



Review

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

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ARTICLE INFO

Article history:

Received 24 November 2015

Received in revised form

30 December 2015

Accepted 26 January 2016

Available online 3 February 2016

Keywords:

Theta-burst stimulation (TBS)

Transcranial magnetic stimulation (TMS)

Motor cortex

Motor-evoked potentials (MEPs)

Cortical excitability

Neuromodulation

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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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 from 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

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 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
Interventions	iTBS or cTBS applied over M1	No baseline measurement Other type of measurement (e.g behavioural, fMRI, NIRS, EEG)
Comparison	Before and after intervention	–
Outcomes	MEP amplitudes measured by single pulse TMS SICI or ICF measured by paired pulse TMS	–
Study design	Pre-post studies Cross-over or parallel group	Unpublished data Data without SD/SEM Data collected from non-stimulated area
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	Non-English articles Review articles, case reports, grey literature
Type of publications	Peer-reviewed journal Written in English	–

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.

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.

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

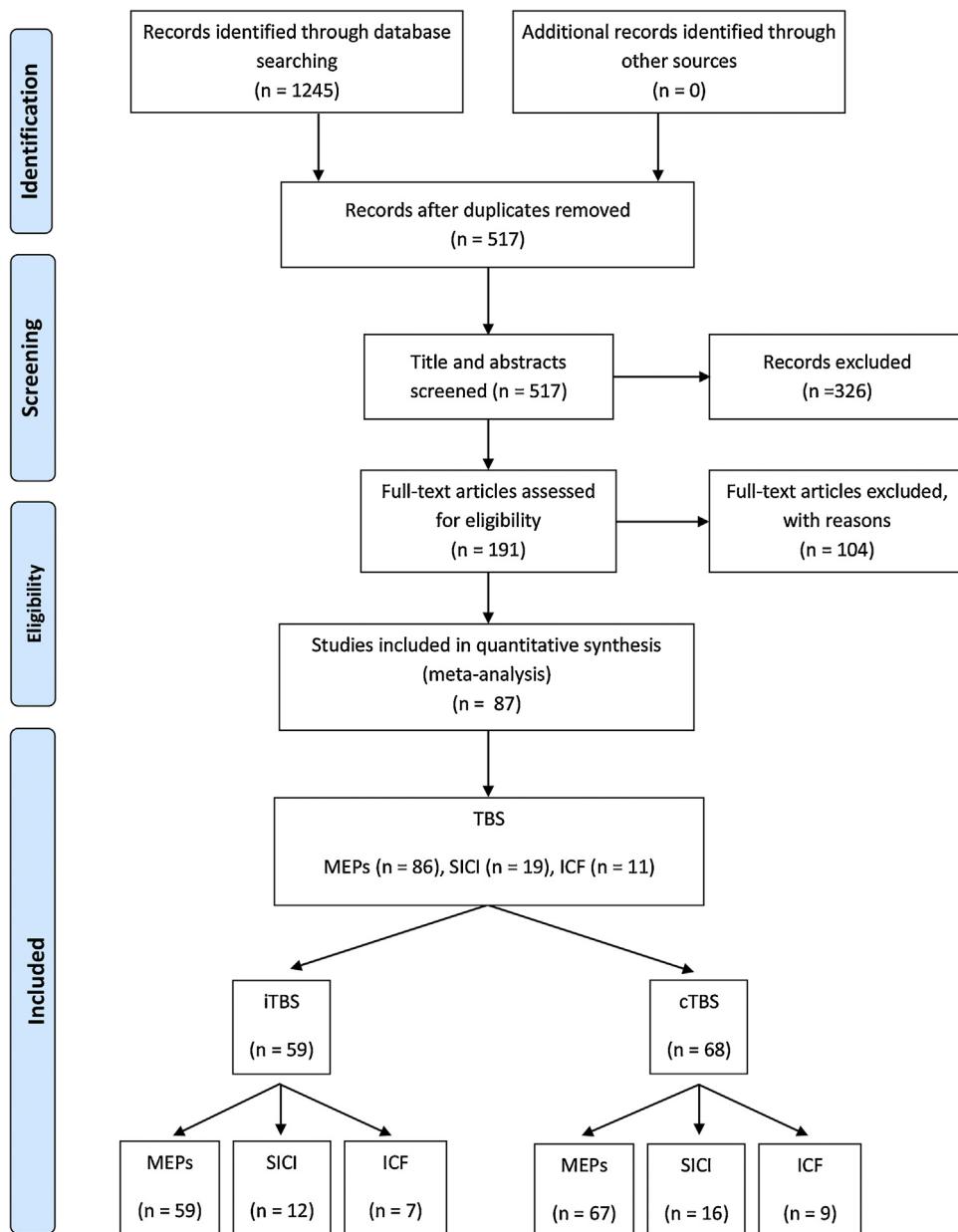


Fig. 1. Flow diagram of selected studies (n = number of articles).

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 [\pm 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 ($\tauau=-0.4085, p<0.00001$), 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 ($\tauau=-0.3748, p<0.00001$) and Egger's regression test ($t=-5.1970, p<0.00001$) were both highly significant. Bayesian

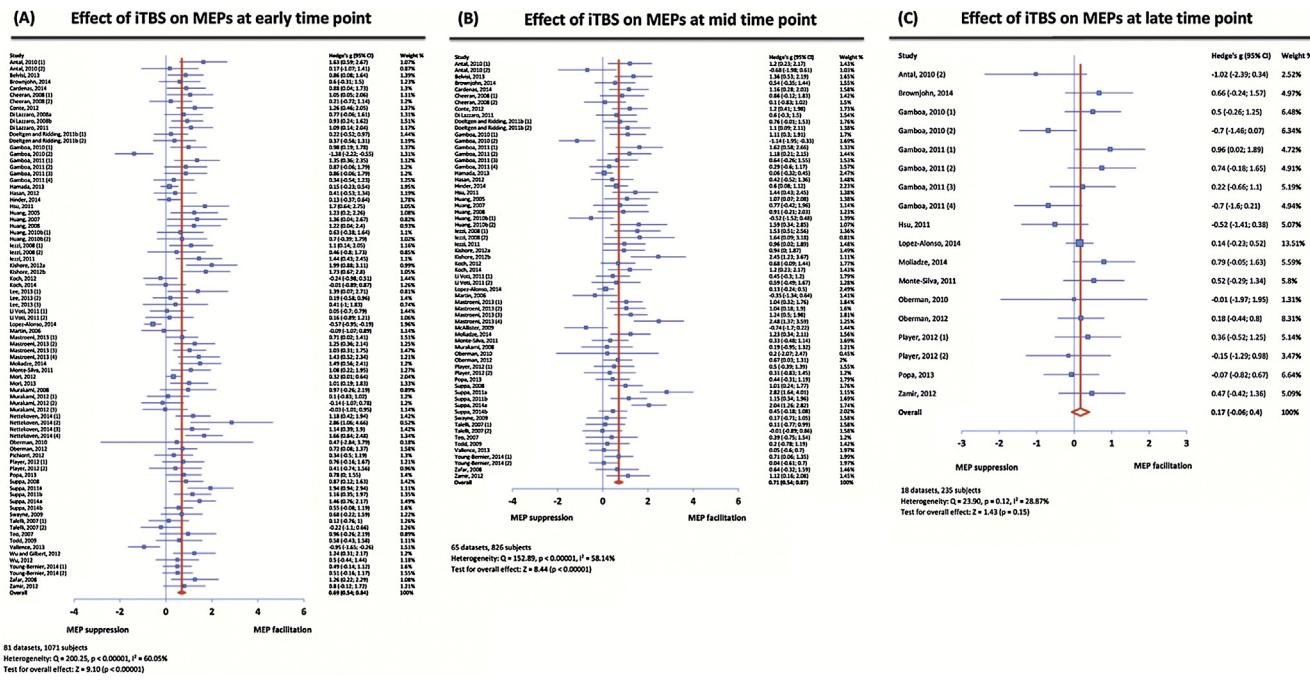


Fig. 2. Forest plot of the Hedge's adjusted g analysis for all studies for MEPs amplitude after iTBS measured post 0–5 min (A), 20–30 min (B) and 50–60 min (C).

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
Doelgent 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	FDI
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-

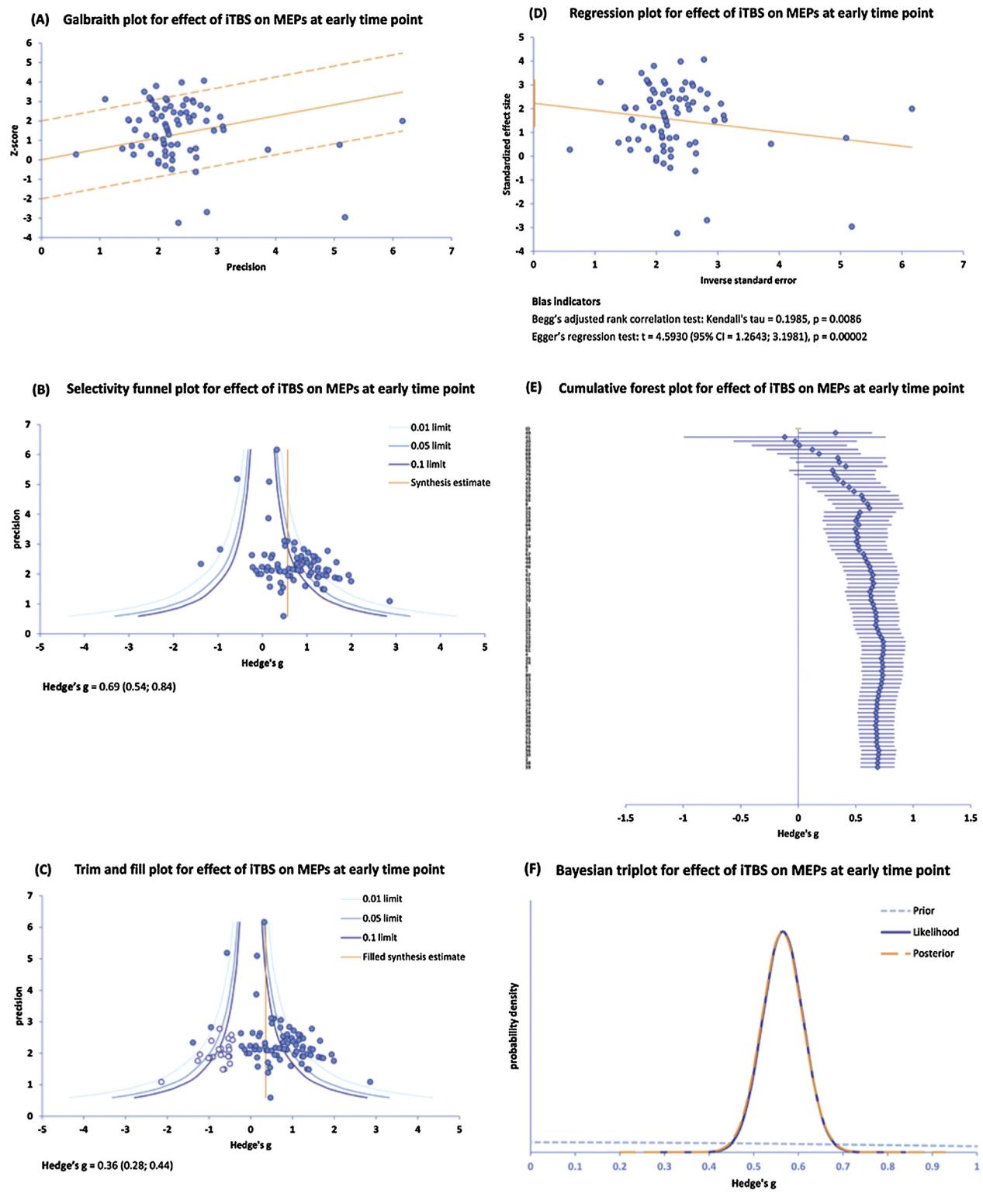


Fig. 3. Series of tests for heterogeneity and publication bias for all studies for MEPs amplitude after iTBS measured post 0–5 min; (A) Galbraith plot, (B) Selectivity funnel plot, (C) Trim and fill plot, (D) Regression plot, (E) Cumulative forest plot and (F) Bayesian triplot.

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 pro-

duced 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 ,

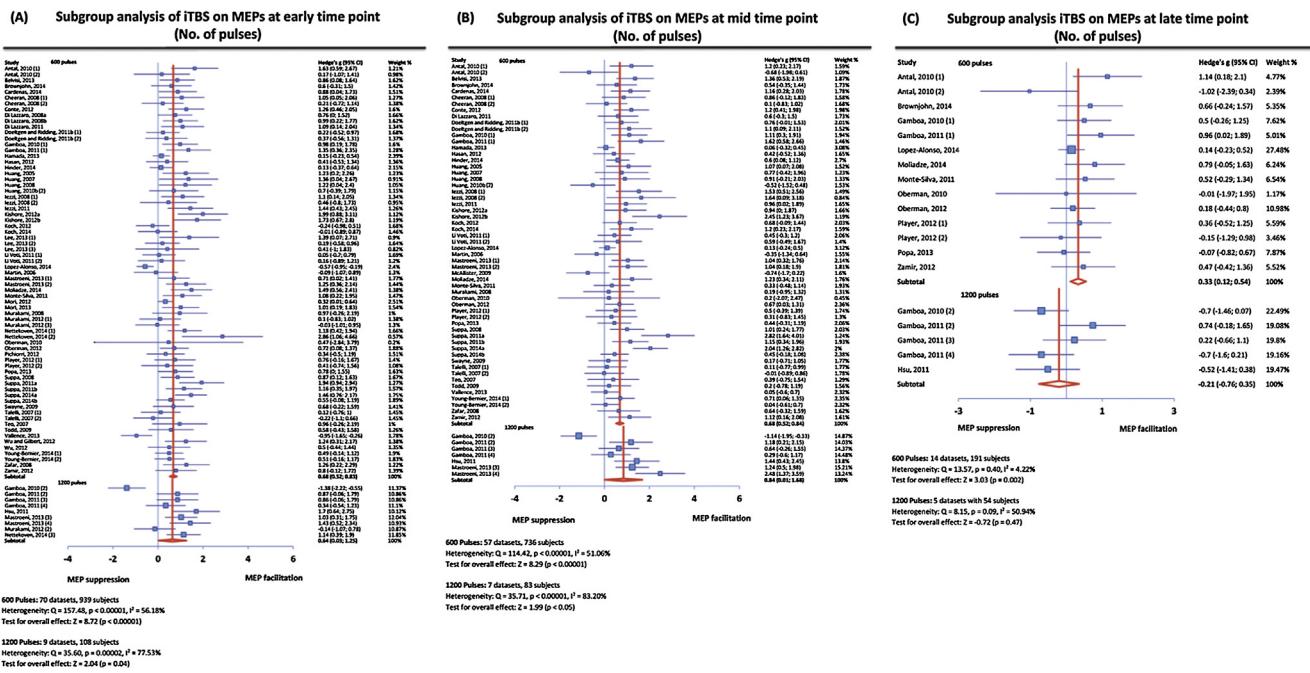


Fig. 4. Forest plot of the Hedge's adjusted g analysis for subgroup studies (no. of pulses) of MEPs amplitude after iTBS measured post 0–5 min (A), 20–30 min (B) and 50–60 min (C).

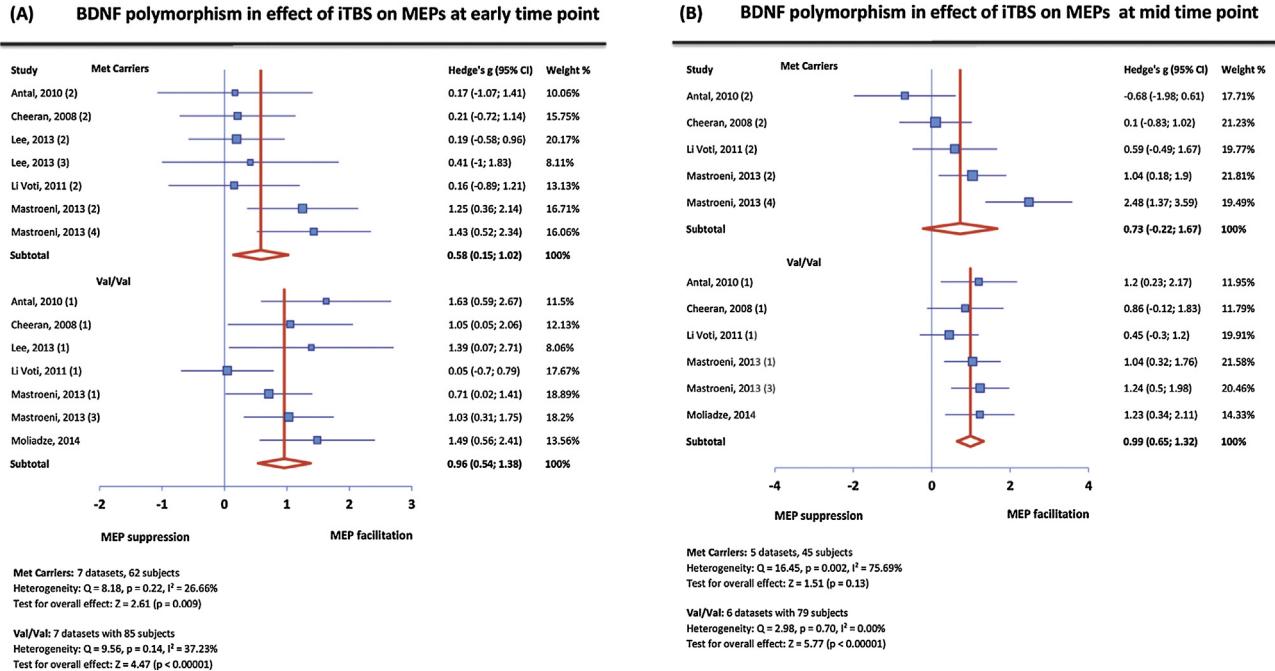


Fig. 5. Forest plot of the Hedge's adjusted g analysis for influence of BDNF polymorphism on MEPs amplitude after iTBS measured post 0–5 min (A) and 20–30 min (B).

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 \pm SD (age range)	iTBS parameters (variable)	ICF ISI	Target muscle
Di Lazzaro et al. (2011)	10	—	26.6 \pm 4.1	80% aMT, 50 Hz/5 Hz, 600 pulses	15 ms	FDI
Hasan et al. (2012)	9	7 M: 2F	30.3 \pm 1.5	80% aMT, 50 Hz/5 Hz, 600 pulses (with sham tDCS)	10 & 12 ms	FDI
Huang et al. (2005)	7*	—	33.6 \pm 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 \pm 3.1	80% aMT, 50 Hz/5 Hz, 150 pulses	10 & 12 ms	FDI
Lee et al. (2013)	23	10 M: 13F	31.9 \pm 4.4	80% rMT, 50 Hz/5 Hz, 600 pulses	15 ms	FDI
McAllister et al. (2009)	9	4 M: 5F	28.3 \pm 11.1	70% aMT, 50 Hz/5 Hz, 600 pulses	10 ms	FDI
Zamir et al. (2012)	10	4 M: 6F	63.1 \pm 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

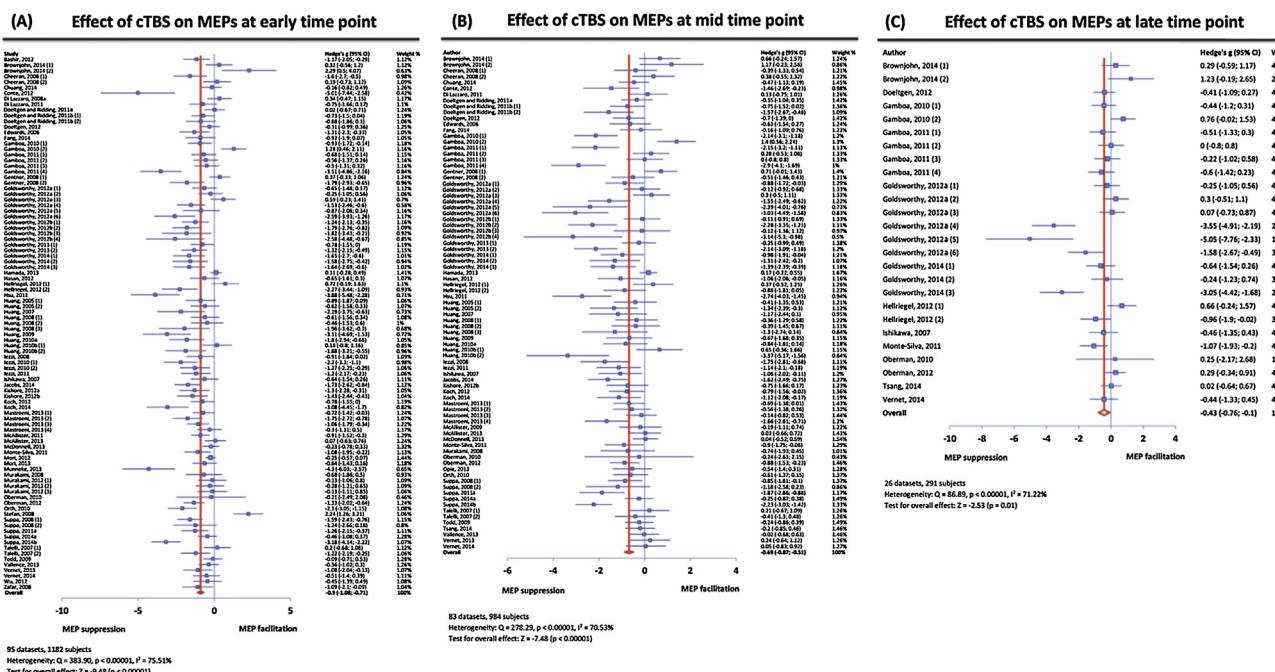


Fig. 6. Forest plots of the Hedge's adjusted g analysis for all studies for MEPs amplitude after cTBS measured post 0–5 min (A), 20–30 min (B) and 50–60 min (C).

decrease with SMD of -1.49 (95% CI: -2.29 ; -0.68 , $p = 0.003$). The 50Hz 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 30Hz cTBS at the mid time point, whereas a significant but decreased effect was found with 50Hz 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% rMT, 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	1 M: 5F	29 ± 6	80% aMT, 50 Hz/5 Hz	600	FDI	—
Huang et al. (2007)	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 (18 – 60)	27 ± 8.2	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 (22 – 54)	38.6 ± 13.8	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 (28 – 62)	42.4	80% aMT, 50 Hz/5 Hz	300	FDI	—
Stefan et al. (2008)	14*	10 M: 8F (20 – 40)	25.7 ± 5.6	70% rMT, 50 Hz/5 Hz	300	APB	—
Suppa et al. (2008) (1)	15	11 M: 7F (26 – 45)	31 ± 5	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 (25 – 40)	30 ± 4.9	80% aMT, 50 Hz/5 Hz	600	FDI	—
Suppa et al. (2014a)	20	14 M: 6F (36 – 81)	32.8 ± 11.2	80% aMT, 50 Hz/5 Hz	600	FDI	—
Suppa et al. (2014b)	20	10 M: 10F (36 – 81)	58.6 ± 11.5	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: 12 F	25 ± 8	80% aMT, 50 Hz/5 Hz	600	FDI	—
Tsang et al. (2014)	18	7 M: 11 F	21 ± 2.0 (19 – 25)	70% rMT, 30 Hz/6 Hz	600	FDI	—
Vallence et al. (2013)	18	9 M: 9 F	23.3 ± 2.7	80% aMT, 50 Hz/5 Hz	600	APB	—
Vernet et al. (2013)	10	6 M: 4 F	21 ± 2 (18 – 24)	80% aMT, 50 Hz/4.17 Hz	600	APB	—
Vernet et al. (2014)	10	5 M: 5 F	33 ± 18 (21 – 67)	80% aMT, 50 Hz/4.17 Hz	600	FDI	—
Wu et al. (2012)	9*	8 M: 10 F	33 ± 9.0	90% rMT, 30 Hz/5 Hz	600	FDI	—
Zafar et al. (2008)	9	4 M: 5 F	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: 7 F	26 ± 2.5 (21 – 45)	70% aMT, 50 Hz/5 Hz, 600 pulses	3 ms	BB
Brownjohn et al. (2014)	9*	9 M: 1 F	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: 8 F	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: 8 F	25.2 ± 3.5	60 rTM, 50 Hz/5 Hz, 300 pulses	2 & 3 ms	FDI
Doeltgen and Ridding (2011b)	14	4 M: 10 F	24.5 ± 3.1	80% aMT, 50 Hz/5 Hz, 600 pulses	2 & 3 ms	FDI
Goldsworthy et al. (2013)	14	7 M: 7 F	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: 2 F	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: 4 F	30.3 ± 3.1	80% aMT, 50 Hz/5 Hz, 150 pulses	2 & 3 ms	FDI
Jacobs et al. (2014)	14	5 M: 9 F	21.3 ± 1.6 (18 – 23)	55% rMT, 30 Hz/6 Hz, 600 pulses	2 ms	FDI
McAllister et al. (2009)	9	4 M: 5 F	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: 15 F	27.1 ± 4.8	80% aMT, 50 Hz/5 Hz, 600 pulses	2 ms	FDI
Murakami et al. (2012)(1)	9	7 M: 2 F	29.2 ± 6.9	80% aMT, 50 Hz/4.2 Hz, 600 pulses	2 ms	FDI
Murakami et al. (2012)(2)	8	5 M: 3 F	27.4 ± 4.7	70, 80% aMT, 50 Hz/4.2 Hz, 600 pulses	2 ms	FDI
Suppa et al. (2008)	5*	11 M: 7 F	31 ± 5 (26 – 45)	80% aMT, 50 Hz/5 Hz, 600 pulses	3 ms	FDI
Talelli et al. (2007)	8*	9 M: 9 F	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

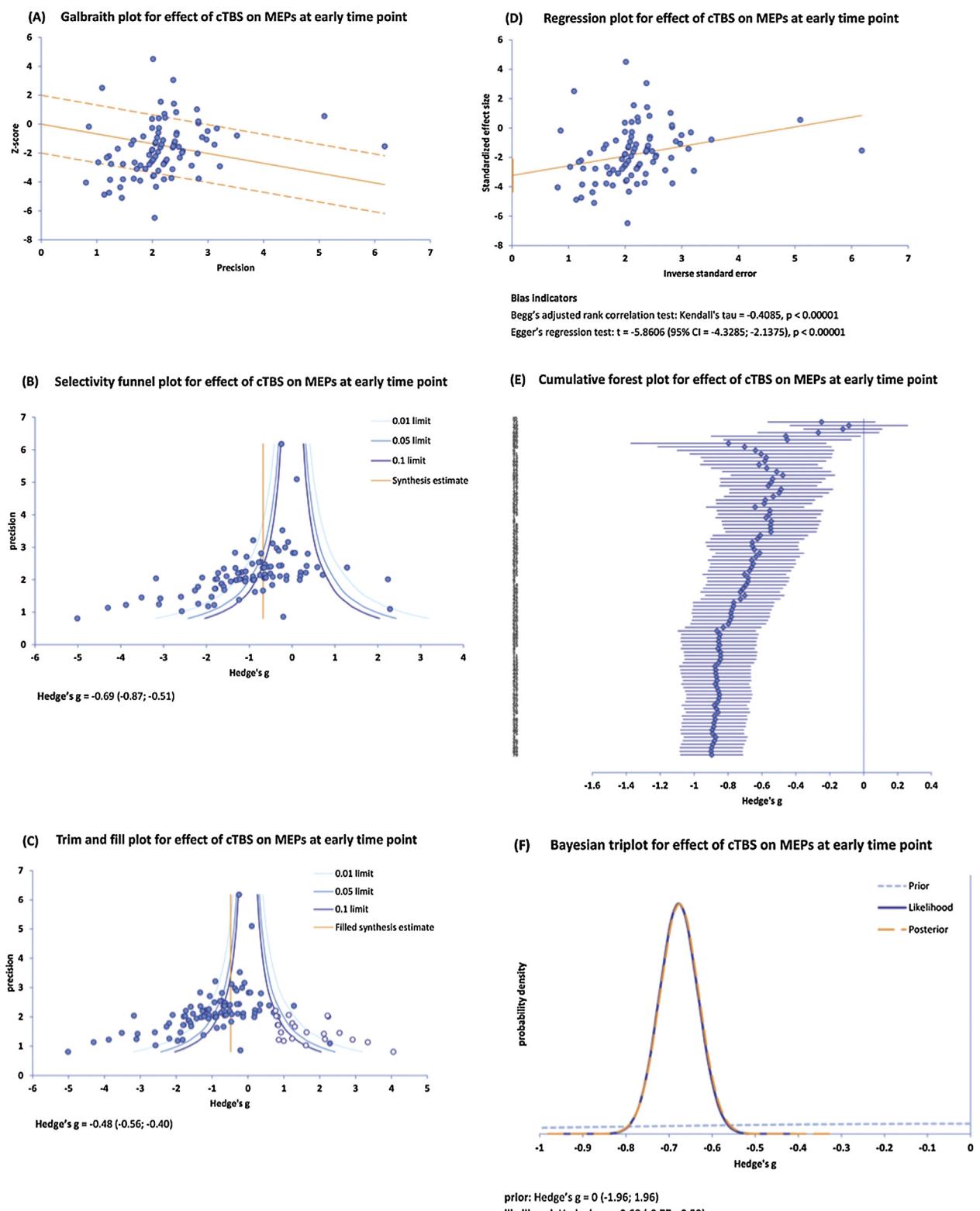


Fig. 7. Series of tests for heterogeneity and publication bias for all studies for MEPs amplitude after cTBS measured post 0–5 min; (A) Galbraith plot, (B) Selectivity funnel plot, (C) Trim and fill plot, (D) Regression plot, (E) Cumulative forest plot and (F) Bayesian triplot.

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.

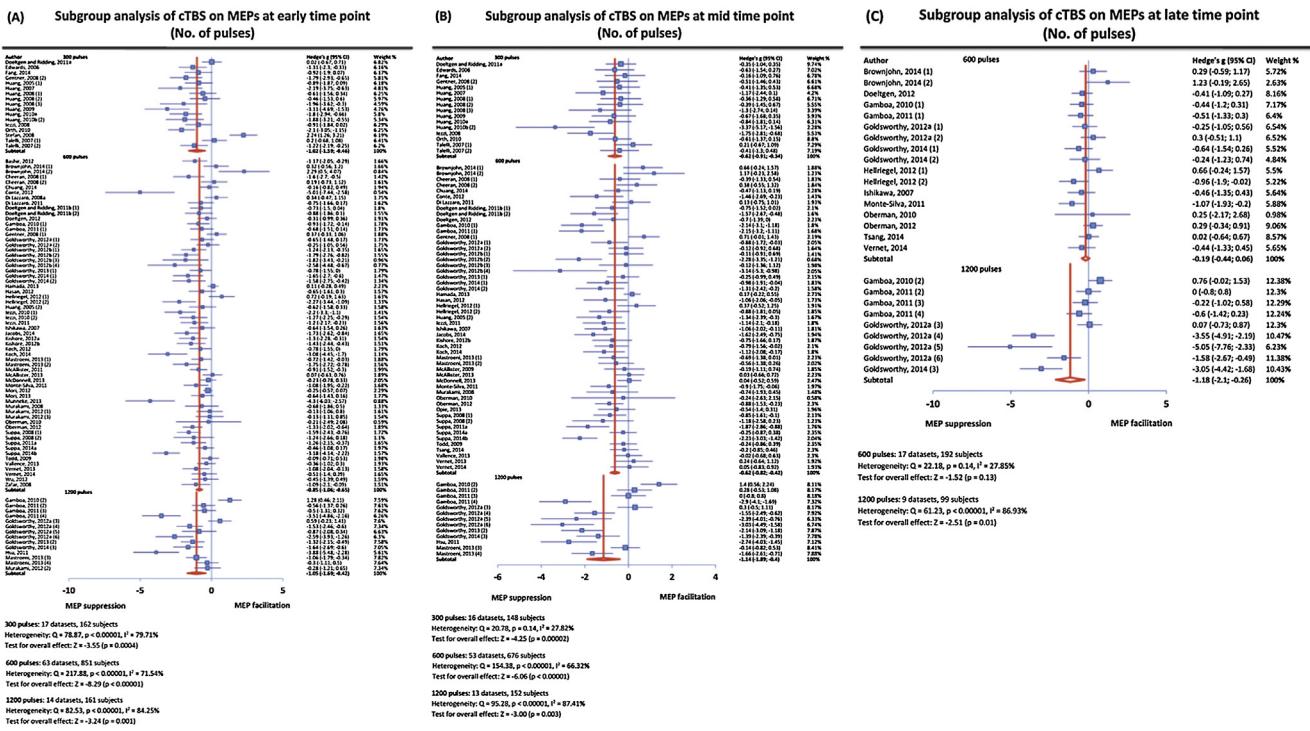


Fig. 8. Forest plot of the Hedge's adjusted g analysis for subgroup studies (no. of pulses) of MEPs amplitude after cTBS measured post 0–5 min (A), 20–30 min (B) and 50–60 min (C).

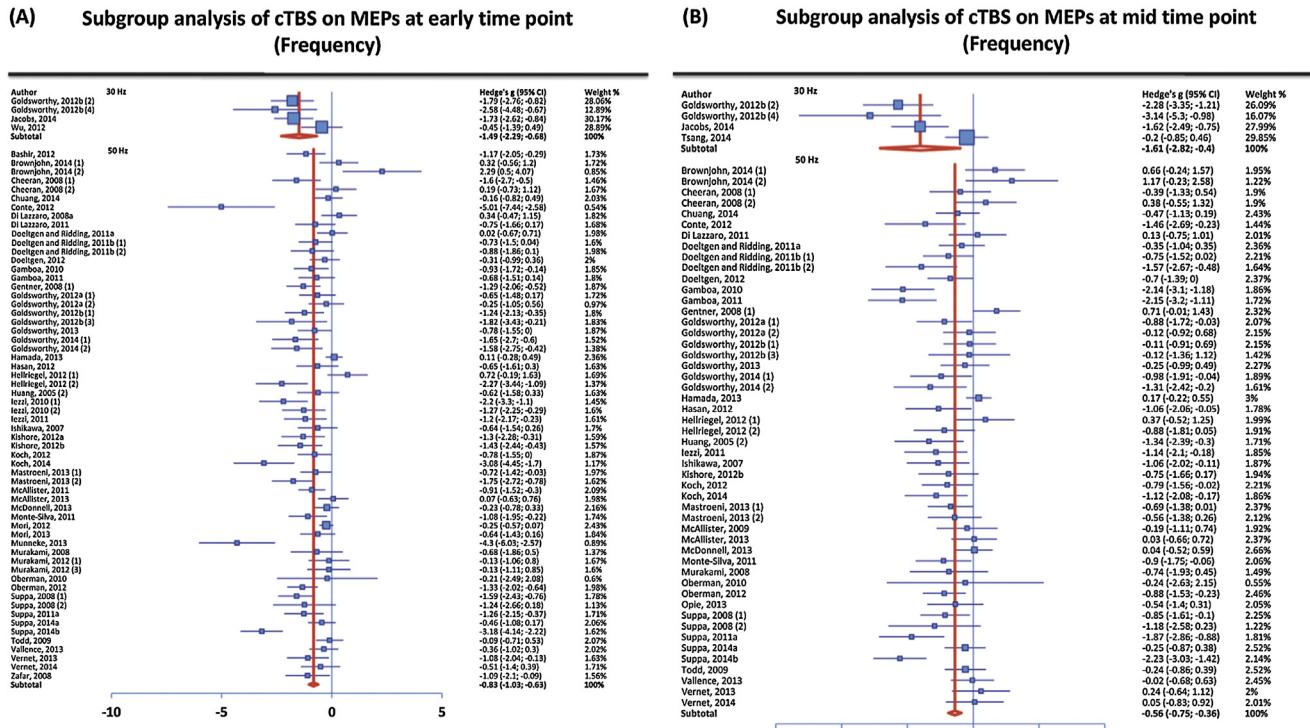


Fig. 9. Forest plot of the Hedge's adjusted g analysis for subgroup studies (frequency of stimulation) of MEPs amplitude after cTBS measured post 0–5 min (A) and 20–30 min (B).

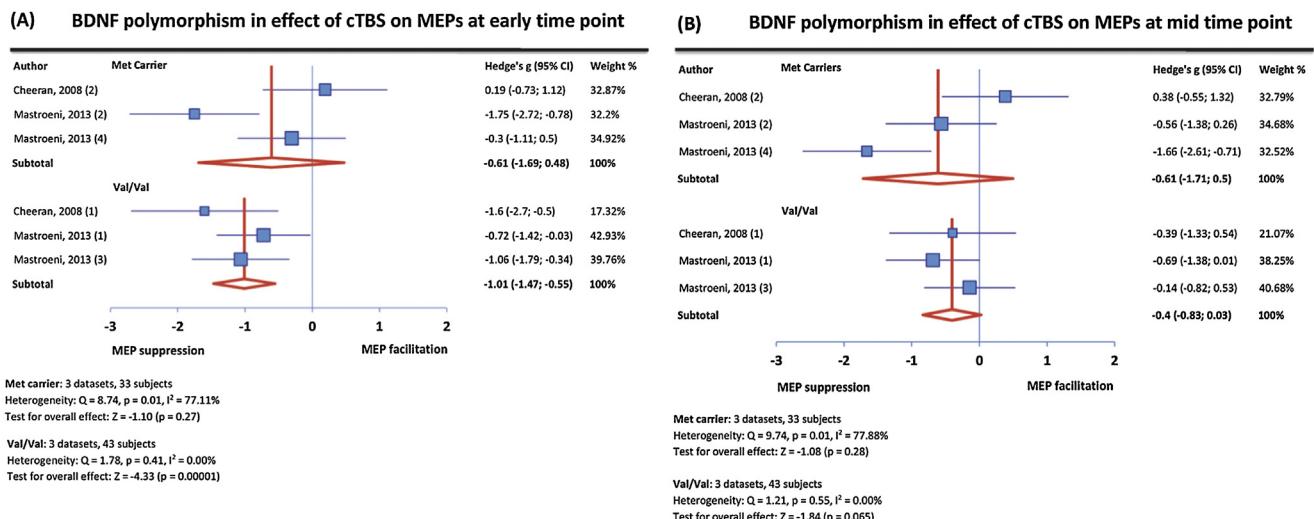


Fig. 10. Forest plot of the Hedge's adjusted g analysis for influence of BDNF polymorphism on MEPs amplitude after cTBS measured post 0–5 min (A) and 20–30 min (B).

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	7M: 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	2M: 4F	30.3 ± 3.1	80% aMT, 50 Hz/5 Hz, 150 pulses	10 & 12 ms	FDI
Jacobs et al. (2014)	14	6M: 9F	21.3 ± 1.6 (18–23)	55% rMT, 30 Hz/6 Hz, 600 pulses	10 ms	FDI
McAllister et al. (2009)	9	4M: 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*	11M: 7F	31 ± 5 (26–45)	80% aMT, 50 Hz/5 Hz, 600 pulses	10 ms	FDI
Talelli et al. (2007)	8*	9M: 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.

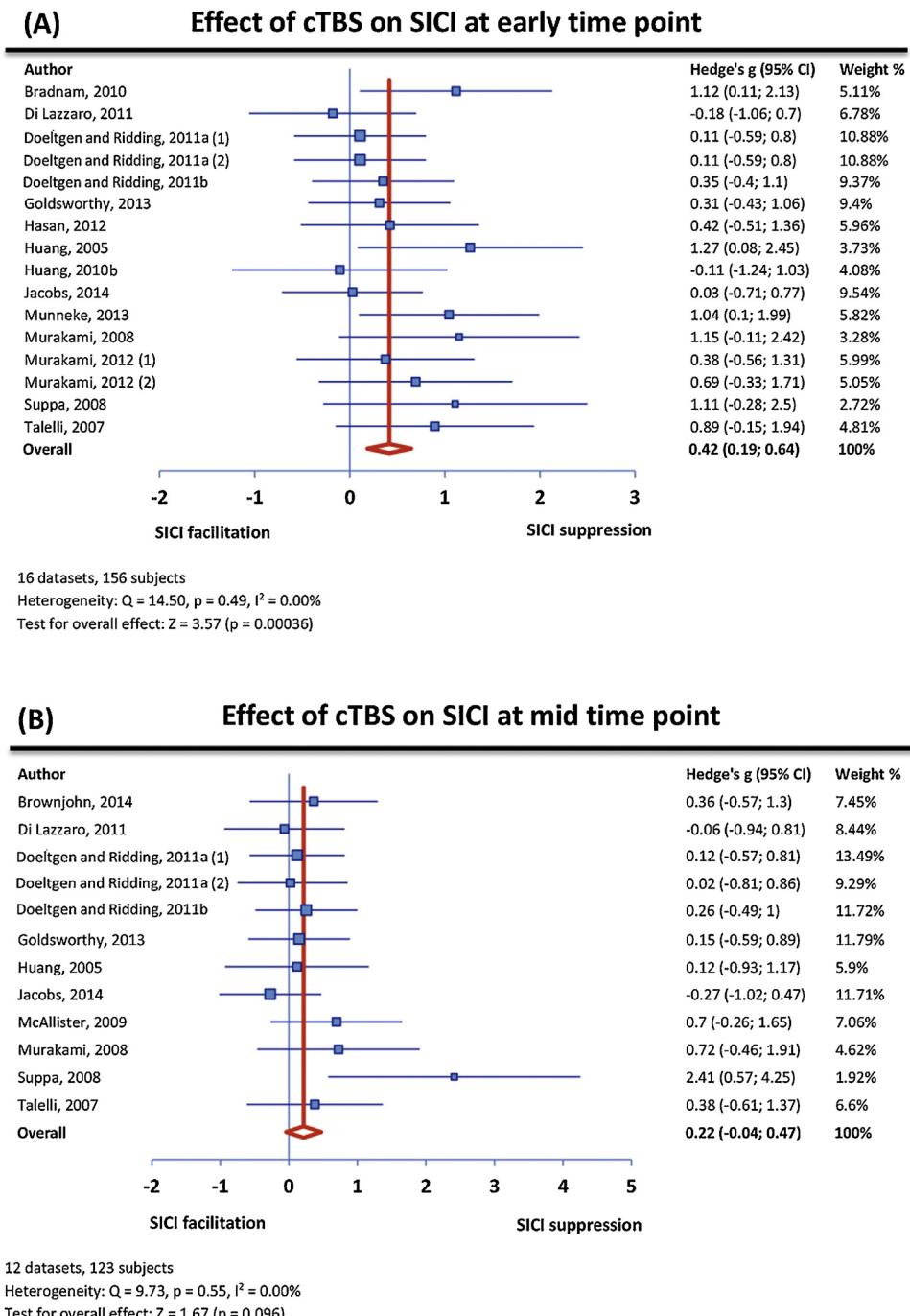


Fig. 11. Forest plot of the Hedge's adjusted g analysis for SICI after cTBS measured post 0–5 min (A) and 20–30 min (B).

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 intensities 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 inter-stimulus 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

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 (606907). PBF has received equipment for research from MagVenture A/S, Medtronic Ltd., Cervel Neurotech and Brainsway Ltd., and funding for research from Cervel Neurotech. There are no other conflicts.

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>.

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