and working memory performance. There were three main findings to this study. First, while no group-level effects were seen following either 30 Hz or 50 Hz iTBS, possibly due to inter-individual variability, individualised iTBS resulted in robust overall neurophysiological changes in TEPs such as P60, N100 and P200. Second, mirroring the neurophysiological changes, mood rating increased following individualised stimulation and the change in mood scores correlated with the change in P60 and N100 amplitude. Third, both 50 Hz and individualised iTBS showed a well-maintained change in P60 and N100 amplitude (a potential metric for E/I balance) which may have played an important role in the processes of working memory.

The findings from this study are significant as they demonstrate that the existing "one-size-fits-all" approach may be one of the reasons for the inter-individual variability in response to iTBS, and more individualised strategy could increase the efficacy of stimulation. In addition, the neurophysiological changes have functional relevance with respect to mood and working memory performance.

Implications

The findings from these studies have significant implications for the ways in which iTBS is applied in the prefrontal cortex, illustrating the sensitivity of iTBS to various manipulations in parameter space and highlighting the importance of investigating these elements in order to obtain a more desirable outcome. In addition, these results contribute to our

understanding of the mechanisms of iTBS in conjunction with TMS-EEG methodology and pave the path for the facilitation of more efficacious form of iTBS in clinical settings.

Effects of TBS

More than a decade has passed since TBS was first adapted for the use in humans. Since then, TBS has become one of the most popular methods of inducing plastic change in the motor cortex due to its effects following short stimulation durations at low intensities. Initially, TBS was thought to be more powerful and robust in changing cortical excitability than conventional rTMS, however, recent studies with larger sample sizes have shown a large inter-and intra-variability in response to TBS (Hamada et al., 2013; Hinder et al., 2014). In addition, the vast majority of studies to date have investigated the effects of TBS in the motor cortex, and there is growing interest in applying TBS to other brain regions such as prefrontal cortex due to its clinical relevance. Despite the advantages of TBS, it has not had a widespread clinical uptake which is likely to be due to the lack of knowledge of the effects of TBS in the prefrontal cortex. Chapters 7 and 8 contribute to this knowledge gap by providing information on the neurobiological effects of TBS in both motor and prefrontal cortex and identifying factors that may affect the stimulation outcome.

Before the pursuit of identifying the parameters that impact the outcome of TBS in the motor cortex, it was necessary to first determine what the actual effects of TBS in the motor cortex are. Although trends in the literature followed the results of the original TBS study (Huang et al., 2005), more recent studies with sample sizes of more than 50 have shown no overall effect (Hamada et al., 2013; Lopez-Alonso et al., 2014). As such, the findings in Chapter 7 that both iTBS and cTBS are able to alter corticospinal excitability provide the

evidence for the efficacy of TBS in the motor cortex which is important for the field. The duration of the after-effect was shorter and the overall effect size was smaller for iTBS (facilitatory paradigm) than that of cTBS (suppressive paradigm) which suggested that iTBS may not be as effective as cTBS in modulating corticospinal excitability. Other forms of non-invasive brain stimulation techniques such as rTMS (Maeda et al., 2000), PAS (Wischnewski and Schutter, 2016) and tDCS (Nitsche and Paulus, 2000) have shown greater effects following facilitatory paradigms than suppressive paradigms but with larger standard deviations. Effect sizes are affected by the standard deviation values, and therefore variance should be accounted for when interpreting the results of systematic reviews. Another important factor to consider is publication bias. Several methods of assessing publication bias were employed and all of these approaches indicated a large degree of publication bias, suggesting that the observed effects in the literature may be overestimated. In addition, factors contributing to the efficacy of stimulation were identified such as frequency, number of pulses (or repeated application) and BDNF polymorphism. These findings informed the decision on what parameters to test in the prefrontal cortex. The intensity of TBS is an important parameter to consider (Cardenas-Morales et al., 2010), however the majority of motor cortex studies adhered to the originally described study (Huang et al., 2005) with an intensity of 70 – 80 % a/rMT which limited the subgroup analysis of this variable.

In preparation for examining the impact of the aforementioned TBS parameters in the prefrontal cortex, a preliminary investigation of the efficacy of 'standard' TBS was necessary for this brain region. A growing number of studies have used TMS-EEG to track changes following neuromodulatory techniques such as rTMS (Casula et al., 2014; Esser et al., 2006; Hamidi et al., 2010; Helfrich et al., 2012), tDCS (Pellicciari et al., 2013; Romero Lauro et al., 2014), PAS (Rajji et al., 2013; Veniero et al., 2013) and TBS (Harrington and Hammond-

Tooke, 2015; Vernet et al., 2013). While the majority of the studies were conducted in the motor cortex which provided insight into the origin of TEP components to a certain extent, researchers have begun exploring the effects of neuromodulation in non-motor regions using TMS-EEG. In Chapter 8, this technique was utilised to characterise the effects of TBS in the prefrontal cortex via TEPs and TMS-evoked oscillations which laid the groundwork for subsequent studies.

Firstly, the insight on the neurophysiological basis of short-term plasticity following TBS was provided, showing an increase in N100 amplitude and TMS-evoked theta power following iTBS, whereas cTBS resulted in decreased TMS-evoked theta power. TBS-induced changes in N100 have been described in different brain regions (Casula et al., 2016b; Harrington and Hammond-Tooke, 2015), and appears to be the most prominent TMS-EEG component with a high reproducibility and signal-to-noise ratio (SNR) (Lioumis et al., 2009). These results provided indices of measurement for tracking TBS-induced changes using single-pulse TMS which could be used to infer the size of plastic changes in a similar manner to the change in the amplitude of MEPs following motor cortex stimulation. Secondly, the assessment of long-intracortical inhibition (LICI) using paired-pulse paradigm following TBS showed significantly increased LICI of theta following iTBS, which suggests that iTBS increases $GABA_B$-mediated inhibition in the prefrontal cortex. Lastly, the N100 component of TEPs in the prefrontal cortex was better understood. The paired-pulse TMS largely inhibited the N100-P200 component without affecting the early peaks (i.e. N45 and P60), and TBS-induced change in N100 showed a strong correlation with the LICI of theta, suggesting both of these measures share similar mechanisms. Several lines of evidence from the motor cortex suggest that the amplitude of the N100 reflects the strength of cortical inhibition; 1) N100 amplitude is increased by a $GABA_B$-agonist (Premoli et al., 2014a), 2) the slope of the

N100 correlated with paired-pulse measures of cortical inhibition (LICI) measured using both MEPs and early TEPs (Rogasch et al., 2013a), and 3) N100 amplitude is increased when attempting to inhibit a motor movement (Bonnard et al., 2009). In the prefrontal cortex, the slope of the N100 also correlates with LICI of early TEPs (Rogasch et al., 2015), agreeing with the above findings that N100 may represent a marker of cortical inhibition. In the current study, further evidence that the N100 amplitude following prefrontal TMS represents cortical inhibition was provided by showing that the change in N100 amplitude following TBS correlates with changes in LICI of TMS-evoked theta power following TBS. Together, these findings strongly suggest that the amplitude of the TMS-evoked N100 reflects the strength of cortical inhibition.

Several studies have suggested that the N100 peak represents an inhibitory origin likely mediated via a $GABA_B$ mechanism (Farzan et al., 2013; Premoli et al., 2014a; Rogasch et al., 2013a). Therefore, an increase in $GABA_B$ -mediated inhibition is one candidate mechanism that could explain the changes in N100 following iTBS in DLPFC. However, until a similar pharmacological study is conducted in the DLPFC, the result should be interpreted with caution. In the motor cortex, TBS appears to modulate glutamatergic (Huang et al., 2007) and GABAergic (Stagg et al., 2009) neurotransmission. Changes in MEP amplitude mainly reflect excitatory glutamatergic neurotransmission, whereas LICI and cortical silent period (CSP) reflect $GABA_B$ intracortical activity (Paulus et al., 2008). TBS studies on motor cortex have shown no change in CSP (Brownjohn et al., 2014; Di Lazzaro et al., 2011) or LICI (Goldsworthy et al., 2013; Suppa et al., 2008) which might suggest different intracortical circuits are involved in the effects of TBS in different brain regions. Another alternative is that LICI is often close to saturation in MEP studies, therefore lack of change could represent a ceiling effect.

Taken together, TBS is able to exert plastic changes in both motor and prefrontal cortex. Even though iTBS showed more variability in the motor cortex, it was found to be more robust in the prefrontal cortex. This is somewhat consistent with the observation that depressed patients who received protocols involving iTBS in the prefrontal cortex showed better overall clinical outcome than cTBS alone in a recent meta-analysis (Berlim et al., 2017). In addition, stimulation parameters which could improve TBS outcomes were identified, as well as neurophysiological indices of measurement for optimisation of TBS.

Importance of stimulation parameters of iTBS in the prefrontal cortex

The importance of the parameters of stimulation, such as intensity, duration and frequency is often highlighted (de Jesus et al., 2014; Hannah et al., 2016; Rossi et al., 2009), yet the optimal parameter of rTMS protocols remain elusive. In addition, the neural basis of the mechanisms of the beneficial effect produced by different stimulation parameters are still largely unknown (Hoogendam et al., 2010; Miniussi and Thut, 2010). Chapter 9, 10 and 11 were dedicated to optimising the effects of stimulation by varying the parameter space of iTBS and elucidating underlying mechanisms of action in the prefrontal cortex. First, Chapter 9 describes the impact of intensity on the effect of iTBS. Typically, the propensity of the change in brain plasticity increases with increasing intensity of conventional rTMS protocols (Fitzgerald et al., 2002b; Padberg et al., 2002; Speer et al., 2003). This pattern, however, was not present with iTBS which instead exhibited an inverse-U shaped influence of intensity on plastic effects. Corroborating the result of Chapter 8, iTBS at 75% rMT, and 50% rMT to a smaller degree, increased the amplitude of N100 and theta power, while these effects were absent at a higher intensity of 100% rMT. The change in the plastic effect of iTBS was further

supported by changes in TMS-evoked gamma power, which increased following iTBS at 75% rMT and decreased following 100% rMT iTBS. Gamma oscillations are involved in cortical processing and are thought to promote synaptic strength (Fries, 2009) and therefore, it is likely that 75% iTBS resulted in increased synaptic plasticity compared to when iTBS was given at 100% rMT. The inhibitory interneurons play an important role in the synchronisation of gamma oscillations (Cobb et al., 1995; Whittington et al., 1995). The correlations found in this study between iTBS-induced change in N100 (associated with inhibitory mechanisms) and TMS-evoked gamma power suggest that $GABA_B$ receptor-mediated inhibition may act as a 'gate-keeper' in modulating gamma oscillations (Kohl and Paulsen, 2010). The involvement of cortical inhibition in TEP N100 was further substantiated by the iTBS-induced change in the 2-back task, in particular ERP N200 which is thought to be involved in cognitive and inhibitory processing (Aron, 2007; Kopp et al., 1996). These findings further indicate that iTBS modulates cortical inhibition in the prefrontal cortex, and it does so in an intensity-dependent manner. The behavioural outcome of the 3-back task on accurate reaction time partially supports the inverse U-shaped plastic effects of iTBS in regards to the intensity of stimulation. Despite there being no significant differences between active conditions, 75% iTBS resulted in faster reaction time compared to sham stimulation which was mirrored by increased alpha power during the maintenance period. Lateral prefrontal cortex plays an important role in maintaining top-down attentional control in reaction time tasks (Bellgrove et al., 2004; Stuss et al., 2003), and therefore, it is possible that iTBS exerted a positive influence on the attentional processes which was maximal at 75% rMT. The results from Chapter 9 provide the first evidence demonstrating that intermediate intensity of iTBS produces the maximal effect in the prefrontal cortex, unlike conventional rTMS protocols.

In Chapter 10, the effects of repeated application of prefrontal iTBS were investigated in attempts to obtain more robust and prolonged outcomes. While several studies have shown additive effects of iTBS in humans (Nettekoven et al., 2014) and animals (Thimm and Funke, 2015; Volz et al., 2013), such dose-dependent effect is not always present (Gamboa et al., 2011; Murakami et al., 2012). Corroborating the studies with no improvement following repeated applications, no evidence of dose-dependent efficacy was seen following prefrontal application of iTBS which may have been due to homeostatic mechanisms. Increasing the number of iTBS blocks or the duration of the interval between each block may increase the effect of iTBS, however it may not be the most optimal approach if the total duration of the treatment is as long as conventional rTMS. Perhaps the most interesting findings of Chapter 10 were the relationships between neurophysiological and behavioural changes following a single application of iTBS. The association found in the previous chapter between TEP N100 and ERP N200 was replicated, and in turn, the changes in the amplitude of these peaks correlated with the accuracy of the 3-back task, which provides insight into an aspect of enhancement in inhibitory control following prefrontal iTBS. Therefore, the findings from Chapter 10 further support the evidence that iTBS modulates cortical inhibition in the prefrontal cortex, which is not increased with a repeated application.

The optimisation of iTBS was most successful when the individualised approach was applied as described in Chapter 11. The inter-individual variability in response to TBS is one of the major impediments to the widespread clinical use of this technique. Studies with larger

sample sizes have shown substantial variability following conventional TBS in the motor cortex (Hamada et al., 2013; Hinder et al., 2014) which is to some extent in line with what was observed following two most commonly used forms of iTBS, 30 Hz and 50 Hz, in the prefrontal cortex. These results are contradictory to the previous chapters (Chapter 8, 9 and 10) where more robust neurophysiological changes were obtained following 50 Hz iTBS. The application of individualised iTBS using theta-gamma coupling based on the original animal study of TBS (Larson et al., 1986) yielded extended after-effects in both neurophysiology, mood and working memory (to a certain extent) which stresses the importance of individualised methods of stimulation.

The findings from the study described in Chapter 11 on the impact of frequency of stimulation, specifically the intervals between each pulse and burst, support the notion that the temporal precision of the stimulation affects iTBS outcome as described in Chapter 9. The influence of frequency of stimulus relates directly to the unique temporal aspects that underlie the fundamental mechanisms of TBS (Larson and Munkacsy, 2015). It is believed that TBS is effective because it targets a phase of presynaptic $GABA_B$-mediated disinhibition which is sustained in theta rhythms (Davies and Collingridge, 1996; Larson and Munkacsy, 2015; Mott and Lewis, 1991). A TMS pulse elicits both postsynaptic $GABA_B$-mediated inhibition and presynaptic $GABA_B$ autoreceptor-mediated disinhibition. Presynaptic disinhibition outlasts postsynaptic inhibition, and this temporal disparity results in a late period at 200 ms during which disinhibition is prevalent (Deisz, 1999; Otis et al., 1993). Postsynaptic depolarisation (Larson et al., 1986; Pacelli et al., 1989) and NMDA receptor activation (Davies and Collingridge, 1996) at excitatory synapses are enhanced during this

period of disinhibition, resulting in a brief window during which plasticity induction is facilitated (Davies and Collingridge, 1996; Larson et al., 1986; Mott and Lewis, 1991; Pacelli et al., 1989). Delivery of stimulus bursts at this interval resulted in a rapid and robust LTP (Larson et al., 1986). A similar period of late disinhibition has also been demonstrated in the human motor cortex (Cash et al., 2010; Cash et al., 2011) where plasticity induction was enhanced (Cash et al., 2016). The individualised frequency of stimulation was developed by mimicking the original animal study where application of patterned stimulation resembling such spike discharge patterns of hippocampal neurons during exploratory behaviours that led to a robust LTP (Larson et al., 1986). The within-burst timing (i.e. theta rhythm) was an important factor determining the efficacy of LTP, and shorter or longer interval resulted in reduced LTP (Larson and Lynch, 1989). Therefore, it is likely that tailoring the temporal dynamics of pulses for each individual yielded a robust LTP-like effect following individualised iTBS. Involvement of similar mechanism was observed in Chapter 9 using different intensities of iTBS, where decreasing (50% rMT) or increasing (100% rMT) the intensity reduced the after-effects due to possible shortening or lengthening of the late cortical disinhibition, respectively.

Although the largest neurophysiological changes were observed following Ind iTBS, these changes were different from the outcome of previous chapters, particularly in N100. The reasons for this discrepancy are not clear, and it is likely due to inter-individual variability. It is interesting to note that although the change in N100 was in an opposite direction to the previous studies, a similar positive correlation (increase in P60 resulting in increased N100, and vice versa) to Chapter 9 was observed. Assuming P60 is related to excitability and N100 to inhibition, the correlation analyses between Δ P60 and Δ N100 suggests a tightly controlled E/I balance. In such instances, the disparity between studies can then be

explained by Δ N100 reflecting a shift to maintain the ratio between the two peaks, rather than an increase in the ratio. The change in working memory performance was assessed as a behavioural marker of iTBS-induced neurophysiological changes, and the ratio between the two peaks exhibited a close association to the behavioural outcome. The Δ P60 and Δ N100 did not correlate with the performance change by themselves, but rather the ratio between the changes in these peaks corresponded with the change in performance. This finding indicates that well-balanced change is more important for working memory. The balance between excitation and inhibition is thought to play an important role in cortical processing and working memory (Kirkwood, 2015; Legon et al., 2016; Lim and Goldman, 2013) and alteration in the balance may lead to cognitive impairment (Cline, 2005; Vogels and Abbott, 2009). Taken together, these findings highlight the importance of the frequency of stimulation, and more individualised approach may enhance the effects of iTBS.

Limitations

Limitations to individual studies are included in the relevant chapters, however, some of the common limitations across studies are outlined hereinafter. First, the TMS click sound was not completely masked by the application of white noise and the coil click sound transmitted through bone conduction could not be avoided. It has been shown that N100-P180 components are partially related to auditory processing, which also results in cortical activity (ter Braack et al., 2015). Because of the repeated measures design, any auditory artefacts should be consistent across time, and therefore changes in TEP amplitude can be attributed to TMS-evoked neural activity. In addition, sham conditions did not have any impact on the N100-P180 components. Furthermore, correlations often found between the

Δ N100 and neurophysiological change during N-back task as well as behaviour changes indicate the likelihood of neural origin unrelated to auditory processing. Second, the number of pulses used for TMS-EEG was likely suboptimal and hence any change in early TEP components may have been undetected. Signal-to-noise ratio inevitably increases with more number of trials included in the data, which could increase the sensitivity to detect small changes in early TMS-EEG peaks reflecting iTBS-induced plasticity. However, it is also possible that changes in early TEP peaks suffer from high inter-individual variability in response to conventional TBS paradigms. Furthermore, increasing the number of pulses did not show a group-level effect on early TEPs in Chapter 11. In addition, change in P60 has been observed using ~50 single TMS pulses following tDCS (Hill et al., 2017). Finally, neuronavigation was unavailable for the localisation of stimulation target. The direction of the induced electrical current relative to the cortical structures has an impact on the effectiveness of the stimulation (Bashir et al., 2013; Brasil-Neto et al., 1992; Mills et al., 1992). Optimal MEPs can be obtained when the coil is perpendicular to the underlying gyrus (Richter et al., 2013) in the motor cortex. However, it is unclear if the same applies in the prefrontal cortex where the stimulated neuronal population could be different from the motor cortex. The positioning of the coil was instead based on 10-20 electrode positions at either F3 (Chapter 8) or F1 (Chapter 9, 10 and 11), both of which are within the range of DLPFC (Koessler et al., 2009). Steps were taken to ensure consistent re-positioning of the coil before and after TBS application to minimise the margin of error. Comparable results have been reported using EEG-guided methods (Rogasch et al., 2014) and MRI-guided neuronavigation (Lioumis et al., 2009) and the TEP waveforms were consistent across the studies in the thesis. However, future studies should employ the use of neuronavigation which could potentially reduce any variability across sessions.

Challenges in the current research

There were several challenges during the course of this research. TMS-EEG is in its infancy, and as such, the availability of analysis method is limited. This has been overcome in the last year or so with the release of open-source TMS-EEG toolboxes, however considerable development of analysis code and pipelines were required for the work in this thesis. For instance, pipelines were developed which took into account for the repeated TMS-EEG blocks over time, and concatenating the data allowed for the consistent effects of ICA across time blocks.

Pipeline development was particularly important for the final study, which involved developing an analysis pipeline for theta-gamma coupling that required both speed and accuracy in order to be performed during the experiment. This involved hours of research in a topic of speculation which led to no real solution but limitations in each measuring method for phase-amplitude coupling. A large number of different analysis methods available in the literature can be daunting, especially when each study presents itself to be superior to others. More than 10 different methods were tested on previously collected data, each taking several hours to analyse, however led to a series of failures in its attempt. Guided by recommendations, numerous modifications to the procedure by trial and error and fine-tuning the selected method improved the outcome, and further adjustment was made to reduce the analysis duration (~15 min). Devising and developing a prototype for the micro-controller further expedited the experimental procedure which was another major challenge.

Techniques used in this study are relatively new such as the prefrontal application of TMS-EEG and TBS, and while it is an exciting field to explore, many limitations follow when analysing the data and interpreting the results.

Future directions

In accordance with limitations, the future directions for individual study are outlined in each chapter. Most importantly, the optimisation of TBS protocols is critical in order to facilitate its use in clinical settings. Prefrontal application of rTMS is one therapeutic option for treatment-resistant depression and is being investigated for use in various other mood and cognitive disorders. An increase in the exploratory use of TBS as a therapeutic tool is evident in recent years (Chung et al., 2015a; Li et al., 2014; Plewnia et al., 2014; Prasser et al., 2015), however no systematic investigation on the effect of stimulation parameters is currently available, especially in the prefrontal cortex. The parameter space (e.g. the combination of intensity, frequency and number of pulses) available for TBS is enormous, and has surprisingly undergone little optimisation in either the motor cortex or non-motor regions, with most studies using the parameters reported in the original study (Huang et al., 2005). Methods applied in this study allow the examination of optimal stimulation parameters which can aid in developing more efficacious protocols for clinical applications. While TMS-EEG can be a powerful tool in tracking neuromodulatory changes in the prefrontal cortex, the origin of the TEPs needs to be better characterised. This study provided some evidence linking N100 to inhibitory activity in the prefrontal cortex, and the possible association of P60 to excitability. Studies are suggesting P60 may provide a marker of excitability (Cash et al., 2017b; Hill et al., 2017), however pharmacological research would provide more

accurate inference to excitatory or inhibitory mechanisms, which would aid in precise interpretation of TBS-induced changes using this technique. Finally, exploration of whether findings of this study would translate into the clinical population is required. The observation of robust neurophysiological changes following iTBS holds great promise for therapeutic applications because neuropsychiatric cohorts often exhibit altered TMS-induced activity (Casarotto et al., 2011; Julkunen et al., 2008; Noda et al., 2017a) and some of the characteristics of TMS-evoked activities can be restored following NIBS including TBS (Pellicciari et al., 2017a). It remains to be determined if positive behavioural outcome such as improved working memory performance could be achieved in the clinical population.

Conclusions

TMS-EEG can be used to track plastic changes following TBS in the prefrontal cortex, and these plastic changes are influenced by intensity, but not repeated application of stimulation. Most importantly, the individualised form of iTBS appears to be more effective than conventional TBS paradigms in altering both neurophysiological mechanisms and behaviour. The findings from this thesis contribute to the development of more effective TBS protocol in the prefrontal cortex for both basic and applied research, and allows for better understanding of its mechanism in healthy individuals.

REFERENCES

Ahearn, E.P., 1997. The use of visual analog scales in mood disorders: a critical review. J Psychiatr Res 31, 569-579.

Aron, A.R., 2007. The neural basis of inhibition in cognitive control. Neuroscientist 13, 214-228.

Artola, A., Brocher, S., Singer, W., 1990. Different voltage-dependent thresholds for inducing long-term depression and long-term potentiation in slices of rat visual cortex. Nature 347, 69-72.

Aru, J., Aru, J., Priesemann, V., Wibral, M., Lana, L., Pipa, G., Singer, W., Vicente, R., 2015. Untangling cross-frequency coupling in neuroscience. Curr Opin Neurobiol 31, 51-61.

Baddeley, A., 2010. Working memory. Curr Biol 20, R136-140.

Bakker, N., Shahab, S., Giacobbe, P., Blumberger, D.M., Daskalakis, Z.J., Kennedy, S.H., Downar, J., 2015. rTMS of the dorsomedial prefrontal cortex for major depression: safety, tolerability, effectiveness, and outcome predictors for 10 Hz versus intermittent theta-burst stimulation. Brain Stimul 8, 208-215.

Baldassarre, A., Capotosto, P., Committeri, G., Corbetta, M., 2016. Magnetic stimulation of visual cortex impairs perceptual learning. Neuroimage 143, 250-255.

Barker, A.T., Jalinous, R., Freeston, I.L., 1985. Non-invasive magnetic stimulation of human motor cortex. Lancet 1, 1106-1107.

Bashir, S., Perez, J.M., Horvath, J.C., Pascual-Leone, A., 2013. Differentiation of motor cortical representation of hand muscles by navigated mapping of optimal TMS current directions in healthy subjects. J Clin Neurophysiol 30, 390-395.

Bashir, S., Perez, J.M., Horvath, J.C., Pena-Gomez, C., Vernet, M., Capia, A., Alonso-Alonso, M., Pascual-Leone, A., 2014. Differential effects of motor cortical excitability and plasticity in young and old individuals: a Transcranial Magnetic Stimulation (TMS) study. Front Aging Neurosci 6, 111.

Batsikadze, G., Moliadze, V., Paulus, W., Kuo, M.F., Nitsche, M.A., 2013. Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. J Physiol 591, 1987-2000.

Bellgrove, M.A., Hester, R., Garavan, H., 2004. The functional neuroanatomical correlates of response variability: evidence from a response inhibition task. Neuropsychologia 42, 1910-1916.

Benali, A., Trippe, J., Weiler, E., Mix, A., Petrasch-Parwez, E., Girzalsky, W., Eysel, U.T., Erdmann, R., Funke, K., 2011. Theta-burst transcranial magnetic stimulation alters cortical inhibition. J Neurosci 31, 1193-1203.

Berlim, M.T., McGirr, A., Rodrigues Dos Santos, N., Tremblay, S., Martins, R., 2017. Efficacy of theta burst stimulation (TBS) for major depression: An exploratory meta-analysis of randomized and sham-controlled trials. J Psychiatr Res 90, 102-109.

Bestmann, S., Baudewig, J., Siebner, H.R., Rothwell, J.C., Frahm, J., 2003. Subthreshold high-frequency TMS of human primary motor cortex modulates interconnected frontal motor areas as detected by interleaved fMRI-TMS. Neuroimage 20, 1685-1696.

Birba, A., Ibanez, A., Sedeno, L., Ferrari, J., Garcia, A.M., Zimerman, M., 2017. Non-Invasive Brain Stimulation: A New Strategy in Mild Cognitive Impairment? Front Aging Neurosci 9, 16.

Bliss, T.V., Lomo, T., 1973. Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. J Physiol 232, 331-356.

Boniface, S.J., 2001. Plasticity after acute ischaemic stroke studied by transcranial magnetic stimulation. J Neurol Neurosurg Psychiatry 71, 713-715.

Bonnard, M., Spieser, L., Meziane, H.B., de Graaf, J.B., Pailhous, J., 2009. Prior intention can locally tune inhibitory processes in the primary motor cortex: direct evidence from combined TMS-EEG. Eur J Neurosci 30, 913-923.

Bonnefond, M., Jensen, O., 2012. Alpha oscillations serve to protect working memory maintenance against anticipated distracters. Curr Biol 22, 1969-1974.
Brasil-Neto, J.P., Cohen, L.G., Panizza, M., Nilsson, J., Roth, B.J., Hallett, M., 1992. Optimal focal transcranial magnetic activation of the human motor cortex: effects of coil orientation, shape of the induced current pulse, and stimulus intensity. J Clin Neurophysiol 9, 132-136.
Braver, T.S., Cohen, J.D., Nystrom, L.E., Jonides, J., Smith, E.E., Noll, D.C., 1997. A parametric study of prefrontal cortex involvement in human working memory. Neuroimage 5, 49-62.
Brownjohn, P.W., Reynolds, J.N., Matheson, N., Fox, J., Shemmell, J.B., 2014. The effects of individualized theta burst stimulation on the excitability of the human motor system. Brain Stimul 7, 260-268.
Brunoni, A.R., Vanderhasselt, M.A., 2014. Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: a systematic review and meta-analysis. Brain Cogn 86, 1-9.
Bulteau, S., Sebille, V., Fayet, G., Thomas-Ollivier, V., Deschamps, T., Bonnin-Rivalland, A., Laforgue, E., Pichot, A., Valriviere, P., Auffray-Calvier, E., Fortin, J., Pereon, Y., Vanelle, J.M., Sauvaget, A., 2017. Efficacy of intermittent Theta Burst Stimulation (iTBS) and 10-Hz high-frequency repetitive transcranial magnetic stimulation (rTMS) in treatment-resistant unipolar depression: study protocol for a randomised controlled trial. Trials 18, 17.
Caparelli, E., Backus, W., Telang, F., Wang, G., Maloney, T., Goldstein, R., Henn, F., 2012. Is 1 Hz rTMS Always Inhibitory in Healthy Individuals? Open Neuroimag J 6, 69-74.
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 Res 591, 332-336.
Cardenas-Morales, L., Nowak, D.A., Kammer, T., Wolf, R.C., Schonfeldt-Lecuona, C., 2010. Mechanisms and applications of theta-burst rTMS on the human motor cortex. Brain Topogr 22, 294-306.
Cardenas-Morales, L., Volz, L.J., Michely, J., Rehme, A.K., Pool, E.M., Nettekoven, C., Eickhoff, S.B., Fink, G.R., Grefkes, C., 2014. Network connectivity and individual responses to brain stimulation in the human motor system. Cereb Cortex 24, 1697-1707.
Casarotto, S., Maatta, S., Herukka, S.K., Pigorini, A., Napolitani, M., Gosseries, O., Niskanen, E., Kononen, M., Mervaala, E., Rosanova, M., Soininen, H., Massimini, M., 2011. Transcranial magnetic stimulation-evoked EEG/cortical potentials in physiological and pathological aging. Neuroreport 22, 592-597.
Cash, R.F., Jegatheeswaran, G., Ni, Z., Chen, R., 2017a. Modulation of the Direction and Magnitude of Hebbian Plasticity in Human Motor Cortex by Stimulus Intensity and Concurrent Inhibition. Brain Stimul 10, 83-90.
Cash, R.F., Mastaglia, F.L., Thickbroom, G.W., 2013. Evidence for high-fidelity timing-dependent synaptic plasticity of human motor cortex. J Neurophysiol 109, 106-112.
Cash, R.F., Murakami, T., Chen, R., Thickbroom, G.W., Ziemann, U., 2016. Augmenting Plasticity Induction in Human Motor Cortex by Disinhibition Stimulation. Cereb Cortex 26, 58-69.
Cash, R.F., Noda, Y., Zomorrodi, R., Radhu, N., Farzan, F., Rajji, T.K., Fitzgerald, P.B., Chen, R., Daskalakis, Z.J., Blumberger, D.M., 2017b. Characterization of Glutamatergic and GABAA-Mediated Neurotransmission in Motor and Dorsolateral Prefrontal Cortex Using Paired-Pulse TMS-EEG. Neuropsychopharmacology 42, 502-511.
Cash, R.F., Ziemann, U., Murray, K., Thickbroom, G.W., 2010. Late cortical disinhibition in human motor cortex: a triple-pulse transcranial magnetic stimulation study. J Neurophysiol 103, 511-518.
Cash, R.F., Ziemann, U., Thickbroom, G.W., 2011. Inhibitory and disinhibitory effects on I-wave facilitation in motor cortex. J Neurophysiol 105, 100-106.
Casula, E.P., Pellicciari, M.C., Picazio, S., Caltagirone, C., Koch, G., 2016a. Spike-timing-dependent plasticity in the human dorso-lateral prefrontal cortex. Neuroimage 143, 204-213.

Casula, E.P., Pellicciari, M.C., Ponzo, V., Stampanoni Bassi, M., Veniero, D., Caltagirone, C., Koch, G., 2016b. Cerebellar theta burst stimulation modulates the neural activity of interconnected parietal and motor areas. Sci Rep 6, 36191.
Casula, E.P., Tarantino, V., Basso, D., Arcara, G., Marino, G., Toffolo, G.M., Rothwell, J.C., Bisiacchi, P.S., 2014. Low-frequency rTMS inhibitory effects in the primary motor cortex: Insights from TMS-evoked potentials. Neuroimage 98, 225-232.
Chaieb, L., Leszczynski, M., Axmacher, N., Hohne, M., Elger, C.E., Fell, J., 2015. Theta-gamma phase-phase coupling during working memory maintenance in the human hippocampus. Cogn Neurosci 6, 149-157.
Chen, R., Classen, J., Gerloff, C., Celnik, P., Wassermann, E.M., Hallett, M., Cohen, L.G., 1997. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology 48, 1398-1403.
Chen, R., Tam, A., Butefisch, C., Corwell, B., Ziemann, U., Rothwell, J.C., Cohen, L.G., 1998. Intracortical inhibition and facilitation in different representations of the human motor cortex. J Neurophysiol 80, 2870-2881.
Chen, Y., Huang, X., 2015. Modulation of Alpha and Beta Oscillations during an n-back Task with Varying Temporal Memory Load. Front Psychol 6, 2031.
Cheng, C.M., Juan, C.H., Chen, M.H., Chang, C.F., Lu, H.J., Su, T.P., Lee, Y.C., Li, C.T., 2016. Different forms of prefrontal theta burst stimulation for executive function of medication- resistant depression: Evidence from a randomized sham-controlled study. Prog Neuropsychopharmacol Biol Psychiatry 66, 35-40.
Chistyakov, A.V., Rubicsek, O., Kaplan, B., Zaaroor, M., Klein, E., 2010. Safety, tolerability and preliminary evidence for antidepressant efficacy of theta-burst transcranial magnetic stimulation in patients with major depression. Int J Neuropsychopharmacol 13, 387-393.
Chung, S.W., Hill, A.T., Rogasch, N.C., Hoy, K.E., Fitzgerald, P.B., 2016. Use of theta-burst stimulation in changing excitability of motor cortex: A systematic review and meta-analysis. Neurosci Biobehav Rev 63, 43-64.
Chung, S.W., Hoy, K.E., Fitzgerald, P.B., 2015a. Theta-burst stimulation: a new form of TMS treatment for depression? Depress Anxiety 32, 182-192.
Chung, S.W., Lewis, B.P., Rogasch, N.C., Saeki, T., Thomson, R.H., Hoy, K.E., Bailey, N.W., Fitzgerald, P.B., 2017a. Demonstration of short-term plasticity in the dorsolateral prefrontal cortex with theta burst stimulation: A TMS-EEG study. Clin Neurophysiol 128, 1117-1126.
Chung, S.W., Rogasch, N.C., Hoy, K.E., Fitzgerald, P.B., 2015b. Measuring Brain Stimulation Induced Changes in Cortical Properties Using TMS-EEG. Brain Stimul 8, 1010-1020.
Chung, S.W., Rogasch, N.C., Hoy, K.E., Fitzgerald, P.B., 2017b. More is not always better: impact of different intensities of intermittent theta burst stimulation in prefrontal cortex using TMS-EEG. Poster session presented at the 2nd International Brain Stimulation Conference, Barcelona, Spain, p. 0231.
Chung, S.W., Rogasch, N.C., Hoy, K.E., Sullivan, C.M., Cash, R.F.H., Fitzgerald, P.B., 2017c. Impact of different intensities of intermittent theta burst stimulation on the cortical properties during TMS-EEG and working memory performance. bioRxiv, doi: https://doi.org/10.1101/157917.
Citri, A., Malenka, R.C., 2008. Synaptic plasticity: multiple forms, functions, and mechanisms. Neuropsychopharmacology 33, 18-41.
Clark, V.P., Parasuraman, R., 2014. Neuroenhancement: enhancing brain and mind in health and in disease. Neuroimage 85 Pt 3, 889-894.
Cobb, S.R., Buhl, E.H., Halasy, K., Paulsen, O., Somogyi, P., 1995. Synchronization of neuronal activity in hippocampus by individual GABAergic interneurons. Nature 378, 75-78.
Coffman, B.A., Clark, V.P., Parasuraman, R., 2014. Battery powered thought: enhancement of attention, learning, and memory in healthy adults using transcranial direct current stimulation. Neuroimage 85 Pt 3, 895-908.

Conforto, A.B., Z'Graggen, W.J., Kohl, A.S., Rosler, K.M., Kaelin-Lang, A., 2004. Impact of coil position and electrophysiological monitoring on determination of motor thresholds to transcranial magnetic stimulation. Clin Neurophysiol 115, 812-819.
Cortes, M., Black-Schaffer, R.M., Edwards, D.J., 2012. Transcranial magnetic stimulation as an investigative tool for motor dysfunction and recovery in stroke: an overview for neurorehabilitation clinicians. Neuromodulation 15, 316-325.
Coull, J.T., 1998. Neural correlates of attention and arousal: insights from electrophysiology, functional neuroimaging and psychopharmacology. Prog Neurobiol 55, 343-361.
Cowan, N., Elliott, E.M., Scott Saults, J., Morey, C.C., Mattox, S., Hismjatullina, A., Conway, A.R., 2005. On the capacity of attention: its estimation and its role in working memory and cognitive aptitudes. Cogn Psychol 51, 42-100.
Cowey, A., Walsh, V., 2001. Tickling the brain: studying visual sensation, perception and cognition by transcranial magnetic stimulation. Prog Brain Res 134, 411-425.
D'Ausilio, A., 2012. Arduino: a low-cost multipurpose lab equipment. Behav Res Methods 44, 305-313.
Daskalakis, Z.J., Farzan, F., Barr, M.S., Maller, J.J., Chen, R., Fitzgerald, P.B., 2008. Long-interval cortical inhibition from the dorsolateral prefrontal cortex: a TMS-EEG study. Neuropsychopharmacology 33, 2860-2869.
Davies, C.H., Collingridge, G.L., 1996. Regulation of EPSPs by the synaptic activation of GABAB autoreceptors in rat hippocampus. J Physiol 496 (Pt 2), 451-470.
Davies, C.H., Davies, S.N., Collingridge, G.L., 1990. Paired-pulse depression of monosynaptic GABA-mediated inhibitory postsynaptic responses in rat hippocampus. J Physiol 424, 513-531.
Davies, C.H., Starkey, S.J., Pozza, M.F., Collingridge, G.L., 1991. GABA autoreceptors regulate the induction of LTP. Nature 349, 609-611.
de Jesus, D.R., Favalli, G.P., Hoppenbrouwers, S.S., Barr, M.S., Chen, R., Fitzgerald, P.B., Daskalakis, Z.J., 2014. Determining optimal rTMS parameters through changes in cortical inhibition. Clin Neurophysiol 125, 755-762.
Debarnot, U., Crepon, B., Orriols, E., Abram, M., Charron, S., Lion, S., Roca, P., Oppenheim, C., Gueguen, B., Ergis, A.M., Baron, J.C., Piolino, P., 2015. Intermittent theta burst stimulation over left BA10 enhances virtual reality-based prospective memory in healthy aged subjects. Neurobiol Aging 36, 2360-2369.
Debener, S., De Vos, M., 2011. The benefits of simultaneous EEG-fMRI for EEG analysis. Clin Neurophysiol 122, 217-218.
Dedoncker, J., Brunoni, A.R., Baeken, C., Vanderhasselt, M.A., 2016. A Systematic Review and Meta-Analysis of the Effects of Transcranial Direct Current Stimulation (tDCS) Over the Dorsolateral Prefrontal Cortex in Healthy and Neuropsychiatric Samples: Influence of Stimulation Parameters. Brain Stimul 9, 501-517.
Deisz, R.A., 1999. The GABA(B) receptor antagonist CGP 55845A reduces presynaptic GABA(B) actions in neocortical neurons of the rat in vitro. Neuroscience 93, 1241-1249.
Delorme, A., Makeig, S., 2004. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods 134, 9-21.
Demeter, E., 2016a. Enhancing Cognition with Theta Burst Stimulation. Current Behavioral Neuroscience Reports 3, 87-94.
Demeter, E., 2016b. Enhancing Cognition with Theta Burst Stimulation. Current Behavioral Neuroscience Reports 3, 97-94.
Demeter, E., Mirdamadi, J.L., Meehan, S.K., Taylor, S.F., 2016. Short theta burst stimulation to left frontal cortex prior to encoding enhances subsequent recognition memory. Cogn Affect Behav Neurosci 16, 724-735.
Deng, Z.D., Lisanby, S.H., Peterchev, A.V., 2013. Electric field depth-focality tradeoff in transcranial magnetic stimulation: simulation comparison of 50 coil designs. Brain Stimul 6, 1-13.

Desmyter, S., Duprat, R., Baeken, C., Van Autreve, S., Audenaert, K., van Heeringen, K., 2016. Accelerated Intermittent Theta Burst Stimulation for Suicide Risk in Therapy-Resistant Depressed Patients: A Randomized, Sham-Controlled Trial. Front Hum Neurosci 10, 480.
Di Lazzaro, V., Dileone, M., Pilato, F., Capone, F., Musumeci, G., Ranieri, F., Ricci, V., Bria, P., Di Iorio, R., de Waure, C., Pasqualetti, P., Profice, P., 2011. Modulation of motor cortex neuronal networks by rTMS: comparison of local and remote effects of six different protocols of stimulation. J Neurophysiol 105, 2150-2156.
Di Lazzaro, V., Oliviero, A., Profice, P., Saturno, E., Pilato, F., Insola, A., Mazzone, P., Tonali, P., Rothwell, J.C., 1998. Comparison of descending volleys evoked by transcranial magnetic and electric stimulation in conscious humans. Electroencephalogr Clin Neurophysiol 109, 397-401.
Di Lazzaro, V., Oliviero, A., Saturno, E., Pilato, F., Insola, A., Mazzone, P., Profice, P., Tonali, P., Rothwell, J.C., 2001. The effect on corticospinal volleys of reversing the direction of current induced in the motor cortex by transcranial magnetic stimulation. Exp Brain Res 138, 268-273.
Di Lazzaro, V., Pilato, F., Dileone, M., Profice, P., Oliviero, A., Mazzone, P., Insola, A., Ranieri, F., Meglio, M., Tonali, P.A., Rothwell, J.C., 2008. The physiological basis of the effects of intermittent theta burst stimulation of the human motor cortex. J Physiol 586, 3871-3879.
Doeltgen, S.H., Ridding, M.C., 2011. Low-intensity, short-interval theta burst stimulation modulates excitatory but not inhibitory motor networks. Clin Neurophysiol 122, 1411-1416.
Dosenbach, N.U., Fair, D.A., Cohen, A.L., Schlaggar, B.L., Petersen, S.E., 2008. A dual-networks architecture of top-down control. Trends Cogn Sci 12, 99-105.
Douglas, R.M., 1977. Long lasting synaptic potentiation in the rat dentate gyrus following brief high frequency stimulation. Brain Res 126, 361-365.
Douglas, R.M., Goddard, G.V., 1975. Long-term potentiation of the perforant path-granule cell synapse in the rat hippocampus. Brain Res 86, 205-215.
Dudek, S.M., Bear, M.F., 1993. Bidirectional long-term modification of synaptic effectiveness in the adult and immature hippocampus. J Neurosci 13, 2910-2918.
Duncan, C.C., Barry, R.J., Connolly, J.F., Fischer, C., Michie, P.T., Naatanen, R., Polich, J., Reinvang, I., Van Petten, C., 2009. Event-related potentials in clinical research: guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400. Clin Neurophysiol 120, 1883-1908.
Duprat, R., Desmyter, S., Rudi de, R., van Heeringen, K., Van den Abbeele, D., Tandt, H., Bakic, J., Pourtois, G., Dedoncker, J., Vervaet, M., Van Autreve, S., Lemmens, G.M., Baeken, C., 2016. Accelerated intermittent theta burst stimulation treatment in medication-resistant major depression: A fast road to remission? J Affect Disord 200, 6-14.
Dvorak, D., Fenton, A.A., 2014. Toward a proper estimation of phase-amplitude coupling in neural oscillations. J Neurosci Methods 225, 42-56.
Elfant, D., Pal, B.Z., Emptage, N., Capogna, M., 2008. Specific inhibitory synapses shift the balance from feedforward to feedback inhibition of hippocampal CA1 pyramidal cells. Eur J Neurosci 27, 104-113.
Ellaway, P.H., Catley, M., Davey, N.J., Kuppuswamy, A., Strutton, P., Frankel, H.L., Jamous, A., Savic, G., 2007. Review of physiological motor outcome measures in spinal cord injury using transcranial magnetic stimulation and spinal reflexes. J Rehabil Res Dev 44, 69-76.
Epstein, C.M., Davey, K.R., 2002. Iron-core coils for transcranial magnetic stimulation. J Clin Neurophysiol 19, 376-381.
Esser, S.K., Huber, R., Massimini, M., Peterson, M.J., Ferrarelli, F., Tononi, G., 2006. A direct demonstration of cortical LTP in humans: a combined TMS/EEG study. Brain Res Bull 69, 86-94.
Faraday, M., 1832. Experimental researches in electricity. Philosophical Transactions of the Royal Society of London 122, 125.
Farzan, F., Barr, M.S., Hoppenbrouwers, S.S., Fitzgerald, P.B., Chen, R., Pascual-Leone, A., Daskalakis, Z.J., 2013. The EEG correlates of the TMS-induced EMG silent period in humans. Neuroimage 83, 120-134.

Farzan, F., Barr, M.S., Levinson, A.J., Chen, R., Wong, W., Fitzgerald, P.B., Daskalakis, Z.J., 2010. Reliability of long-interval cortical inhibition in healthy human subjects: a TMS-EEG study. J Neurophysiol 104, 1339-1346.
Farzan, F., Barr, M.S., Wong, W., Chen, R., Fitzgerald, P.B., Daskalakis, Z.J., 2009. Suppression of gamma-oscillations in the dorsolateral prefrontal cortex following long interval cortical inhibition: a TMS-EEG study. Neuropsychopharmacology 34, 1543-1551.
Farzan, F., Vernet, M., Shafi, M.M., Rotenberg, A., Daskalakis, Z.J., Pascual-Leone, A., 2016. Characterizing and Modulating Brain Circuitry through Transcranial Magnetic Stimulation Combined with Electroencephalography. Front Neural Circuits 10, 73.
Ferrarelli, F., Sarasso, S., Guller, Y., Riedner, B.A., Peterson, M.J., Bellesi, M., Massimini, M., Postle, B.R., Tononi, G., 2012. Reduced natural oscillatory frequency of frontal thalamocortical circuits in schizophrenia. Arch Gen Psychiatry 69, 766-774.
Ferreri, F., Ponzo, D., Hukkanen, T., Mervaala, E., Kononen, M., Pasqualetti, P., Vecchio, F., Rossini, P.M., Maatta, S., 2012. Human brain cortical correlates of short-latency afferent inhibition: a combined EEG-TMS study. J Neurophysiol 108, 314-323.
Ferreri, F., Rossini, P.M., 2013. TMS and TMS-EEG techniques in the study of the excitability, connectivity, and plasticity of the human motor cortex. Rev Neurosci 24, 431-442.
Filipovic, S.R., Rothwell, J.C., Bhatia, K., 2010. Slow (1 Hz) repetitive transcranial magnetic stimulation (rTMS) induces a sustained change in cortical excitability in patients with Parkinson's disease. Clin Neurophysiol 121, 1129-1137.
Fitzgerald, P.B., Benitez, J., de Castella, A., Daskalakis, Z.J., Brown, T.L., Kulkarni, J., 2006. A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. Am J Psychiatry 163, 88-94.
Fitzgerald, P.B., Brown, T.L., Daskalakis, Z.J., 2002a. The application of transcranial magnetic stimulation in psychiatry and neurosciences research. Acta Psychiatr Scand 105, 324-340.
Fitzgerald, P.B., Brown, T.L., Daskalakis, Z.J., Chen, R., Kulkarni, J., 2002b. Intensity-dependent effects of 1 Hz rTMS on human corticospinal excitability. Clin Neurophysiol 113, 1136-1141.
Fitzgerald, P.B., Brown, T.L., Marston, N.A., Daskalakis, Z.J., De Castella, A., Kulkarni, J., 2003. Transcranial magnetic stimulation in the treatment of depression: a double-blind, placebo-controlled trial. Arch Gen Psychiatry 60, 1002-1008.
Folstein, J.R., Van Petten, C., 2008. Influence of cognitive control and mismatch on the N2 component of the ERP: a review. Psychophysiology 45, 152-170.
Foltys, H., Sparing, R., Boroojerdi, B., Krings, T., Meister, I.G., Mottaghy, F.M., Topper, R., 2001. Motor control in simple bimanual movements: a transcranial magnetic stimulation and reaction time study. Clin Neurophysiol 112, 265-274.
Fregni, F., Boggio, P.S., Nitsche, M., Bermpohl, F., Antal, A., Feredoes, E., Marcolin, M.A., Rigonatti, S.P., Silva, M.T., Paulus, W., Pascual-Leone, A., 2005. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp Brain Res 166, 23-30.
Fries, P., 2009. Neuronal gamma-band synchronization as a fundamental process in cortical computation. Annu Rev Neurosci 32, 209-224.
Friese, U., Koster, M., Hassler, U., Martens, U., Trujillo-Barreto, N., Gruber, T., 2013. Successful memory encoding is associated with increased cross-frequency coupling between frontal theta and posterior gamma oscillations in human scalp-recorded EEG. Neuroimage 66, 642-647.
Gagnon, G., Schneider, C., Grondin, S., Blanchet, S., 2011. Enhancement of episodic memory in young and healthy adults: a paired-pulse TMS study on encoding and retrieval performance. Neurosci Lett 488, 138-142.
Gamboa, O.L., Antal, A., Laczo, B., Moliadze, V., Nitsche, M.A., Paulus, W., 2011. Impact of repetitive theta burst stimulation on motor cortex excitability. Brain Stimul 4, 145-151.
Gamboa, O.L., Antal, A., Moliadze, V., Paulus, W., 2010. Simply longer is not better: reversal of theta burst after-effect with prolonged stimulation. Exp Brain Res 204, 181-187.

Garcia, J.O., Grossman, E.D., Srinivasan, R., 2011. Evoked potentials in large-scale cortical networks elicited by TMS of the visual cortex. J Neurophysiol 106, 1734-1746.
Gaynes, B.N., Lloyd, S.W., Lux, L., Gartlehner, G., Hansen, R.A., Brode, S., Jonas, D.E., Swinson Evans, T., Viswanathan, M., Lohr, K.N., 2014. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis. J Clin Psychiatry 75, 477-489; quiz 489.
Gentner, R., Wankerl, K., Reinsberger, C., Zeller, D., Classen, J., 2008. Depression of human corticospinal excitability induced by magnetic theta-burst stimulation: evidence of rapid polarity-reversing metaplasticity. Cereb Cortex 18, 2046-2053.
George, M.S., Lisanby, S.H., Avery, D., McDonald, W.M., Durkalski, V., Pavlicova, M., Anderson, B., Nahas, Z., Bulow, P., Zarkowski, P., Holtzheimer, P.E., 3rd, Schwartz, T., Sackeim, H.A., 2010. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry 67, 507-516.
George, M.S., Taylor, J.J., Short, E.B., 2013. The expanding evidence base for rTMS treatment of depression. Curr Opin Psychiatry 26, 13-18.
Gevins, A., Smith, M.E., McEvoy, L., Yu, D., 1997. High-resolution EEG mapping of cortical activation related to working memory: effects of task difficulty, type of processing, and practice. Cereb Cortex 7, 374-385.
Goldsworthy, M.R., Pitcher, J.B., Ridding, M.C., 2012a. The application of spaced theta burst protocols induces long-lasting neuroplastic changes in the human motor cortex. Eur J Neurosci 35, 125-134.
Goldsworthy, M.R., Pitcher, J.B., Ridding, M.C., 2012b. A comparison of two different continuous theta burst stimulation paradigms applied to the human primary motor cortex. Clin Neurophysiol 123, 2256-2263.
Goldsworthy, M.R., Pitcher, J.B., Ridding, M.C., 2013. Neuroplastic modulation of inhibitory motor cortical networks by spaced theta burst stimulation protocols. Brain Stimul 6, 340-345.
Gosling, A., Thoma, V., de Fockert, J.W., Richardson-Klavehn, A., 2016. Event-Related Potential Effects of Object Repetition Depend on Attention and Part-Whole Configuration. Front Hum Neurosci 10, 478.
Gramfort, A., Papadopoulo, T., Olivi, E., Clerc, M., 2010. OpenMEEG: opensource software for quasistatic bioelectromagnetics. Biomed Eng Online 9, 45.
Haatveit, B.C., Sundet, K., Hugdahl, K., Ueland, T., Melle, I., Andreassen, O.A., 2010. The validity of d prime as a working memory index: results from the "Bergen n-back task". J Clin Exp Neuropsychol 32, 871-880.
Hallett, M., 1996a. Transcranial magnetic stimulation: a tool for mapping the central nervous system. Electroencephalogr Clin Neurophysiol Suppl 46, 43-51.
Hallett, M., 1996b. Transcranial magnetic stimulation: a useful tool for clinical neurophysiology. Ann Neurol 40, 344-345.
Hamada, M., Murase, N., Hasan, A., Balaratnam, M., Rothwell, J.C., 2013. The role of interneuron networks in driving human motor cortical plasticity. Cereb Cortex 23, 1593-1605.
Hameed, M.Q., Dhamne, S.C., Gersner, R., Kaye, H.L., Oberman, L.M., Pascual-Leone, A., Rotenberg, A., 2017. Transcranial Magnetic and Direct Current Stimulation in Children. Curr Neurol Neurosci Rep 17, 11.
Hamidi, M., Slagter, H.A., Tononi, G., Postle, B.R., 2010. Brain responses evoked by high-frequency repetitive transcranial magnetic stimulation: an event-related potential study. Brain Stimul 3, 2-14.
Hannah, R., Rocchi, L., Tremblay, S., Rothwell, J.C., 2016. Controllable Pulse Parameter TMS and TMS-EEG As Novel Approaches to Improve Neural Targeting with rTMS in Human Cerebral Cortex. Front Neural Circuits 10, 97.
Hara, Y., 2015. Brain plasticity and rehabilitation in stroke patients. J Nippon Med Sch 82, 4-13.
Harrington, A., Hammond-Tooke, G.D., 2015. Theta Burst Stimulation of the Cerebellum Modifies the TMS-Evoked N100 Potential, a Marker of GABA Inhibition. PLoS One 10, e0141284.

Hasler, G., Drevets, W.C., Manji, H.K., Charney, D.S., 2004. Discovering endophenotypes for major depression. Neuropsychopharmacology 29, 1765-1781.
Hedges, L.V., & Olkin, I., 1985. Statistical Methods for Meta-Analysis. Academic Press., Orlando, FL.
Heiss, J.E., Katz, Y., Ganmor, E., Lampl, I., 2008. Shift in the balance between excitation and inhibition during sensory adaptation of S1 neurons. J Neurosci 28, 13320-13330.
Helfrich, C., Pierau, S.S., Freitag, C.M., Roeper, J., Ziemann, U., Bender, S., 2012. Monitoring cortical excitability during repetitive transcranial magnetic stimulation in children with ADHD: a single-blind, sham-controlled TMS-EEG study. PLoS One 7, e50073.
Hill, A.T., Rogasch, N.C., Fitzgerald, P.B., Hoy, K.E., 2016. TMS-EEG: A window into the neurophysiological effects of transcranial electrical stimulation in non-motor brain regions. Neurosci Biobehav Rev 64, 175-184.
Hill, A.T., Rogasch, N.C., Fitzgerald, P.B., Hoy, K.E., 2017. Effects of prefrontal bipolar and high-definition transcranial direct current stimulation on cortical reactivity and working memory in healthy adults. Neuroimage 152, 142-157.
Hinder, M.R., Goss, E.L., Fujiyama, H., Canty, A.J., Garry, M.I., Rodger, J., Summers, J.J., 2014. Inter- and Intra-individual variability following intermittent theta burst stimulation: implications for rehabilitation and recovery. Brain Stimul 7, 365-371.
Hong, Y.H., Wu, S.W., Pedapati, E.V., Horn, P.S., Huddleston, D.A., Laue, C.S., Gilbert, D.L., 2015. Safety and tolerability of theta burst stimulation vs. single and paired pulse transcranial magnetic stimulation: a comparative study of 165 pediatric subjects. Front Hum Neurosci 9, 29.
Hoogendam, J.M., Ramakers, G.M., Di Lazzaro, V., 2010. Physiology of repetitive transcranial magnetic stimulation of the human brain. Brain Stimul 3, 95-118.
Hordacre, B., Goldsworthy, M.R., Vallence, A.M., Darvishi, S., Moezzi, B., Hamada, M., Rothwell, J.C., Ridding, M.C., 2017. Variability in neural excitability and plasticity induction in the human cortex: A brain stimulation study. Brain Stimul 10, 588-595.
Howard, M.W., Rizzuto, D.S., Caplan, J.B., Madsen, J.R., Lisman, J., Aschenbrenner-Scheibe, R., Schulze-Bonhage, A., Kahana, M.J., 2003. Gamma oscillations correlate with working memory load in humans. Cereb Cortex 13, 1369-1374.
Hoy, K.E., Bailey, N., Michael, M., Fitzgibbon, B., Rogasch, N.C., Saeki, T., Fitzgerald, P.B., 2015. Enhancement of Working Memory and Task-Related Oscillatory Activity Following Intermittent Theta Burst Stimulation in Healthy Controls. Cereb Cortex.
Hoy, K.E., Bailey, N., Michael, M., Fitzgibbon, B., Rogasch, N.C., Saeki, T., Fitzgerald, P.B., 2016. Enhancement of Working Memory and Task-Related Oscillatory Activity Following Intermittent Theta Burst Stimulation in Healthy Controls. Cereb Cortex 26, 4563-4573.
Hsieh, L.T., Ranganath, C., 2014. Frontal midline theta oscillations during working memory maintenance and episodic encoding and retrieval. Neuroimage 85 Pt 2, 721-729.
Hsu, Y.F., Liao, K.K., Lee, P.L., Tsai, Y.A., Yeh, C.L., Lai, K.L., Huang, Y.Z., Lin, Y.Y., Lee, I.H., 2011. Intermittent theta burst stimulation over primary motor cortex enhances movement-related beta synchronisation. Clin Neurophysiol 122, 2260-2267.
Hu, L., Mouraux, A., Hu, Y., Iannetti, G.D., 2010. A novel approach for enhancing the signal-to-noise ratio and detecting automatically event-related potentials (ERPs) in single trials. Neuroimage 50, 99-111.
Huang, G., Mouraux, A., 2015. MEP Latencies Predict the Neuromodulatory Effect of cTBS Delivered to the Ipsilateral and Contralateral Sensorimotor Cortex. PLoS One 10, e0133893.
Huang, Y.Z., Chen, R.S., Rothwell, J.C., Wen, H.Y., 2007. The after-effect of human theta burst stimulation is NMDA receptor dependent. Clin Neurophysiol 118, 1028-1032.
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, 201-206.
Ilmoniemi, R.J., Kicic, D., 2010. Methodology for combined TMS and EEG. Brain Topogr 22, 233-248.
Itier, R.J., Taylor, M.J., 2004. N170 or N1? Spatiotemporal differences between object and face processing using ERPs. Cereb Cortex 14, 132-142.

Iyer, M.B., Schleper, N., Wassermann, E.M., 2003. Priming stimulation enhances the depressant effect of low-frequency repetitive transcranial magnetic stimulation. J Neurosci 23, 10867-10872.
Jacobs, J., 2014. Hippocampal theta oscillations are slower in humans than in rodents: implications for models of spatial navigation and memory. Philos Trans R Soc Lond B Biol Sci 369, 20130304.
Jansma, J.M., Ramsey, N.F., Coppola, R., Kahn, R.S., 2000. Specific versus nonspecific brain activity in a parametric N-back task. Neuroimage 12, 688-697.
Jeneson, A., Squire, L.R., 2012. Working memory, long-term memory, and medial temporal lobe function. Learn Mem 19, 15-25.
Johansson, B.B., 2011. Current trends in stroke rehabilitation. A review with focus on brain plasticity. Acta Neurol Scand 123, 147-159.
Jones, C.B., Lulic, T., Bailey, A.Z., Mackenzie, T.N., Mi, Y.Q., Tommerdahl, M., Nelson, A.J., 2016. Metaplasticity in human primary somatosensory cortex: effects on physiology and tactile perception. J Neurophysiol 115, 2681-2691.
Jones, S.M., Streletz, L.J., Raab, V.E., Knobler, R.L., Lublin, F.D., 1991. Lower extremity motor evoked potentials in multiple sclerosis. Arch Neurol 48, 944-948.
Jonides, J., Smith, E.E., Koeppe, R.A., Awh, E., Minoshima, S., Mintun, M.A., 1993. Spatial working memory in humans as revealed by PET. Nature 363, 623-625.
Jorgensen, L.M., Nielsen, J.E., Ravnborg, M., 2005. MEP recruitment curves in multiple sclerosis and hereditary spastic paraplegia. J Neurol Sci 237, 25-29.
Julkunen, P., Jauhiainen, A.M., Westeren-Punnonen, S., Pirinen, E., Soininen, H., Kononen, M., Paakkonen, A., Maatta, S., Karhu, J., 2008. Navigated TMS combined with EEG in mild cognitive impairment and Alzheimer's disease: a pilot study. J Neurosci Methods 172, 270-276.
Jung, J., Bungert, A., Bowtell, R., Jackson, S.R., 2016. Vertex Stimulation as a Control Site for Transcranial Magnetic Stimulation: A Concurrent TMS/fMRI Study. Brain Stimul 9, 58-64.
Kahkonen, 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 (Berl) 181, 16-20.
Kahkonen, S., Wilenius, J., Nikulin, V.V., Ollikainen, M., Ilmoniemi, R.J., 2003. Alcohol reduces prefrontal cortical excitability in humans: a combined TMS and EEG study. Neuropsychopharmacology 28, 747-754.
Kappenman, E.S., Luck, S.J., 2010. The effects of electrode impedance on data quality and statistical significance in ERP recordings. Psychophysiology 47, 888-904.
Keck, M.E., Pijnappels, M., Schubert, M., Colombo, G., Curt, A., Dietz, V., 1998. Stumbling reactions in man: influence of corticospinal input. Electroencephalogr Clin Neurophysiol 109, 215-223.
Kernell, D., Chien-Ping, W.U., 1967. Responses of the pyramidal tract to stimulation of the baboon's motor cortex. J Physiol 191, 653-672.
Kirschen, M.P., Davis-Ratner, M.S., Jerde, T.E., Schraedley-Desmond, P., Desmond, J.E., 2006. Enhancement of phonological memory following transcranial magnetic stimulation (TMS). Behav Neurol 17, 187-194.
Klimesch, W., Doppelmayr, M., Russegger, H., Pachinger, T., 1996. Theta band power in the human scalp EEG and the encoding of new information. Neuroreport 7, 1235-1240.
Klomjai, W., Katz, R., Lackmy-Vallee, A., 2015. Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). Ann Phys Rehabil Med 58, 208-213.
Kobayashi, M., Pascual-Leone, A., 2003. Transcranial magnetic stimulation in neurology. Lancet Neurol 2, 145-156.
Koessler, L., Maillard, L., Benhadid, A., Vignal, J.P., Felblinger, J., Vespignani, H., Braun, M., 2009. Automated cortical projection of EEG sensors: anatomical correlation via the international 10-10 system. Neuroimage 46, 64-72.
Kohl, M.M., Paulsen, O., 2010. The roles of GABAB receptors in cortical network activity. Adv Pharmacol 58, 205-229.

Kok, A., 2001. On the utility of P3 amplitude as a measure of processing capacity. Psychophysiology 38, 557-577.
Kolb, B., Whishaw, I.Q., 1998. Brain plasticity and behavior. Annu Rev Psychol 49, 43-64.
Kopp, B., Rist, F., Mattler, U., 1996. N200 in the flanker task as a neurobehavioral tool for investigating executive control. Psychophysiology 33, 282-294.
Korhonen, R.J., Hernandez-Pavon, J.C., Metsomaa, J., Maki, H., Ilmoniemi, R.J., Sarvas, J., 2011. Removal of large muscle artifacts from transcranial magnetic stimulation-evoked EEG by independent component analysis. Med Biol Eng Comput 49, 397-407.
Koster, M., Friese, U., Schone, B., Trujillo-Barreto, N., Gruber, T., 2014. Theta-gamma coupling during episodic retrieval in the human EEG. Brain Res 1577, 57-68.
Kramar, E.A., Babayan, A.H., Gavin, C.F., Cox, C.D., Jafari, M., Gall, C.M., Rumbaugh, G., Lynch, G., 2012. Synaptic evidence for the efficacy of spaced learning. Proc Natl Acad Sci U S A 109, 5121-5126.
Kumpulainen, S., Mrachacz-Kersting, N., Peltonen, J., Voigt, M., Avela, J., 2012. The optimal interstimulus interval and repeatability of paired associative stimulation when the soleus muscle is targeted. Exp Brain Res 221, 241-249.
Larson, J., Lynch, G., 1986. Induction of synaptic potentiation in hippocampus by patterned stimulation involves two events. Science 232, 985-988.
Larson, J., Lynch, G., 1989. Theta pattern stimulation and the induction of LTP: the sequence in which synapses are stimulated determines the degree to which they potentiate. Brain Res 489, 49-58.
Larson, J., Munkacsy, E., 2015. Theta-burst LTP. Brain Res 1621, 38-50.
Larson, J., Wong, D., Lynch, G., 1986. Patterned stimulation at the theta frequency is optimal for the induction of hippocampal long-term potentiation. Brain Res 368, 347-350.
Le-Niculescu, H., Kurian, S.M., Yehyawi, N., Dike, C., Patel, S.D., Edenberg, H.J., Tsuang, M.T., Salomon, D.R., Nurnberger, J.I., Jr., Niculescu, A.B., 2009. Identifying blood biomarkers for mood disorders using convergent functional genomics. Mol Psychiatry 14, 156-174.
Leggett, L.E., Soril, L.J., Coward, S., Lorenzetti, D.L., MacKean, G., Clement, F.M., 2015. Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression in Adult and Youth Populations: A Systematic Literature Review and Meta-Analysis. Prim Care Companion CNS Disord 17.
Li, C.T., Chen, M.H., Juan, C.H., Huang, H.H., Chen, L.F., Hsieh, J.C., Tu, P.C., Bai, Y.M., Tsai, S.J., Lee, Y.C., Su, T.P., 2014. Efficacy of prefrontal theta-burst stimulation in refractory depression: a randomized sham-controlled study. Brain 137, 2088-2098.
Li, Y., Wang, L., Jia, M., Guo, J., Wang, H., Wang, M., 2017. The effects of high-frequency rTMS over the left DLPFC on cognitive control in young healthy participants. PLoS One 12, e0179430.
Liew, S.L., Santarnecchi, E., Buch, E.R., Cohen, L.G., 2014. Non-invasive brain stimulation in neurorehabilitation: local and distant effects for motor recovery. Front Hum Neurosci 8, 378.
Lin, F.H., Belliveau, J.W., Dale, A.M., Hamalainen, M.S., 2006. Distributed current estimates using cortical orientation constraints. Hum Brain Mapp 27, 1-13.
Lioumis, P., Kicic, D., Savolainen, P., Makela, J.P., Kahkonen, S., 2009. Reproducibility of TMS-Evoked EEG responses. Hum Brain Mapp 30, 1387-1396.
Lisman, J., 2010. Working memory: the importance of theta and gamma oscillations. Curr Biol 20, R490-492.
Lisman, J.E., Jensen, O., 2013. The theta-gamma neural code. Neuron 77, 1002-1016.
Lopez-Alonso, V., Cheeran, B., Rio-Rodriguez, D., Fernandez-Del-Olmo, M., 2014. Inter-individual variability in response to non-invasive brain stimulation paradigms. Brain Stimul 7, 372-380.
Luscher, C., Malenka, R.C., 2012. NMDA receptor-dependent long-term potentiation and long-term depression (LTP/LTD). Cold Spring Harb Perspect Biol 4.
Machado, S., Arias-Carrion, O., Paes, F., Vieira, R.T., Caixeta, L., Novaes, F., Marinho, T., Almada, L.F., Silva, A.C., Nardi, A.E., 2013. Repetitive transcranial magnetic stimulation for clinical applications in neurological and psychiatric disorders: an overview. Eurasian J Med 45, 191-206.

Maeda, F., Keenan, J.P., Tormos, J.M., Topka, H., Pascual-Leone, A., 2000. Interindividual variability of the modulatory effects of repetitive transcranial magnetic stimulation on cortical excitability. Exp Brain Res 133, 425-430.
Manza, P., Hau, C.L., Leung, H.C., 2014. Alpha power gates relevant information during working memory updating. J Neurosci 34, 5998-6002.
McAllister, S.M., Rothwell, J.C., Ridding, M.C., 2009. Selective modulation of intracortical inhibition by low-intensity Theta Burst Stimulation. Clin Neurophysiol 120, 820-826.
McEvoy, L.K., Smith, M.E., Gevins, A., 1998. Dynamic cortical networks of verbal and spatial working memory: effects of memory load and task practice. Cereb Cortex 8, 563-574.
Merton, P.A., Morton, H.B., 1980. Stimulation of the cerebral cortex in the intact human subject. Nature 285, 227.
Meule, A., 2017. Reporting and Interpreting Working Memory Performance in n-back Tasks. Front Psychol 8, 352.
Mills, K.R., Boniface, S.J., Schubert, M., 1992. Magnetic brain stimulation with a double coil: the importance of coil orientation. Electroencephalogr Clin Neurophysiol 85, 17-21.
Miniussi, C., Cappa, S.F., Cohen, L.G., Floel, A., Fregni, F., Nitsche, M.A., Oliveri, M., Pascual-Leone, A., Paulus, W., Priori, A., Walsh, V., 2008. Efficacy of repetitive transcranial magnetic stimulation/transcranial direct current stimulation in cognitive neurorehabilitation. Brain Stimul 1, 326-336.
Miniussi, C., Ruzzoli, M., 2013. Transcranial stimulation and cognition. Handb Clin Neurol 116, 739-750.
Miniussi, C., Thut, G., 2010. Combining TMS and EEG offers new prospects in cognitive neuroscience. Brain Topogr 22, 249-256.
Miyata, K., Honbo, M., Nejima, R., Minami, K., Amano, S., 2015. Long-term observation of surface light scattering in a foldable acrylic intraocular lens. J Cataract Refract Surg 41, 1205-1209.
Moliadze, V., Atalay, D., Antal, A., Paulus, W., 2012. Close to threshold transcranial electrical stimulation preferentially activates inhibitory networks before switching to excitation with higher intensities. Brain Stimul 5, 505-511.
Moore, R.A., Gale, A., Morris, P.H., Forrester, D., 2008. Alpha power and coherence primarily reflect neural activity related to stages of motor response during a continuous monitoring task. Int J Psychophysiol 69, 79-89.
Mott, D.D., Lewis, D.V., 1991. Facilitation of the induction of long-term potentiation by GABAB receptors. Science 252, 1718-1720.
Murakami, T., Muller-Dahlhaus, F., Lu, M.K., Ziemann, U., 2012. Homeostatic metaplasticity of corticospinal excitatory and intracortical inhibitory neural circuits in human motor cortex. J Physiol 590, 5765-5781.
Nahas, Z., Lomarev, M., Roberts, D.R., Shastri, A., Lorberbaum, J.P., Teneback, C., McConnell, K., Vincent, D.J., Li, X., George, M.S., Bohning, D.E., 2001. Unilateral left prefrontal transcranial magnetic stimulation (TMS) produces intensity-dependent bilateral effects as measured by interleaved BOLD fMRI. Biol Psychiatry 50, 712-720.
Nakamura, H., Kitagawa, H., Kawaguchi, Y., Tsuji, H., 1996. Direct and indirect activation of human corticospinal neurons by transcranial magnetic and electrical stimulation. Neurosci Lett 210, 45-48.
Nasr, S., Moeeny, A., Esteky, H., 2008. Neural correlate of filtering of irrelevant information from visual working memory. PLoS One 3, e3282.
Nenert, R., Viswanathan, S., Dubuc, D.M., Visscher, K.M., 2012. Modulations of ongoing alpha oscillations predict successful short-term visual memory encoding. Front Hum Neurosci 6, 127.
Nettekoven, C., Volz, L.J., Kutscha, M., Pool, E.M., Rehme, A.K., Eickhoff, S.B., Fink, G.R., Grefkes, C., 2014. Dose-dependent effects of theta burst rTMS on cortical excitability and resting-state connectivity of the human motor system. J Neurosci 34, 6849-6859.
Nikouline, V., Ruohonen, J., Ilmoniemi, R.J., 1999. The role of the coil click in TMS assessed with simultaneous EEG. Clin Neurophysiol 110, 1325-1328.

Nikulin, V.V., Kicic, D., Kahkonen, S., Ilmoniemi, R.J., 2003. Modulation of electroencephalographic responses to transcranial magnetic stimulation: evidence for changes in cortical excitability related to movement. Eur J Neurosci 18, 1206-1212.
Nitsche, M.A., Paulus, W., 2000. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol 527 Pt 3, 633-639.
Noda, Y., Barr, M.S., Zomorrodi, R., Cash, R.F., Rajji, T.K., Farzan, F., Chen, R., George, T.P., Daskalakis, Z.J., Blumberger, D.M., 2017a. Reduced Short-latency Afferent Inhibition in Prefrontal but not Motor Cortex and its Association With Executive Function in Schizophrenia: A Combined TMS-EEG Study. Schizophr Bull.
Noda, Y., Cash, R.F., Zomorrodi, R., Dominguez, L.G., Farzan, F., Rajji, T.K., Barr, M.S., Chen, R., Daskalakis, Z.J., Blumberger, D.M., 2016. A combined TMS-EEG study of short-latency afferent inhibition in the motor and dorsolateral prefrontal cortex. J Neurophysiol 116, 938-948.
Noda, Y., Zomorrodi, R., Backhouse, F., Cash, R.F.H., Barr, M.S., Rajji, T.K., Chen, R., Daskalakis, Z.J., Blumberger, D.M., 2017b. Reduced Prefrontal Short-Latency Afferent Inhibition in Older Adults and Its Relation to Executive Function: A TMS-EEG Study. Front Aging Neurosci 9, 119.
Noda, Y., Zomorrodi, R., Cash, R.F., Barr, M.S., Farzan, F., Rajji, T.K., Chen, R., Daskalakis, Z.J., Blumberger, D.M., 2017c. Characterization of the influence of age on GABAA and glutamatergic mediated functions in the dorsolateral prefrontal cortex using paired-pulse TMS-EEG. Aging (Albany NY) 9, 556-572.
Nyffeler, T., Cazzoli, D., Hess, C.W., Muri, R.M., 2009. One session of repeated parietal theta burst stimulation trains induces long-lasting improvement of visual neglect. Stroke 40, 2791-2796.
Nyffeler, T., Cazzoli, D., Wurtz, P., Luthi, M., von Wartburg, R., Chaves, S., Deruaz, A., Hess, C.W., Muri, R.M., 2008. Neglect-like visual exploration behaviour after theta burst transcranial magnetic stimulation of the right posterior parietal cortex. Eur J Neurosci 27, 1809-1813.
O'Reardon, J.P., Cristancho, P., Pilania, P., Bapatla, K.B., Chuai, S., Peshek, A.D., 2007a. Patients with a major depressive episode responding to treatment with repetitive transcranial magnetic stimulation (rTMS) are resistant to the effects of rapid tryptophan depletion. Depress Anxiety 24, 537-544.
O'Reardon, J.P., Solvason, H.B., Janicak, P.G., Sampson, S., Isenberg, K.E., Nahas, Z., McDonald, W.M., Avery, D., Fitzgerald, P.B., Loo, C., Demitrack, M.A., George, M.S., Sackeim, H.A., 2007b. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry 62, 1208-1216.
Oberman, L., Edwards, D., Eldaief, M., Pascual-Leone, A., 2011. Safety of theta burst transcranial magnetic stimulation: a systematic review of the literature. J Clin Neurophysiol 28, 67-74.
Ohl, F.W., Scheich, H., 2005. Learning-induced plasticity in animal and human auditory cortex. Curr Opin Neurobiol 15, 470-477.
Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97-113.
Oostenveld, R., Fries, P., Maris, E., Schoffelen, J.M., 2011. FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Comput Intell Neurosci 2011, 156869.
Opie, G.M., Rogasch, N.C., Goldsworthy, M.R., Ridding, M.C., Semmler, J.G., 2017. Investigating TMS-EEG Indices of Long-Interval Intracortical Inhibition at Different Interstimulus Intervals. Brain Stimul 10, 65-74.
Osaka, N., Otsuka, Y., Hirose, N., Ikeda, T., Mima, T., Fukuyama, H., Osaka, M., 2007. Transcranial magnetic stimulation (TMS) applied to left dorsolateral prefrontal cortex disrupts verbal working memory performance in humans. Neurosci Lett 418, 232-235.
Otis, T.S., De Koninck, Y., Mody, I., 1993. Characterization of synaptically elicited GABAB responses using patch-clamp recordings in rat hippocampal slices. J Physiol 463, 391-407.
Owen, A.M., McMillan, K.M., Laird, A.R., Bullmore, E., 2005. N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. Hum Brain Mapp 25, 46-59.

Pacelli, G.J., Su, W., Kelso, S.R., 1989. Activity-induced depression of synaptic inhibition during LTP-inducing patterned stimulation. Brain Res 486, 26-32.
Padberg, F., George, M.S., 2009. Repetitive transcranial magnetic stimulation of the prefrontal cortex in depression. Exp Neurol 219, 2-13.
Padberg, F., Zwanzger, P., Keck, M.E., Kathmann, N., Mikhaiel, P., Ella, R., Rupprecht, P., Thoma, H., Hampel, H., Toschi, N., Moller, H.J., 2002. Repetitive transcranial magnetic stimulation (rTMS) in major depression: relation between efficacy and stimulation intensity. Neuropsychopharmacology 27, 638-645.
Paes, F., Machado, S., Arias-Carrion, O., Velasques, B., Teixeira, S., Budde, H., Cagy, M., Piedade, R., Ribeiro, P., Huston, J.P., Sack, A.T., Nardi, A.E., 2011. The value of repetitive transcranial magnetic stimulation (rTMS) for the treatment of anxiety disorders: an integrative review. CNS Neurol Disord Drug Targets 10, 610-620.
Park, J.Y., Jhung, K., Lee, J., An, S.K., 2013. Theta-gamma coupling during a working memory task as compared to a simple vigilance task. Neurosci Lett 532, 39-43.
Pascual-Leone, A., Bartres-Faz, D., Keenan, J.P., 1999. Transcranial magnetic stimulation: studying the brain-behaviour relationship by induction of 'virtual lesions'. Philos Trans R Soc Lond B Biol Sci 354, 1229-1238.
Pascual-Leone, A., Valls-Sole, J., Wassermann, E.M., Hallett, M., 1994. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain 117 (Pt 4), 847-858.
Pascual-Leone A., H.J.C., Robertson E.M., 2012. Enhancement of Normal Cognitive Abilities Through Noninvasive Brain Stimulation. Springer Berlin Heidelberg, Berlin, Heidelberg.
Paulus, W., Classen, J., Cohen, L.G., Large, C.H., Di Lazzaro, V., Nitsche, M., Pascual-Leone, A., Rosenow, F., Rothwell, J.C., Ziemann, U., 2008. State of the art: Pharmacologic effects on cortical excitability measures tested by transcranial magnetic stimulation. Brain Stimul 1, 151-163.
Paus, T., Castro-Alamancos, M.A., Petrides, M., 2001. Cortico-cortical connectivity of the human mid-dorsolateral frontal cortex and its modulation by repetitive transcranial magnetic stimulation. Eur J Neurosci 14, 1405-1411.
Pedapati, E.V., Gilbert, D.L., Erickson, C.A., Horn, P.S., Shaffer, R.C., Wink, L.K., Laue, C.S., Wu, S.W., 2016. Abnormal Cortical Plasticity in Youth with Autism Spectrum Disorder: A Transcranial Magnetic Stimulation Case-Control Pilot Study. J Child Adolesc Psychopharmacol 26, 625-631.
Pedapati, E.V., Gilbert, D.L., Horn, P.S., Huddleston, D.A., Laue, C.S., Shahana, N., Wu, S.W., 2015. Effect of 30 Hz theta burst transcranial magnetic stimulation on the primary motor cortex in children and adolescents. Front Hum Neurosci 9, 91.
Pellicciari, M.C., Brignani, D., Miniussi, C., 2013. Excitability modulation of the motor system induced by transcranial direct current stimulation: a multimodal approach. Neuroimage 83, 569-580.
Pellicciari, M.C., Ponzo, V., Caltagirone, C., Koch, G., 2017a. Restored Asymmetry of Prefrontal Cortical Oscillatory Activity after Bilateral Theta Burst Stimulation Treatment in a Patient with Major Depressive Disorder: A TMS-EEG Study. Brain Stimul 10, 147-149.
Pellicciari, M.C., Veniero, D., Miniussi, C., 2017b. Characterizing the Cortical Oscillatory Response to TMS Pulse. Front Cell Neurosci 11, 38.
Penny, W.D., Duzel, E., Miller, K.J., Ojemann, J.G., 2008. Testing for nested oscillation. J Neurosci Methods 174, 50-61.
Petrides, M., Pandya, D.N., 2002. Comparative cytoarchitectonic analysis of the human and the macaque ventrolateral prefrontal cortex and corticocortical connection patterns in the monkey. Eur J Neurosci 16, 291-310.
Piccoli, T., Valente, G., Linden, D.E., Re, M., Esposito, F., Sack, A.T., Di Salle, F., 2015. The default mode network and the working memory network are not anti-correlated during all phases of a working memory task. PLoS One 10, e0123354.
Pittenger, C., 2013. Disorders of memory and plasticity in psychiatric disease. Dialogues Clin Neurosci 15, 455-463.

Plewnia, C., Pasqualetti, P., Grosse, S., Schlipf, S., Wasserka, B., Zwissler, B., Fallgatter, A., 2014. Treatment of major depression with bilateral theta burst stimulation: a randomized controlled pilot trial. J Affect Disord 156, 219-223.
Prasser, J., Schecklmann, M., Poeppl, T.B., Frank, E., Kreuzer, P.M., Hajak, G., Rupprecht, R., Landgrebe, M., Langguth, B., 2015. Bilateral prefrontal rTMS and theta burst TMS as an add-on treatment for depression: a randomized placebo controlled trial. World J Biol Psychiatry 16, 57-65.
Premoli, I., Castellanos, N., Rivolta, D., Belardinelli, P., Bajo, R., Zipser, C., Espenhahn, S., Heidegger, T., Muller-Dahlhaus, F., Ziemann, U., 2014a. TMS-EEG signatures of GABAergic neurotransmission in the human cortex. J Neurosci 34, 5603-5612.
Premoli, I., Rivolta, D., Espenhahn, S., Castellanos, N., Belardinelli, P., Ziemann, U., Muller-Dahlhaus, F., 2014b. Characterization of GABAB-receptor mediated neurotransmission in the human cortex by paired-pulse TMS-EEG. Neuroimage 103, 152-162.
Raffaele, N., 2015. Enhanced motor cortex excitability after spinal cord injury. Neural Regen Res 10, 1943-1944.
Rajji, T.K., Sun, Y., Zomorrodi-Moghaddam, R., Farzan, F., Blumberger, D.M., Mulsant, B.H., Fitzgerald, P.B., Daskalakis, Z.J., 2013. PAS-induced potentiation of cortical-evoked activity in the dorsolateral prefrontal cortex. Neuropsychopharmacology 38, 2545-2552.
Reis, J., Swayne, O.B., Vandermeeren, Y., Camus, M., Dimyan, M.A., Harris-Love, M., Perez, M.A., Ragert, P., Rothwell, J.C., Cohen, L.G., 2008. Contribution of transcranial magnetic stimulation to the understanding of cortical mechanisms involved in motor control. J Physiol 586, 325-351.
Richter, L., Neumann, G., Oung, S., Schweikard, A., Trillenberg, P., 2013. Optimal coil orientation for transcranial magnetic stimulation. PLoS One 8, e60358.
Roberts, D.R., Ramsey, D., Johnson, K., Kola, J., Ricci, R., Hicks, C., Borckardt, J.J., Bloomberg, J.J., Epstein, C., George, M.S., 2010. Cerebral cortex plasticity after 90 days of bed rest: data from TMS and fMRI. Aviat Space Environ Med 81, 30-40.
Robinson, O.J., Cools, R., Crockett, M.J., Sahakian, B.J., 2010. Mood state moderates the role of serotonin in cognitive biases. J Psychopharmacol 24, 573-583.
Robinson, O.J., Sahakian, B.J., 2009. A double dissociation in the roles of serotonin and mood in healthy subjects. Biol Psychiatry 65, 89-92.
Rogasch, N.C., Daskalakis, Z.J., Fitzgerald, P.B., 2013a. Mechanisms underlying long-interval cortical inhibition in the human motor cortex: a TMS-EEG study. J Neurophysiol 109, 89-98.
Rogasch, N.C., Daskalakis, Z.J., Fitzgerald, P.B., 2015. Cortical inhibition of distinct mechanisms in the dorsolateral prefrontal cortex is related to working memory performance: a TMS-EEG study. Cortex 64, 68-77.
Rogasch, N.C., Sullivan, C., Thomson, R.H., Rose, N.S., Bailey, N.W., Fitzgerald, P.B., Farzan, F., Hernandez-Pavon, J.C., 2017a. Analysing concurrent transcranial magnetic stimulation and electroencephalographic data: a review and introduction to the open-source TESA software. Neuroimage.
Rogasch, N.C., Sullivan, C., Thomson, R.H., Rose, N.S., Bailey, N.W., Fitzgerald, P.B., Farzan, F., Hernandez-Pavon, J.C., 2017b. Analysing concurrent transcranial magnetic stimulation and electroencephalographic data: A review and introduction to the open-source TESA software. Neuroimage 147, 934-951.
Rogasch, N.C., Thomson, R.H., Daskalakis, Z.J., Fitzgerald, P.B., 2013b. Short-latency artifacts associated with concurrent TMS-EEG. Brain Stimul 6, 868-876.
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.
Romero Lauro, L.J., Rosanova, M., Mattavelli, G., Convento, S., Pisoni, A., Opitz, A., Bolognini, N., Vallar, G., 2014. TDCS increases cortical excitability: direct evidence from TMS-EEG. Cortex 58, 99-111.

Rossi, S., Hallett, M., Rossini, P.M., Pascual-Leone, A., Safety of, T.M.S.C.G., 2009. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 120, 2008-2039.
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., Rothwell, J.C., Siebner, H.R., Ugawa, Y., Walsh, V., 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. Clin Neurophysiol 126, 1071-1107.
Rossini, P.M., Rossi, S., 2007. Transcranial magnetic stimulation: diagnostic, therapeutic, and research potential. Neurology 68, 484-488.
Rousselet, G.A., 2012. Does Filtering Preclude Us from Studying ERP Time-Courses? Front Psychol 3, 131.
Rudell, A.P., Fox, S.E., Ranck, J.B., Jr., 1980. Hippocampal excitability phase-locked to the theta rhythm in walking rats. Exp Neurol 68, 87-96.
Rushworth, M.F., Taylor, P.C., 2006. TMS in the parietal cortex: updating representations for attention and action. Neuropsychologia 44, 2700-2716.
Russmann, H., Lamy, J.C., Shamim, E.A., Meunier, S., Hallett, M., 2009. Associative plasticity in intracortical inhibitory circuits in human motor cortex. Clin Neurophysiol 120, 1204-1212.
Ryals, A.J., Rogers, L.M., Gross, E.Z., Polnaszek, K.L., Voss, J.L., 2016. Associative Recognition Memory Awareness Improved by Theta-Burst Stimulation of Frontopolar Cortex. Cereb Cortex 26, 1200-1210.
Salinas, F.S., Lancaster, J.L., Fox, P.T., 2007. Detailed 3D models of the induced electric field of transcranial magnetic stimulation coils. Phys Med Biol 52, 2879-2892.
Sasaki, K., Gemba, H., Tsujimoto, T., 1989. Suppression of visually initiated hand movement by stimulation of the prefrontal cortex in the monkey. Brain Res 495, 100-107.
Schack, B., Vath, N., Petsche, H., Geissler, H.G., Moller, E., 2002. Phase-coupling of theta-gamma EEG rhythms during short-term memory processing. Int J Psychophysiol 44, 143-163.
Scharinger, C., Soutschek, A., Schubert, T., Gerjets, P., 2017. Comparison of the Working Memory Load in N-Back and Working Memory Span Tasks by Means of EEG Frequency Band Power and P300 Amplitude. Front Hum Neurosci 11, 6.
Schicktanz, N., Fastenrath, M., Milnik, A., Spalek, K., Auschra, B., Nyffeler, T., Papassotiropoulos, A., de Quervain, D.J., Schwegler, K., 2015. Continuous theta burst stimulation over the left dorsolateral prefrontal cortex decreases medium load working memory performance in healthy humans. PLoS One 10, e0120640.
Schmajuk, M., Liotti, M., Busse, L., Woldorff, M.G., 2006. Electrophysiological activity underlying inhibitory control processes in normal adults. Neuropsychologia 44, 384-395.
Schubert, T.W., D'Ausilio, A., Canto, R., 2013. Using Arduino microcontroller boards to measure response latencies. Behav Res Methods 45, 1332-1346.
Schultz, B.G., van Vugt, F.T., 2016. Tap Arduino: An Arduino microcontroller for low-latency auditory feedback in sensorimotor synchronization experiments. Behav Res Methods 48, 1591-1607.
Schutter, D.J., 2009. Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in double-blind sham-controlled designs: a meta-analysis. Psychol Med 39, 65-75.
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. J Clin Psychiatry 59 Suppl 20, 22-33;quiz 34-57.
Siebner, H.R., Hartwigsen, G., Kassuba, T., Rothwell, J.C., 2009. How does transcranial magnetic stimulation modify neuronal activity in the brain? Implications for studies of cognition. Cortex 45, 1035-1042.

Siebner, H.R., Rothwell, J., 2003. Transcranial magnetic stimulation: new insights into representational cortical plasticity. Exp Brain Res 148, 1-16.
Silvanto, J., Cattaneo, Z., Battelli, L., Pascual-Leone, A., 2008. Baseline cortical excitability determines whether TMS disrupts or facilitates behavior. J Neurophysiol 99, 2725-2730.
Speer, A.M., Willis, M.W., Herscovitch, P., Daube-Witherspoon, M., Shelton, J.R., Benson, B.E., Post, R.M., Wassermann, E.M., 2003. Intensity-dependent regional cerebral blood flow during 1-Hz repetitive transcranial magnetic stimulation (rTMS) in healthy volunteers studied with H215O positron emission tomography: II. Effects of prefrontal cortex rTMS. Biol Psychiatry 54, 826-832.
Stagg, C.J., Wylezinska, M., Matthews, P.M., Johansen-Berg, H., Jezzard, P., Rothwell, J.C., Bestmann, S., 2009. Neurochemical effects of theta burst stimulation as assessed by magnetic resonance spectroscopy. J Neurophysiol 101, 2872-2877.
Staubli, U., Lynch, G., 1987. Stable hippocampal long-term potentiation elicited by 'theta' pattern stimulation. Brain Res 435, 227-234.
Strube, W., Bunse, T., Malchow, B., Hasan, A., 2015. Efficacy and interindividual variability in motor-cortex plasticity following anodal tDCS and paired-associative stimulation. Neural Plast 2015, 530423.
Stuss, D.T., Murphy, K.J., Binns, M.A., Alexander, M.P., 2003. Staying on the job: the frontal lobes control individual performance variability. Brain 126, 2363-2380.
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. Brain Stimul 9, 323-335.
Suppa, A., Ortu, E., Zafar, N., Deriu, F., Paulus, W., Berardelli, A., Rothwell, J.C., 2008. Theta burst stimulation induces after-effects on contralateral primary motor cortex excitability in humans. J Physiol 586, 4489-4500.
Tadel, F., Baillet, S., Mosher, J.C., Pantazis, D., Leahy, R.M., 2011. Brainstorm: a user-friendly application for MEG/EEG analysis. Comput Intell Neurosci 2011, 879716.
Tanner, D., Morgan-Short, K., Luck, S.J., 2015. How inappropriate high-pass filters can produce artifactual effects and incorrect conclusions in ERP studies of language and cognition. Psychophysiology 52, 997-1009.
Taylor, P.C., Walsh, V., Eimer, M., 2008. Combining TMS and EEG to study cognitive function and cortico-cortico interactions. Behav Brain Res 191, 141-147.
ter Braack, E.M., de Vos, C.C., van Putten, M.J., 2015. Masking the Auditory Evoked Potential in TMS-EEG: A Comparison of Various Methods. Brain Topogr 28, 520-528.
Thielscher, A., Kammer, T., 2004. Electric field properties of two commercial figure-8 coils in TMS: calculation of focality and efficiency. Clin Neurophysiol 115, 1697-1708.
Thimm, A., Funke, K., 2015. Multiple blocks of intermittent and continuous theta-burst stimulation applied via transcranial magnetic stimulation differently affect sensory responses in rat barrel cortex. J Physiol 593, 967-985.
Thomson, R.H., Cleve, T.J., Bailey, N.W., Rogasch, N.C., Maller, J.J., Daskalakis, Z.J., Fitzgerald, P.B., 2013. Blood oxygenation changes modulated by coil orientation during prefrontal transcranial magnetic stimulation. Brain Stimul 6, 576-581.
Tort, A.B., Komorowski, R.W., Manns, J.R., Kopell, N.J., Eichenbaum, H., 2009. Theta-gamma coupling increases during the learning of item-context associations. Proc Natl Acad Sci U S A 106, 20942-20947.
Tortella, G., Selingardi, P.M., Moreno, M.L., Veronezi, B.P., Brunoni, A.R., 2014. Does non-invasive brain stimulation improve cognition in major depressive disorder? A systematic review. CNS Neurol Disord Drug Targets 13, 1759-1769.
Tsang, P., Jacobs, M.F., Lee, K.G., Asmussen, M.J., Zapallow, C.M., Nelson, A.J., 2014. Continuous theta-burst stimulation over primary somatosensory cortex modulates short-latency afferent inhibition. Clin Neurophysiol 125, 2253-2259.

Turrigiano, G.G., Nelson, S.B., 2004. Homeostatic plasticity in the developing nervous system. Nat Rev Neurosci 5, 97-107.
Turriziani, P., Smirni, D., Zappala, G., Mangano, G.R., Oliveri, M., Cipolotti, L., 2012. Enhancing memory performance with rTMS in healthy subjects and individuals with Mild Cognitive Impairment: the role of the right dorsolateral prefrontal cortex. Front Hum Neurosci 6, 62.
Vallence, A.M., Goldsworthy, M.R., Hodyl, N.A., Semmler, J.G., Pitcher, J.B., Ridding, M.C., 2015. Inter- and intra-subject variability of motor cortex plasticity following continuous theta-burst stimulation. Neuroscience 304, 266-278.
van Ede, F., Maris, E., 2016. Physiological Plausibility Can Increase Reproducibility in Cognitive Neuroscience. Trends Cogn Sci 20, 567-569.
Veniero, D., Ponzo, V., Koch, G., 2013. Paired associative stimulation enforces the communication between interconnected areas. J Neurosci 33, 13773-13783.
Vernet, M., Bashir, S., Yoo, W.K., Perez, J.M., Najib, U., Pascual-Leone, A., 2013. Insights on the neural basis of motor plasticity induced by theta burst stimulation from TMS-EEG. Eur J Neurosci 37, 598-606.
Vicario, C.M., Nitsche, M.A., 2013. Non-invasive brain stimulation for the treatment of brain diseases in childhood and adolescence: state of the art, current limits and future challenges. Front Syst Neurosci 7, 94.
Viejo-Sobera, R., Redolar-Ripoll, D., Boixados, M., Palaus, M., Valero-Cabre, A., Marron, E.M., 2017. Impact of Prefrontal Theta Burst Stimulation on Clinical Neuropsychological Tasks. Front Neurosci 11, 462.
Vogel, E.K., Luck, S.J., 2000. The visual N1 component as an index of a discrimination process. Psychophysiology 37, 190-203.
Volz, L.J., Benali, A., Mix, A., Neubacher, U., Funke, K., 2013. Dose-dependence of changes in cortical protein expression induced with repeated transcranial magnetic theta-burst stimulation in the rat. Brain Stimul 6, 598-606.
Voss, M.W., Vivar, C., Kramer, A.F., van Praag, H., 2013. Bridging animal and human models of exercise-induced brain plasticity. Trends Cogn Sci 17, 525-544.
Vossen, A., Gross, J., Thut, G., 2015. Alpha Power Increase After Transcranial Alternating Current Stimulation at Alpha Frequency (alpha-tACS) Reflects Plastic Changes Rather Than Entrainment. Brain Stimul 8, 499-508.
Wagner, T., Valero-Cabre, A., Pascual-Leone, A., 2007. Noninvasive human brain stimulation. Annu Rev Biomed Eng 9, 527-565.
Walsh, V., Ashbridge, E., Cowey, A., 1998. Cortical plasticity in perceptual learning demonstrated by transcranial magnetic stimulation. Neuropsychologia 36, 363-367.
Walsh, V., Cowey, A., 2000. Transcranial magnetic stimulation and cognitive neuroscience. Nat Rev Neurosci 1, 73-79.
Watrous, A.J., Lee, D.J., Izadi, A., Gurkoff, G.G., Shahlaie, K., Ekstrom, A.D., 2013. A comparative study of human and rat hippocampal low-frequency oscillations during spatial navigation. Hippocampus 23, 656-661.
Whittington, M.A., Traub, R.D., Jefferys, J.G., 1995. Synchronized oscillations in interneuron networks driven by metabotropic glutamate receptor activation. Nature 373, 612-615.
Wilcox, R.R., 1997. Introduction to robust estimation and hypothesis testing. Academic Press, San Diego, CA.
Wischnewski, M., Schutter, D., 2016. Efficacy and time course of paired associative stimulation in cortical plasticity: Implications for neuropsychiatry. Clin Neurophysiol 127, 732-739.
Wischnewski, M., Schutter, D.J., 2015. Efficacy and Time Course of Theta Burst Stimulation in Healthy Humans. Brain Stimul 8, 685-692.
Wozniak-Kwasniewska, A., Szekely, D., Aussedat, P., Bougerol, T., David, O., 2014. Changes of oscillatory brain activity induced by repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex in healthy subjects. Neuroimage 88, 91-99.

Wu, S.W., Shahana, N., Huddleston, D.A., Gilbert, D.L., 2012a. Effects of 30Hz theta burst transcranial magnetic stimulation on the primary motor cortex. J Neurosci Methods 208, 161-164.
Wu, S.W., Shahana, N., Huddleston, D.A., Lewis, A.N., Gilbert, D.L., 2012b. Safety and tolerability of theta-burst transcranial magnetic stimulation in children. Dev Med Child Neurol 54, 636-639.
Xu, G., Lan, Y., Huang, D., Chen, S., Chen, L., Zeng, J., Pei, Z., 2013. The study on the frontoparietal networks by continuous theta burst stimulation in healthy human subjects. Behav Brain Res 240, 60-68.
Yamanaka, K., Kadota, H., Nozaki, D., 2013. Long-latency TMS-evoked potentials during motor execution and inhibition. Front Hum Neurosci 7, 751.
Yeterian, E.H., Pandya, D.N., Tomaiuolo, F., Petrides, M., 2012. The cortical connectivity of the prefrontal cortex in the monkey brain. Cortex 48, 58-81.
Zaehle, T., Sandmann, P., Thorne, J.D., Jancke, L., Herrmann, C.S., 2011. Transcranial direct current stimulation of the prefrontal cortex modulates working memory performance: combined behavioural and electrophysiological evidence. BMC Neurosci 12, 2.
Zaman, R., 2016. Investigative and therapeutic uses of Transcranial magnetic stimulation (TMS) in Attention Deficit Hyperactivity Disorder (ADHD). Psychiatr Danub 28, 99-102.
Zheng, C., Zhang, T., 2015. Synaptic plasticity-related neural oscillations on hippocampus-prefrontal cortex pathway in depression. Neuroscience 292, 170-180.

APPENDICES

Appendix A

Abstract: Students of Brain Research Symposium. Melbourne, Australia. 2015

Use of theta-burst stimulation in changing excitability of motor cortex: a systematic review and meta-analysis.

Chung SW, Hill AT, Rogasch NC, Hoy KE, Fitzgerald PB

Noninvasive brain stimulation has the unique ability to safely modulate cortical activity. In particular, theta burst stimulation (TBS) has gained notable attention due to its efficacy in short stimulation durations. However, inter- and intra-individual variability to TBS still remains unsolved.

AIM: To provide a meta-analytic synthesis of efficacy of two TBS paradigms; intermittent (iTBS) and continuous (cTBS), on corticomotor excitability.

METHODS: Comprehensive electronic literature searches yielded 87 eligible papers.

RESULTS: The effect of iTBS yielded a moderately large MEP increase up to 30 minutes with pooled SMD of 0.71 ($p < 0.00001$). Subgroup analysis of number of pulses indicated larger SMD with 1200 pulses (0.84, $p < 0.05$), compared to 600 pulses (0.68, $p < 0.00001$) at 30 minutes post iTBS. The effect of cTBS produced a MEP decrease up to 60 minutes, with largest effect size at 5 minutes post cTBS (0.9, $P < 0.00001$), and gradually decreased over time. Subgroup analysis of number of pulses revealed largest effect with 1200 pulses up to

60 minutes (SMD = - 1.18, P = 0.01). 300 and 600 pulses produced identical SMD of -0.62 at 30 minutes post cTBS.

CONCLUSION: Overall, this systemic review and meta-analysis shows that two paradigms of TBS can produce statistically significant effects on corticomotor excitability in healthy individuals. The results also highlight the factors that may affect the outcome of after-effects of TBS. More research is required to identify other factors affecting inter- and intra-individual variability.

Appendix B

Abstract: 2nd Australasian Brain Stimulation Meeting. Melbourne, Australia. 2016

*Top ranked student abstracts, Oral presentation

Intensity-dependent effect of intermittent theta burst stimulation in prefrontal cortex: A TMS-EEG Study.

Chung, SW, Rogasch NC, Hoy KE, Fitzgerald PB.

Introduction: Theta burst stimulation (TBS) has demonstrated similar if not greater effects on brain activity over standard repetitive transcranial magnetic stimulation. There is increasing interest in the use of TBS as a therapeutic tool for disorders such as depression and schizophrenia, however we know very little about the effects of TBS on cortical excitability outside of the motor cortex. In developing clinical applications in psychiatric illnesses, there is a need to explore the effects of different parameters of TBS in non-motor regions.

Objectives: The study aimed to examine the effects of different intensities of intermittent TBS (iTBS; 50, 75 & 100%) on cortical excitability in the dorsolateral prefrontal cortex, a brain region relevant to the treatment of a number of neuropsychiatric disorders. We hypothesized that iTBS would show greatest cortical effects at sub-threshold intensities.

Materials & Methods: 16 healthy participants were stimulated with iTBS at either 50, 75 or 100% rMT on F1 electrode over 3 different sessions. TMS-EEG before and after iTBS was

used to assess cortical excitability change via TMS-evoked potentials (TEPs) and TMS-evoked oscillations.

Results: Increased N120 amplitude was observed with 75% iTBS (p =.026). No significant change was observed with 100% iTBS. Globally, 100% and 75% iTBS showed significant overall difference in centro-frontal region alone (p = .042). TMS-evoked oscillations were significantly decreased after 100% iTBS in the gamma frequency band at F1 (p = .019).

Conclusion: This study provides some of the first evidence that varying intensities of iTBS produces different changes in cortical excitability in the prefrontal cortex. This may aid in optimising stimulation paradigms prior to the conduct of clinical trials.

Appendix C

Abstract: 6th International Conference of Transcranial Brain Stimulation, Göttingen, Germany. 2016

Demonstration of short-term plasticity in the dorsolateral prefrontal cortex with theta burst stimulation.

Chung, SW, Lewis BP, Rogasch NC, Saeki T, Thomson R, Bailey NW, Hoy KE, Fitzgerald PB.

Introduction

Repetitive transcranial magnetic stimulation has the unique ability to modulate cortical activity. In particular, theta burst stimulation (TBS) has gained notable attention due to its efficacy in short stimulation durations. Vast majority of TBS studies have demonstrated corticospinal excitability change, however we know very little about the effects of TBS on cortical excitability outside of the motor cortex. There is increasing interest in the use of TBS as a therapeutic tool for disorders such as depression and schizophrenia. In developing clinical applications in such psychiatric illnesses, there is a need to explore whether the same effects on corticospinal excitability are achieved in non-motor regions.

Objectives

The study aimed to examine the effects of iTBS and cTBS on cortical excitability in the dorsolateral prefrontal cortex, a brain region relevant to the treatment of a number of neuropsychiatric disorders. We hypothesized that iTBS and cTBS protocol would increase and decrease cortical excitability respectively.

Materials & Methods

10 healthy participants were stimulated with either iTBS, cTBS or sham on F3 electrode over 3 different sessions. TMS-EEG was used to assess cortical excitability change via TMS-evoked potentials (TEPs) and TMS-evoked oscillations.

Results

Analysis on F3 revealed increase in N120 amplitude ($p = .009$) from pre to post iTBS. Cluster-based statistics showed one significant negative cluster at N120 ($p = .003$), indicating increased amplitude at the site of stimulation and contralaterally. TBS-induced changes (post – pre) were calculated and compared among different TBS conditions. N120 amplitude post iTBS was higher than cTBS at F3 ($p = .042$). TMS-evoked oscillations were significantly increased after iTBS in theta frequency at F3 from 50 to 250 ms ($p = .044$). TMS-evoked oscillations among different TBS at F3 yielded higher theta power after iTBS compared to cTBS and sham ($p < .05$; Fig 1).

Conclusion

This study provides some of the first evidence that TBS produces direct changes in cortical excitability in the prefrontal cortex. This may be a useful approach to optimise stimulation paradigms prior to the conduct of clinical trials.

Appendix D

Abstract: Students of Brain Research Symposium. Melbourne, Australia. 2016

*2nd Prize Poster Presentation

Demonstration of short-term plasticity in the dorsolateral prefrontal cortex with theta burst stimulation.

Chung, SW, Lewis BP, Rogasch NC, Saeki T, Thomson R, Bailey NW, Hoy KE, Fitzgerald PB.

Theta burst stimulation (TBS), a modified form of repetitive transcranial magnetic stimulation (rTMS), has demonstrated corticospinal excitability change. However, we know very little about the effects of TBS on cortical excitability/inhibition outside the motor cortex. There is increasing interest in the use of TBS as a therapeutic tool for disorders such as depression and schizophrenia, where dorsolateral prefrontal cortex (DLPFC) is the primary target for treatment. In developing clinical applications using TBS, there is a need to explore cortical effects of TBS in non-motor regions.

AIM: To examine the effects of iTBS and cTBS on cortical reactivity in the DLPFC. We hypothesized that iTBS and cTBS would increase and decrease cortical reactivity respectively.

METHODS: 10 healthy participants were stimulated with either iTBS, cTBS or sham at F3 electrode. Single- and paired-pulse TMS and concurrent electroencephalography (EEG) were used to assess change in cortical reactivity and long-interval intracortical inhibition (LICI).

RESULTS: Significant increases in N120 amplitudes ($p = 0.013$) were observed following iTBS over prefrontal cortex. Changes in TMS-evoked theta oscillations and LICI of theta oscillations were also observed following iTBS (↑) and cTBS (↓), and these changes were significantly different between iTBS and cTBS. Change in LICI of theta oscillations correlated with change in N120 amplitude following TBS ($r = -0.419$, $p = 0.021$).

CONCLUSION: This study provides preliminary evidence that TBS produces direct changes in cortical reactivity in the DLPFC. This may be a useful approach to optimise stimulation paradigms prior to the conduct of clinical trials.

Appendix E

Abstract: 2nd International Brain Stimulation Conference, Barcelona, Spain. 2017

*Outstanding Poster Award (1 of 3 out of ~500)

More is not always better: Impact of different intensities of intermittent theta burst stimulation in prefrontal cortex using TMS-EEG.

Chung, SW, Rogasch NC, Hoy KE, Fitzgerald PB.

Introduction: Theta burst stimulation (TBS) can alter cortical excitability, similar to standard repetitive transcranial magnetic stimulation paradigms, with a major advantage of shorter stimulation duration at a lower intensity. There is increasing interest in the use of TBS as a therapeutic tool for disorders such as depression and schizophrenia, where prefrontal cortex is the primary target for treatment. In developing clinical applications for such psychiatric illnesses, there is a need to explore effects of different parameters of TBS in this region. This study aimed to examine the effects of different intensities of intermittent TBS (iTBS) on cortical reactivity in the prefrontal cortex. We hypothesized that iTBS would show greater cortical effects at sub-threshold intensities.

Methods: 16 healthy participants received iTBS over prefrontal cortex (F1 electrode) at either 50, 75 or 100% rMT in separate sessions. Single pulse TMS-EEG was used to assess change in cortical reactivity via TMS-evoked potentials and TMS-evoked oscillations before and after iTBS.

Results: Cluster-based statistics revealed a significant increase in N100 amplitude following 50% ($p = 0.011$) and 75% ($p = 0.010$) iTBS over prefrontal regions. No significant change was observed with 100% iTBS. Between conditions, the iTBS-induced change in N100 was larger following 75% compared to 100% iTBS ($p = 0.008$).

For oscillations, change in TMS-evoked theta ($p = 0.027$) and gamma power ($p = 0.006$) were larger following 75% compared to 100% iTBS (figure below). No significant differences were observed between 50% and 75% iTBS, or 50% and 100% iTBS.

Discussion: Intensity of the stimulation should be carefully considered when administering TBS in the prefrontal cortex, as it may reduce iTBS-induced changes in cortical reactivity at or above individual's motor threshold. This study may aid in optimising stimulation paradigm prior to the conduct of clinical trials.

Appendix F

Abstract: 7th Australasian Cognitive Neuroscience Society Conference, Adelaide, Australia. 2018

* Travel Award

The effects of individualised intermittent theta burst stimulation in the prefrontal cortex: a TMS-EEG study

Chung, SW, Sullivan CM, Rogasch NC, Hoy KE, Cash RFH, Fitzgerald PB.

Recent studies have highlighted the neurophysiological and behavioural variability in response to theta burst stimulation (TBS) in humans. This paradigm was originally developed in rodents to mimic gamma bursts that were coupled with theta rhythms and was shown to elicit long-term potentiation. The protocol was subsequently adapted for humans using similar frequency parameters, however it is known that peak theta frequency differs between rodents and humans, and across individuals. Furthermore the precise frequencies involved in theta-gamma coupling, a cornerstone of cognitive processing, is unique across individuals. The present study sought to explore whether individualised intermittent TBS (Ind-iTBS) could outperform the neurophysiological and behavioural (mood) effects of two conventional iTBS variants.

20 healthy volunteers received iTBS over left prefrontal cortex using 30 Hz, 50 Hz, or individualised frequency in separate sessions. Ind-iTBS was determined using theta-gamma coupling during the 3-back task. Concurrent use of transcranial magnetic stimulation and electroencephalography (TMS-EEG) was used to track changes in cortical plasticity measured. We also utilised mood ratings using a visual analogue scale before and after stimulation.

No group-level effect was observed following either 30 Hz or 50 Hz iTBS. Ind-iTBS yielded significant increase in the amplitude of TMS-evoked P60, and decrease in N100 and P200. A significant positive correlation between neurophysiological change and change in mood rating was also seen.

These findings highlight the critical importance of frequency in the parameter space of iTBS. Our Ind-iTBS protocol outperformed conventional protocols in neurophysiological and behavioural outcomes. This novel approach presents a promising option for enhancing the efficacy and reducing the variability of iTBS and benefits may extend to clinical applications.

Appendix G

Cover of Human Brain Mapping journal

Chung SW, Rogasch NC, Hoy KE, Sullivan CM, Cash RFH, Fitzgerald PB. 2017. Impact of different intensities of intermittent theta burst stimulation on the cortical properties during TMS-EEG and working memory performance.