The effects of rTMS on impulsivity in normal adults: a systematic review and meta-analysis

Authors

Cheng-Chang Yang[1]*, Birgit Völlm[1], Najat Khalifa[1]

[1]Division of Psychiatry and Applied Psychology, School of Medicine,

University of Nottingham, UK

***Author for correspondence**

Contact information:

Institute of Mental Health

University of Nottingham Innovations Park

Triumph Road

Nottingham, NG7 2TU

UK

Cheng-Chang Yang	Email: cheng-chang.yang@nottingham.ac.uk
Birgit Völlm	Email: birgit.vollm@nottingham.ac.uk
Najat Khalifa	Email: najat.khalifa@nottingham.ac.uk

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Abstract

Background: Impulsivity is a multi-dimensional construct that is regarded as a symptom of many psychiatric disorders. Harm resulting from impulsive behaviour can be substantial for the individuals concerned, people around them and the society they live in. Therefore, the importance of developing therapeutic interventions to target impulsivity is paramount.

Aims and methods: We conducted a systematic review and meta-analysis of the literature from AMED, Embase, Medline, and PsycINFO databases on the use of repetitive transcranial magnetic stimulation (rTMS) in healthy adults to modulate different subdomains (motor, temporal and reflection) of impulsivity.

Results: The results indicated that rTMS has distinct effects on different impulsivity subdomains. It has a significant, albeit small, effect on modulating motor impulsivity (g = 0.30, 95% CI, 0.17 to 0.43, p < .001) and a moderate effect on temporal impulsivity (g = 0.59, 95% CI, 0.32 to 0.86, p < .001). Subgroup analyses (e.g., excitatory vs. inhibitory rTMS, conventional rTMS vs. theta burst stimulation, analyses by stimulation sites, and type of outcome measure used) identified key parameters associated with the effects of rTMS on motor and temporal impulsivity. Age, sex, stimulation intensity and the number of pulses were not significant moderators for effects of rTMS on motor impulsivity. Due to lack of sufficient data to inform a meta-analysis, it has not been possible to assess the effects of rTMS on reflection impulsivity.

Conclusions: The present findings provide preliminary evidence that rTMS can be used to modulate motor and temporal impulsivity in healthy individuals.

Further studies are required to extend the use of rTMS to modulate impulsivity in those at most risk of engaging in harmful behaviour as a result of impulsivity, such as patients with offending histories and those with a history of self-harming behaviour.

Key words:

Impulsivity; TMS; theta burst stimulation; brain stimulation; response inhibition; delay discounting

Introduction

Impulsivity is an important behavioural aspect of our daily life. It encompasses such actions as making premature decisions, favouring immediate over delayed reward, and failure to inhibit prepotent motor responses. Impulsivity is a multi-dimensional concept (Caswell, Celio, Morgan, & Duka, 2016; Evenden, 1999) for which three different facets have been identified based on recent laboratory findings, including motor, temporal and reflection impulsivity. Motor impulsivity, also known as response inhibition, reflects the inability to inhibit a prepotent behavioural response. Delay-discounting (also referred to as temporal impulsivity) reflects failure to delay gratification. Reflection or cognitive impulsivity refers to the tendency to make premature decisions without sampling enough information or disadvantageous decisions which favour risky options (Verdejo-Garcia, Lawrence, & Clark, 2008).

Several brain areas have been implicated in impulsivity (Fineberg et al. 2014). A fronto-subcortical network encompassing the right inferior frontal gyrus (rIFG) and basal ganglia (Aron & Poldrack, 2005; Chambers, Garavan, & Bellgrove, 2009; Juan & Muggleton, 2012; Wilbertz et al., 2014) has been implicated in motor impulsivity, whereas a fronto-limbic network encompassing ventromedial prefrontal cortex (VMPFC), anterior cingulate cortices (ACC) and basal ganglia is thought to play an important role in temporal impulsivity (Peters & Buchel, 2011). In contrast, the neurobiological underpinning of reflection impulsivity appears to have received less attention in the literature.

Impulsivity plays a prominent role in psychopathology (Cyders, 2013) and has been regarded as a symptom of several psychiatric disorders, such as attention deficit hyperactivity disorder (Musser, Galloway-Long, Frick, & Nigg, 2013), schizophrenia (Matsuzawa, Shirayama, Niitsu, Hashimoto, & Iyo, 2015), obsessive compulsive disorder (Endrass et al., 2010), impulse-control disorders, borderline personality disorder, antisocial personality disorder, bipolar affective disorder, and substance use disorders (American Psychiatric Association, 2013; Fineberg et al., 2014). Impulsivity may partly explain the high rates of suicide and offending behaviour associated with some of these disorders particularly borderline personality disorder (Brevet-Aeby, Brunelin, Iceta, Padovan, & Poulet, 2016). In addition, impulsivity in early life is regarded as a significant predictor of future physical health and delinquent behaviour (Moffitt et al., 2011). Furthermore, impulsivity has been included as a core criminogenic factor in classical criminology theories (Gottfredson (Gottfredson & Hirschi, 1990) and an important risk factor of violence among both normal (Chamorro et al., 2012) and clinical populations (Bjørkly, 2013; Singh, Serper, Reinharth, & Fazel, 2011).

The literature reviewed above indicates that in some clinical populations, impulsivity may play a role in such behaviours as aggression, self-harm or suicidality and substance abuse and this in conjunction with other emotional and psychological factors, may cause significant distress for the individual concerned and people around them. Given such consequences, the importance of developing interventions to target impulsive behaviour is paramount. While conventional psychological and pharmacological interventions have been used to target impulsivity within the rubric of wider

dysfunctional behaviour (Tomko, Bountress, & Gray, 2016), there currently exist no specific interventions to target impulsivity.

Evidence is accumulating that Transcranial Magnetic Stimulation (TMS) can be used to modulate impulsivity. TMS is a non-invasive technique that has been used to modulate brain activity via brief, high-intensity magnetic pulses delivered through an electromagnetic coil placed on the surface of scalp over the brain area of interest. The stimulation pulses are generated by passing currents with a stimulator through the coil, producing a focal magnetic field which induces localised neuronal depolarization in the area beneath the coil (Wagner, Valero-Cabre, & Pascual-Leone, 2007). Repetitive TMS (rTMS) refers to delivering multiple stimuli in trains instead of single-pulse stimulation over the target cortical region. The frequency of rTMS determines its effect on the neurons of the targeted brain regions. Low frequency rTMS of about 1 Hz, exerts an inhibitory function by reducing cortical excitability, whereas high frequency rTMS of about 5 Hz or more typically has a facilitatory effect, which tends to increase cortical excitability. Recently, a newer form of high-frequency rTMS protocol, namely theta burst stimulation (TBS) which exerts similar effects on brain activity but with lower magnetic intensity, has been utilised (Rossini et al., 2015; Thut & Pascual-Leone, 2010). TBS entails delivering pulses in bursts of three stimuli at 50 Hz with an inter-burst interval of 200 ms. Intermittent TBS (iTBS) enhances cortical excitability whereas continuous TBS (cTBS) has the opposite effect (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005).

The utility of TMS in modulating brain activity has been demonstrated in the field of neuroscience (Luber & Lisanby, 2014). Additionally, over the past two decades, rTMS has widely been used to treat a variety of neurological and psychiatric disorders (Wassermann & Zimmermann, 2012), including depression (Sabesan et al., 2015), obsessive-compulsive disorder (Mantovani, Simpson, Fallon, Rossi, & Lisanby, 2010), migraine, and Parkinson's disease (Benninger et al., 2012). It has also been used to modulate impulsivity with some promising results (Brevet-Aeby et al., 2016). Existing reviews have paid attention to the excitatory or inhibitory effect of rTMS on various dimensions of impulsivity, but to our knowledge, no meta-analysis has been conducted to comprehensively assess the efficacy of rTMS in the neuromodulation of impulsivity. There is a dearth of literature on the use of rTMS to modulate impulsivity in clinical populations, and the extant literature in the field is not sufficiently large to inform a meta-analysis. Therefore, studies involving healthy subjects are potentially relevant and can help elucidate the effects of rTMS on specific domains of impulsivity and provide comparison data for groups diagnosed with specific disorders. This is supported by the view that symptoms of mental disorders are displayed on a continuum along normality, and the difference between the two is one of degree (Holroyd & Umemoto, 2016). In support of this view, Zisner and Beauchaine (2016) found that normal variations in impulsive tendencies are reflected in core aspects of personality while variations in trait impulsivity confer vulnerability to clinical psychopathology.

With this in mind, we aimed to conduct a systematic review and meta-analysis of prospective empirical studies on the effects of rTMS on impulsivity in

healthy adults. Specifically, we aimed to determine which rTMS parameters or brain regions are associated with prominent effects on specific subdomains of impulsivity. The main advantage that this study confers over previous reviews in that is has systematically examined the effects of TMS on domains of impulsivity using meta-analytic technique. This has the added advantage of providing precise estimates of the efficacy of TMS in modulating impulsivity and identifying and measuring sources of heterogeneity among studies. This line of enquiry helps inform the design of future studies to better understand the neurobiology of such behaviour to guide future interventions.

Methods

We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement (Liberati et al., 2009; Moher, Liberati, Tetzlaff, Altman, & The PRISMA Group, 2009) in the reporting of our findings. The predetermined criteria, in terms of population, interventions, comparators, outcomes and study designs (PICOS), were followed to identify potentially eligible studies for the systematic review and meta-analyses.

Eligibility Criteria

Empirical studies were included in the review if they (1) involved healthy adult participants, (2) used rTMS as an active intervention, (3) had a comparison group or control condition, and (4) used at least one behavioural task to measure impulsivity. Studies involving children or people with neuropsychiatric disorders were excluded. The definitions of impulsivity and its subdomains were in accordance with previous literature (Caswell, Bond, Duka, & Morgan, 2015; Verdejo-Garcia et al., 2008). The behavioural tasks measuring impulsivity included, but were not limited to, the following tasks. Tasks measuring motor impulsivity included the Stop Signal Task (SST; Logan, 1994), the Go-No-Go task (GNG; Conners, Epstein, Angold, & Klaric, 2003), and the Stroop Colour and Word Test (SCWT; Stroop, 1935) and their variant versions. Tasks measuring temporal impulsivity included the Delay Discounting Task. The Information Sampling Task (Clark, Robbins, Ersche, & Sahakian, 2006) and tasks involving risky or disadvantageous decisions, such as the Ballon Analogue Risk Task (Lejuez et al., 2002) and the Iowa Gambling Task (Bechara, Damasio, Damasio, & Anderson, 1994), were

included to index reflection impulsivity. No restrictions were imposed in respect of publication date or language.

Information Sources and Search

The literature search was performed on four electronic databases (AMED, Embase, Medline, PsycINFO) until 17th February 2017. ”Transcranial magnetic stimulation”, ”TMS“, "theta burst stimulation" or "TBS" combined with “impulsiv*”, "self-regulation", "inhibitory control", "impulse control", "delay discounting", "response inhibition", "information sampling", "stop signal", "temporal discounting", "stroop", "inhibition", "go-no-go" were searched as keywords. The first author (CCY) performed the search and the search terms were confirmed after discussion with the other two authors (NK and BV). Filters regarding the age of participants (adult) and publication type were added where applicable. No language restriction was set. The full search strings are shown in Table S1. References of candidate citations were searched manually for potentially eligible studies missed by the electronic searches.

Study Selection

The articles identified via the search strategy were initially screened by titles and abstracts by the first author (CCY) to identify potentially eligible studies as defined by the PICOS criteria. The full texts of the potentially eligible articles were then reviewed in detail by the same author. In cases where eligibility for inclusion was unclear, the other two authors (NK and BV) independently reviewed the articles, and the final decision on inclusion was reached through consensus.

Data Collection Process and Data Items

Data extraction was performed by the first author (CCY) in discussion with the other authors. The authors regularly discussed the data collection process to resolve disagreements and to ensure consistency. A standardised form was used to extract information concerning authors, study objectives, sample characteristics, inclusion and exclusion criteria, study design, experimental processes, rTMS protocols, outcome variables, and analytic strategy. In cases where the means and standard deviations of key outcome measures were only presented in the diagrams, these parameters were estimated from the available figures.

Risk of Bias in Individual Studies

The methodological quality and the risk of bias for each study were assessed using the Quality Assessment Tool for Quantitative Studies (National Collaborating Centre for Methods and Tools, 2008). This was in accordance with recommendations by the Cochrane Collaboration (Armstrong, Waters, & Doyle, 2011). The domains of assessment included selection bias, study design, confounders, blinding, data collection method, and withdrawals and dropouts. The quality assessments included supplementary information on adverse effects. This quality assessment allowed us to classify studies as having a low, moderate, or high quality. Study quality was assessed by a single reviewer with verification by a second reviewer (BV).

Summary Measures

The effect size was recorded as a positive value if the effect of active rTMS was in the predicted direction and a negative one if it was in the opposite

direction. For example, post inhibitory rTMS performance would be expected to be worse than the baseline one. Moreover, in cases where a study entailed stimulation of multiple sites within the same study, stimulation at each site was regarded as a standalone trial for the purpose of effect size calculation. Each trial was used as the unit of analysis to obtain the effect size in the meta-analysis. Since some studies included more than one effect, this nesting of effects within studies violates assumptions of independence and may contribute to imprecise effect size calculations (Borenstein, Hedges, Higgins, & Rothstein, 2009b). To adjust for the correlation of effects within studies, a multi-level model analysis was conducted using the Generalized Linear Latent and Mixed Model (gllamm) in STATA (Rabe-Hesketh, Skrondal, & Pickles, 2002, 2005) for meta-analysis. For studies involving more than one control group or condition (e.g., one group receiving rTMS at a control site and another receiving sham stimulation), only the comparison between experimental and sham group (condition) was selected. The effect sizes, represented as unbiased Hedges ' *g* and 95% confidence intervals (CIs), were computed by dividing the pre- and post-stimulation differences between experimental (real stimulation) and control (sham stimulation) conditions by the pooled pre-stimulation standard deviation (Morris, 2008).

Synthesis of Results & Measures of Inconsistency

It is well established that measures of impulsivity subdomains correlate weakly, if at all, with each other (e.g., Caswell et al. 2015; Yang, Khalifa, & Völlm, 2018) due to having distinct neurobiological underpinnings (Fineberg et al., 2014). Therefore, we aimed to conduct a series of meta-analyses with the random-effects model to assess the effect of rTMS by subdomains of

impulsivity; namely motor, temporal and reflection impulsivity. The *Q,* I^2 and T^2 statistics (Higgins & Thompson, 2002; Higgins, Thompson, Deeks, & Altman, 2003) were used to assess heterogeneity between studies. *Q* provides significance testing for heterogeneity (*p*-value ≤ .05) which is calculated as the weighted sum of squared deviations of each study's effect size from the overall mean effect size (Borenstein, Hedges, Higgins, & Rothstein, 2009a). I^2 estimates the percentage of the variability in effect estimates that is due to heterogeneity rather than chance. An I^2 value of greater than 50% was deemed as indicative of moderate heterogeneity (Deeks, Higgins, & Altman, 2011). As I^2 is a measure of relative heterogeneity, T^2 is the variance of the true effect sizes, as an estimate of absolute heterogeneity. When T^2 increases, the observed variance increases or the variance within-studies decreases (Borenstein, Hedges, & Rothstein, 2007).

Risk of Bias - Publication Bias

Funnel plots (Egger & Smith, 1995), the Egger test (Egger, Smith, Schneider, & Minder, 1997), and Begg and Mazumdar rank correlation tests (Begg & Mazumdar, 1994) were used to test for the presence of a potential publication bias.

Additional Analyses

To identify variables contributing to alternation of impulsivity, pre-specified subgroup analyses were performed with the unit of trial by merging the data according to the rTMS parameters, including effects ("excitatory" vs. "inhibitory"), type of rTMS ("conventional rTMS" vs. "TBS"), stimulation sites, and tasks of outcome measurements. Meta-regression was employed to

examine the impact of between-study variation on study effect sizes using mean age and male ratio of the participants, intensity of stimulation, and total number of pulses per condition as predictor variables. All quantitative analyses were performed using Stata 15 (StataCorp, 2017).

Results

Study Selection

Of the 3423 citations originally identified, 28 publications met the study inclusion criteria and were included in the systematic review; however, one article (Upton, Cooper, Laycock, Croft, & Fitzgerald, 2010) was excluded from the meta-analyses due to inability to obtain the effect size (Fig. 1).

Insert Figure 1 Here

Study Characteristics

Characteristics of selected studies categorised by the subtypes of impulsivity are summarised in Table 1.

Insert Table 1 Here

In summary, 28 studies involving a total of 599 participants (51.6% male; mean age: 30.16 years; range: 18-70 years) were included in the quantitative synthesis. Eleven of the included studies were conducted in Europe, seven in East Asia, six in North America, three in Australia, and one in Brazil.

The most common study design employed was a counterbalanced crossover design (19 studies), followed by randomised crossover (6 studies) and randomised controlled parallel-group (3 studies) designs. The majority of studies selected focused on motor impulsivity (22 studies) while five studies (Cho et al., 2010; Cho et al., 2015; Cho et al., 2012; Figner et al., 2010; Sheffer et al., 2013) focused on temporal impulsivity and only one study (Knoch et al., 2006) on reflection impulsivity. Various tasks were used to assess impulsivity. For motor impulsivity, the SST and it variants were used in

twelve studies, GNG in six studies, SCWT in five studies, and the Negative Affective Priming task (NAP) in one study (Leyman, De Raedt, Vanderhasselt, & Baeken, 2009). Five different computerised delay-discounting tasks were used in the studies exploring temporal impulsivity and one risk-taking task (Rogers et al., 1999) was selected to index reflection impulsivity in one study (Knoch et al., 2006). All studies delivered a single rTMS session per condition, except for one study (Kim, Han, Ahn, Kim, & Kim, 2012) which applied five rTMS sessions over five consecutive days. The number of pulses within each experimental session ranged from 150 (Cho et al., 2015) to 1600 (Huang, Su, Shan, & Wei, 2004).

Regarding the stimulation sites, the dorsolateral prefrontal cortex (DLPFC) was the most commonly targeted area; the right DLPFC (RDLPFC) was selected in six studies and the left DLPFC (LDLPFC) in fourteen studies. The rIFG (6 studies) and pre-supplementary motor area (pre-SMA; 5 studies) were targeted in several studies. The most common control condition (17 studies) entailed tilting the coil to divert the magnetic pulses away from the scalp. Six studies (Dambacher et al., 2014; Figner et al., 2010; Muggleton, Chen, Tzeng, Hung, & Juan, 2010; Sheffer et al., 2013; Watanabe et al., 2015) used a sham coil, three (Bermpohl (Bermpohl et al., 2005; Chen, Muggleton, Tzeng, Hung, & Juan, 2009; Cho et al., 2015) used a control site stimulation, one (Grossheinrich et al., 2009) used another stimulation mode, and one study (Knoch et al., 2006) did not report details about the sham method.

Risk of Bias within Studies

All 28 included studies attracted a “moderate” quality rating (Table S2). This was largely due to poor ratings on selection bias. Only eleven studies reported on adverse effects relating to rTMS administration, of which eight studies found no significant adverse effects (Cho et al., 2012; Figner et al., 2010; Huang et al., 2004; Hwang, Kim, Park, Bang, & Kim, 2010; Knoch et al., 2006; Obeso, Robles, Marron, & Redolar-Ripoll, 2013; Verbruggen, Aron, Stevens, & Chambers, 2010; Zandbelt, Bloemendaal, Hoogendam, Kahn, & Vink, 2013), and three studies (Dambacher et al., 2014; Grossheinrich et al., 2009; Wagner, Rihs, Mosimann, Fisch, & Schlaepfer, 2006) reported adverse events in seven participants whereas the other seventeen studies did not provide any information regarding tolerability or adverse events (Table S2).

Synthesis of Results

Separate meta-analyses were conducted for studies involving the subdomains of impulsivity as described below.

Insert Figures 2a to 2b Here

Effects of rTMS on Motor Impulsivity

The meta-analysis of 41 effect sizes from 21 studies on the effects of rTMS on motor impulsivity showed a positive and significant mean effect size (g = 0.30, 95% CI, 0.17 to 0.43, $p < .001$; see also Fig. 2a). No significant heterogeneity was found across trials (Q_{40} = 53.91, p = .070; I^2 = 25.8%; T^2 = 0.047). The results were further confirmed using multi-level modelling analysis to adjust for potential bias resulting from within-studies correlation of multiple effects (g = 0.29, 95% CI, 0.15 to 0.43, $p < .001$). The between-studies (T^2 = 0.026) and between-trials (T^2 = 0.008) variances were all very small. No publication bias

was indexed by the funnel plot (Fig. S2a), the Begg's test (z = 1.20, p = .23), or the Egger's test (intercept$_{41}$ = 1.188, t = 1.64, 2-tailed p = .109).

Insert Table 2 Here

Additional Analyses

The subgroup analyses (Table 2) revealed positive and significant mean effects for both inhibitory (g = 0.27, 95% CI, 0.13 to 0.41, p < .001) and excitatory rTMS (g = 0.36, 95% CI, 0.06 to 0.65, p = .018), and the magnitude of effect sizes did not significantly differ between inhibitory and excitatory rTMS (β = 0.051, p = .730). Moreover, subgroup analysis by rTMS type revealed significant mean effect sizes for both conventional rTMS (g = 0.26, 95% CI, 0.07 to 0.45, p = .009) and TBS (g = 0.39, 95% CI, 0.20 to 0.58, p < .001), with no significant difference between the magnitude of these effects (β = -0.056, p = .694). Sub-analysis by stimulation site revealed significant mean effect sizes only for the LDLPFC (g = 0.26, 95% CI, 0.07 to 0.46, p = .007), rIFG (g = 0.42, 95% CI, 0.11 to 0.73, p = .008), medial prefrontal cortex (MPFC; g = 0.60, 95% CI, -0.16 to 1.36, p = .040), and right frontal eye field (rFEF; g = 1.30, 95% CI, 0.58 to 2.03, p < .001), while the mean effect sizes for RDLPFC (g = 0.24, 95% CI, -0.18 to 0.66, p = .267), SMA (g = -0.09, 95% CI, -0.47 to 0.28, p = .626) and right Pre-SMA (g = 0.29, 95% CI, -0.05 to 0.62, p = .098) were non-significant. Only the magnitude of effect sizes from rFEF significantly differed from those in other locations (β = 1.291, p < .001). Trials targeting other sites were excluded from the subgroup analysis if the number of effect sizes was less than two. Further subgroup analyses were performed to examine the effects of inhibitory and excitatory rTMS at LDLPFC

and rIFG, brain areas that have been consistently implicated in impulsivity. The inhibitory rTMS at LDLPFC yielded an insignificant effect (g = 0.38, 95% CI, -0.01 to 0.78, p = .055). In contrast with this, excitatory rTMS at LDLPFC revealed a small but significant effect (g = 0.23, 95% CI, 0.00 to 0.45, p = .047). However, there was no significant difference between the magnitude of these effects (β = -0.158, p = .508). It has not been possible to conduct similar subgroup analysis in relation to the effects of TMS of the rIFG due to lack of sufficient data. Finally, the subgroup analysis for type of outcome measure used revealed significant mean effect sizes for GNG (g = 0.24, 95% CI, 0.05 to 0.42, p = .012), SST (g = 0.32, 95% CI, 0.10 to 0.55, p = .005) and SCWT tasks (g = 0.35, 95% CI, 0.02 to 0.68, p = .036). However, SST (β = 0.086, p = .826), SCWT (β = 0.041, p = .924), and GNG (β = -0.142, p = .721) were not significantly more sensitive to detect changes than other measurements, combined.

The meta-regression analysis across trials showed that none of the between-study variables significantly predicted the effects of rTMS (mean age of participants: β = 0.008, p = .509; male ratio: β = -0.300, p = .444; intensity of stimulation: β = -0.004, p = .229; number of pulses per condition: β = 0.000, p = .525).

Effects of rTMS on Temporal Impulsivity

The meta-analysis of seven effect sizes from five studies on the effects of rTMS on temporal impulsivity showed a significant medium mean effect (g = 0.59, 95% CI, 0.32 to 0.85, p < .001) without significant heterogeneity (Q_6 = 6.38, p = .382; I^2 = 6.0%; T^2 = 0.008; see also Fig. 2b). The results were

confirmed using the multi-level model analysis after adjusting for the nesting of multiple effects within studies (g = 0.59, 95% CI, 0.31 to 0.87, p < .001) where the between-studies (T^2 < 0.001) and between-trials (T^2 = 0.017) variances were all very small. The funnel plot (Fig. S2b), the Egger's test (intercept$_7$ = -0.655, t = -0.54, 2-tailed p = .615), and the Begg's test (z = 0.00, p = 1.00) did not show evidence of publication bias.

Additional Analyses

The subgroup analyses (Table 2) revealed significant mean effects for both inhibitory (g = 0.71, 95% CI, 0.21 to 1.21, p = .005) and excitatory rTMS (g = 0.54, 95% CI, 0.16 to 0.92, p = .006). Moreover, the subgroup analysis by rTMS type revealed a significant mean effect size for conventional rTMS (g = 0.65, 95% CI, 0.28 to 1.03, p = .001) but not for TBS (g = 0.33, 95% CI, -0.31 to 0.97, p = .315). Furthermore, the subgroup analysis by stimulation sites revealed a significant mean effect size for the LDLPFC (g = 0.76, 95% CI, 0.29 to 1.22, p = .002) but a non-significant mean effect size for the RDLPFC (g = 0.33, 95% CI, -0.31 to 0.97, p = .315). The meta-regression analysis and further comparison of the subgroup analysis were not conducted because there were fewer than ten effects in the meta-analysis (Deeks et al., 2011).

Effects of rTMS on Reflection Impulsivity

The only one study (Knoch et al., 2006) conducted in the field consisted of two effect sizes (1 Hz rTMS at LDLPFC: g = -0.24, 95% CI, -1.42 to 0.95; 1 Hz rTMS at RDLPFC: g = 0.95, 95% CI, -0.21 to 2.12); therefore, no further analysis was conducted.

Discussion

To our knowledge, this is the first systematic review and meta-analysis focusing on the evidence for the effectiveness of rTMS on impulsivity and its subdomains. Our results are broadly compatible with the suggestion (e.g., Zaman, 2014) that rTMS is an efficient tool for modulating impulsivity. Overall, the current evidence is sufficiently robust to determine the effect of rTMS on motor impulsivity in healthy participants, our current positive finding of rTMS on temporal impulsivity might be updated with accumulating literature considering only a limited number of studies in this field. Moreover, a dearth of research on reflection impulsivity was noted and all reviewed studies focused on short-term effect. The findings of differential effects for rTMS on subdomains of impulsivity support the idea that these subdomains are heterogeneous in nature (Bari & Robbins, 2013).

The meta-analysis of rTMS studies relating to motor impulsivity revealed a small but positive and significant effect size, which is consistent with previous review literature (Juan & Muggleton, 2012). A non-significant level of heterogeneity indicated that the variability in effect sizes was relatively small. The subgroup analyses identified the key parameters associated with a positive effect for rTMS on impulsivity. These revealed a number of important findings as follows. Both inhibitory and excitatory rTMS yielded significant though small effects indicating that either protocol can be used to modulate impulsivity (Brevet-Aeby et al., 2016). Although both conventional rTMS and TBS yielded similar effects on motor impulsivity, a significant heterogeneity of the effects in conventional rTMS was noted. This supports the idea that TBS is associated with more consistent magnitude and directions of aftereffects

compared to those found following conventional rTMS (Thut & Pascual-Leone, 2010). Subgroup analysis by the stimulation sites revealed significant effects on certain brain areas including the LDLPFC, rIFG, rFEF and MPFC. A recent review (Brevet-Aeby et al., 2016) has favoured the rIFG as a potential site for stimulation when using rTMS to modulate impulsivity and the functional activation of the rIFG has been consistently linked to response inhibition (Bari & Robbins, 2013). It is notable that no studies to date have examined the effects of excitatory rTMS on the rIFG, an important area for future studies to explore. As the right pre-SMA has been commonly identified in the network connecting the IFG and subthalamic nucleus involved in response inhibition, it is noteworthy that only a non-significant effect was found on the right pre-SMA stimulation. One possible explanation is that the pre-SMA may not play the same role as rIFG during the process of response inhibition and the conventional SST outcome measures may not directly link to the activation level of the pre-SMA (Cai, Cannistraci, Gore, & Leung, 2014). Other studies identified the rFEF as a potential site for stimulation (Hung, Driver, & Walsh, 2011). It is notable that this study entailed the use of visual stimuli, indicating that the rFEF may have a specific role in the top-down control of visual attention. The role of rFEF in controlling motor impulsivity, as indexed by use of non-visual stimuli, is yet to be established. While the DLPFC is regarded as a crucial region implicated in executive control of response inhibition (Bari & Robbins, 2013) and reward-anticipation (Ehrlich et al., 2015), only the stimulation of the LDLPFC was found to have a significant effect on motor impulsivity. It may be too simplistic to deduce that brain stimulation at LDLPFC alone led to changes in motor impulsivity (Loftus,

Yalcin, Baughman, Vanman, & Hagger, 2015). One possible explanation for this is that in normal healthy participants, the finding may be attributable to changes in the interhemispheric balance of activation across the DLPFC. Another possible explanation is that, contrary to conventional views, LDLPFC may play a more important role in motor impulsivity than RDLPFC. For example, reduced LDLPFC activation has been associated with poor response control in obese populations (Brooks, Cedernaes, & Schiöth, 2013). In addition, findings from recent structural neuroimaging studies (e.g., Cho et al., 2013; Tu, Kuan, Li, & Su, 2017) suggest that only the grey matter volume in LDLPFC but not RDLPFC correlates with self-report measures of impulsivity. The third possible explanation is that the rTMS modulation effect on DLPFC may be only reflected by the tasks measuring proactive rather than reactive motor inhibition (Brevet-Aeby et al., 2016). Moreover, neuroimaging studies (e.g., Floden, Vallesi, & Stuss, 2011) have shown that the degree of activation in the LDLPFC correlates with proactive motor inhibition performance. In conclusion, given that both excitatory and inhibitory rTMS exhibit similar effects at LDLPFC in motor impulsivity, LDLPFC is suggested to be a prioritised target for neurostimulation in relation to motor impulsivity.

Subgroup analysis by types of outcome measures used revealed insignificant differences between the magnitude of effects on three key tasks (i.e., GNG, SST, SCWT) indicating their similar utility in assessing motor impulsivity in future studies. Moreover, only the effect sizes from SST yielded a small to moderate level of heterogeneity. The source of variability might be from the different versions of SST used among studies. Furthermore, given that SST is regarded as a measure of reactive motor control (Verbruggen & Logan,

2008) and GNG and SCWT as measures of proactive motor control (Aron, 2011; Smittenaar et al., 2015), future studies should select appropriate outcome measures according to their objectives.

The results of the meta-regression revealed no differential effects in relation to participant characteristics, such as mean age and sex ratio, or stimulation parameters, in terms of intensity and number of pulses. Some commentators (e.g., Thompson & Higgins, 2002) have argued that using mean age or sex ratio within trials may not be appropriate since the information is averaged and may not reflect the true relationship between the parameters of interest. Caution is required when using the same parameters from conventional rTMS and TBS as covariates in the regression analysis because these paradigms deliver magnetic pulses in different ways. Another possibility is that such relationship may be manifested when a sufficient number of sessions or pulses per session reached since the effects of TMS are dose-dependent. Therefore, to test these hypotheses, future research in this field recruiting a variety of age groups with multiple rTMS sessions is warranted.

The meta-analysis of the effects of rTMS on temporal impulsivity, involving seven effect sizes from five studies identified a positive and significant medium effect size. Subgroup analyses revealed positive and significant medium effects for both inhibitory and excitatory rTMS. They also identified the LDLPFC, but not RDLPFC, as a crucial stimulation site for modulation of temporal impulsivity. The finding regarding laterality needs to be interpreted with caution due to the limited number of studies included, although functional neuroimaging studies (e.g., Ballard & Knutson, 2009) have found positive

associations between the activation of the LDLPFC and temporal impulsivity. Future studies concerning motor impulsivity and temporal impulsivity may therefore consider selecting the LDLPFC as the brain regions of interest.

We were not able to perform a meta-analysis of the effects of rTMS on reflection impulsivity due to the dearth of studies in the field. Although there are a considerable number of transcranial Direct Current Stimulation (tDCS) studies aiming at the neuromodulation effect on reflection impulsivity with inconsistent findings (Brevet-Aeby et al., 2016), the innate limitation of tDCS with low spatial resolution and poor localisation restricts its utility and using rTMS studies to explore the issue is still preferred.

Strengths and Limitations

A major advantage of this review over previous reviews is that it involved conducting a meta-analysis to quantify the effects of rTMS on modulating impulsivity, in terms of the effects on subdomains of impulsivity. The studies included in this review were of moderate quality and this can be regarded as a relative strength given that the field is still in its infancy. However, the studies included in the review suffered several limitations in relation to selection bias, small sample sizes, heterogeneity of designs and outcome measures used, and lack of information on the adverse effects of rTMS. It is notable that studies included in this review attracted poor ratings in relation to selection bias. This is likely due to selection of well-educated young adult participants, such as university students, which limits the generalisability of the findings to other populations. Another major limitation of this study is that is does not examine the impact of rTMS on impulsivity in clinical populations. This was

due to lack of sufficient studies in the field. Nevertheless, studies involving healthy controls are relevant and can provide invaluable information in regard to the effects of rTMS on domains of impulsivity. Moreover, there is a relative dearth of studies involving the use of excitatory rTMS paradigms and those involving temporal and reflection impulsivity. Furthermore, whilst the study applied a rigorous search strategy, it is still possible that it failed to capture all relevant studies due to variations in the conceptualisation of impulsivity across studies. Finally, whilst meta-analytic reviews have inherent advantages, it still holds that pooling data through meta-analysis can cause problems such as non-linear correlations (Greco, Zangrillo, Biondi-Zoccai, & Landoni, 2013).

In addition to addressing the limitations highlighted above, future research should define impulsivity consistently and use a range of outcome measures to better define the differential effects of rTMS on subdomains of impulsivity. It should consider using multiple stimulation sessions as opposed to a single session. It should also consider combining rTMS with neuroimaging techniques to assess the differences between the effects of conventional TMS and connectivity guided TMS in modulating impulsivity to help guide future interventions. Whilst TMS is a relatively easy to administer brain stimulation technique, ethical concerns may arise in relation to its use in the context of impulsivity, particularly in relation to safety issues such as seizures and issues surrounding stigmatisation. Therefore, it is important that participants are well informed of the implications of taking part and carefully selected to ensure their safety (Najib & Horvath, 2014; Rossi, Hallett, Rossini, Pascual-Leone, & The Safety of TMS Consensus Group, 2009).

Conclusions

In conclusion, this meta-analysis provides preliminary evidence that rTMS can be used to modulate impulsivity in healthy individuals, particularly motor impulsivity and temporal impulsivity. Further studies are required to extend the use of rTMS to modulate impulsivity to those who experience most harm from impulsive behaviour such as people with a history of offending or self-harming. Applying excitatory rTMS to clinical populations and tailoring parameters of the rTMS, such as the intensity, location, and stimulation mode (conventional rTMS or TBS), implementation of ecologically validated instruments assessing impulsivity are also strongly recommended.

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Figure captions

Figure 1. The Process of Study Selection and Search Results

Figure 2**.** (a) Statistical summary and forest plot of effect sizes for motor impulsivity. (b) Statistical summary and forest plot of effect sizes for temporal impulsivity.

Abbreviations: AG, angular gyrus; rAI, right anterior insula; cTBS, continuous theta burst ;stimulation; ES, effect size; iTBS, intermittent theta burst stimulation; LDLPFC, left dorsolateral prefrontal cortex; ldPM, left dorsal premotor cortex; LFEF, left frontal eye field; lIFG, left inferior frontal gyrus; MFG, middle frontal gyrus; MPFC, medial prefrontal cortex; QPS, Quadro-pulse stimulation; RDLPFC, right dorsolateral prefrontal cortex; rdPM, right dorsal premotor cortex; rFEF, right frontal eye field; rIFG, right inferior frontal gyrus; rIFJ, right inferior frontal junction; rSFG, right superior frontal gyrus; SMA, supplementary motor area

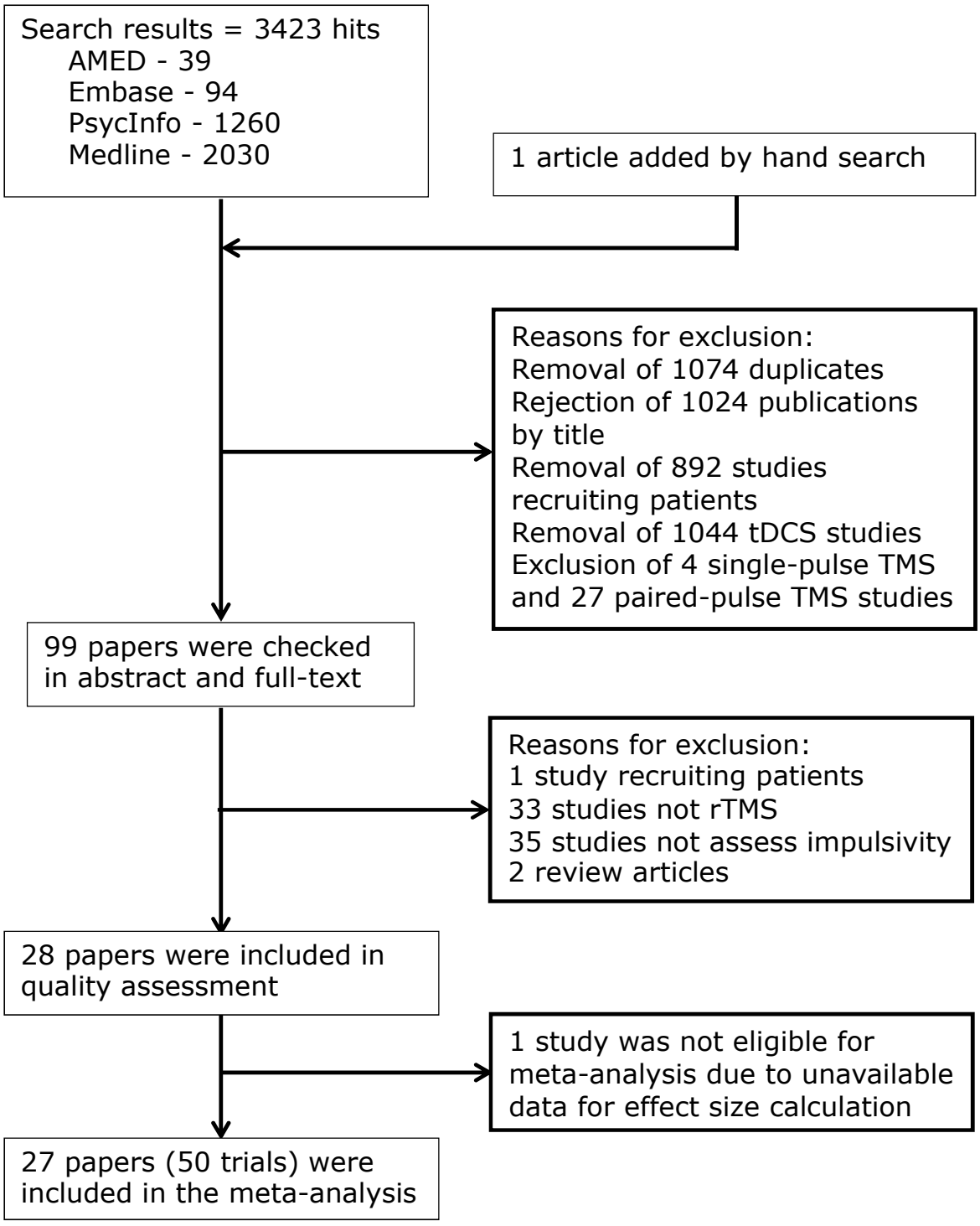
Search results = 3423 hits
AMED - 39
Embase - 94
PsycInfo - 1260
Medline - 2030
1 article added by hand search
Reasons for exclusion:
Removal of 1074 duplicates
Rejection of 1024 publications by title
Removal of 892 studies recruiting patients
Removal of 1044 tDCS studies
Exclusion of 4 single-pulse TMS and 27 paired-pulse TMS studies
99 papers were checked in abstract and full-text
Reasons for exclusion:
1 study recruiting patients
33 studies not rTMS
35 studies not assess impulsivity
2 review articles
28 papers were included in quality assessment
1 study was not eligible for meta-analysis due to unavailable data for effect size calculation
27 papers (50 trials) were included in the meta-analysis

Figure 1

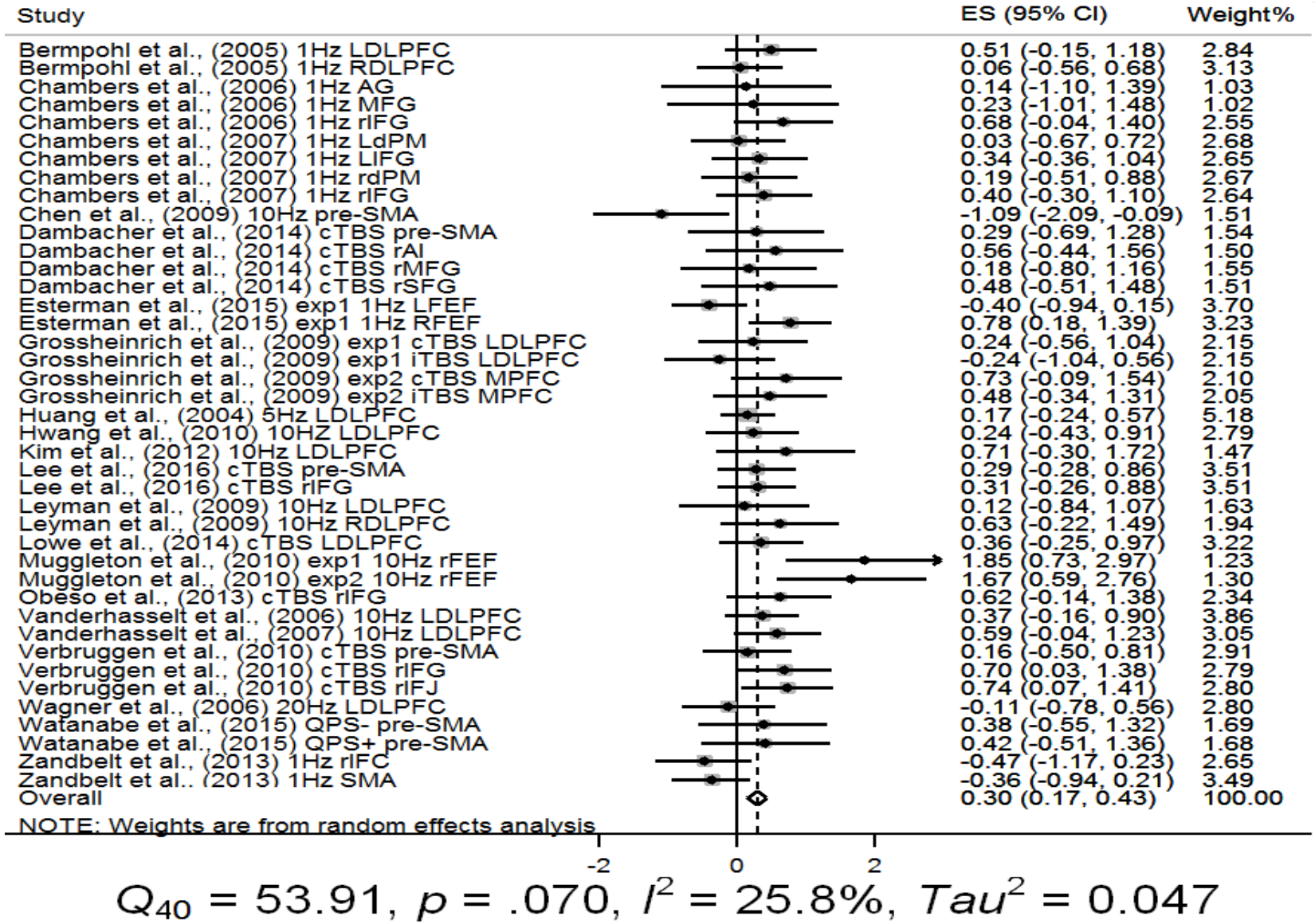
Study
ES (95% CI)
Weight%
Bermpohl et al., (2005) 1Hz LDLPFC 0.51 (-0.15, 1.18) 2.84
Bermpohl et al., (2005) 1Hz RDLPFC 0.06 (-0.56, 0.68) 3.13
Chambers et al., (2006) 1Hz AG 0.14 (-1.10, 1.39) 1.03
Chambers et al., (2006) 1Hz MFG 0.23 (-1.01, 1.48) 1.02
Chambers et al., (2006) 1Hz rIFG 0.68 (-0.04, 1.40) 2.55
Chambers et al., (2007) 1Hz LdPM 0.03 (-0.67, 0.72) 2.68
Chambers et al., (2007) 1Hz LIFG 0.34 (-0.36, 1.04) 2.65
Chambers et al., (2007) 1Hz rdPM 0.19 (-0.51, 0.88) 2.67
Chambers et al., (2007) 1Hz rIFG 0.40 (-0.30, 1.10) 2.64
Chen et al., (2009) 10Hz pre-SMA -1.09 (-2.09, -0.09) 1.51
Dambacher et al., (2014) cTBS pre-SMA 0.29 (-0.69, 1.28) 1.54
Dambacher et al., (2014) cTBS rAI 0.56 (-0.44, 1.56) 1.50
Dambacher et al., (2014) cTBS rMFG 0.18 (-0.80, 1.16) 1.55
Dambacher et al., (2014) cTBS rSFG 0.48 (-0.51, 1.48) 1.51
Esterman et al., (2015) exp1 1Hz LFEF -0.40 (-0.94, 0.15) 3.70
Esterman et al., (2015) exp1 1Hz RFEF 0.78 (0.18, 1.39) 3.23
Grossheinrich et al., (2009) exp1 cTBS LDLPFC 0.24 (-0.56, 1.04) 2.15
Grossheinrich et al., (2009) exp1 iTBS LDLPFC -0.24 (-1.04, 0.56) 2.15
Grossheinrich et al., (2009) exp2 cTBS MPFC 0.73 (-0.09, 1.54) 2.10
Grossheinrich et al., (2009) exp2 iTBS MPFC 0.48 (-0.34, 1.31) 2.05
Huang et al., (2004) 5Hz LDLPFC 0.17 (-0.24, 0.57) 5.18
Hwang et al., (2010) 10HZ LDLPFC 0.24 (-0.43, 0.91) 2.79
Kim et al., (2012) 10Hz LDLPFC 0.71 (-0.30, 1.72) 1.47
Lee et al., (2016) cTBS pre-SMA 0.29 (-0.28, 0.86) 3.51
Lee et al., (2016) cTBS rIFG 0.31 (-0.26, 0.88) 3.51
Leyman et al., (2009) 10Hz LDLPFC 0.12 (-0.84, 1.07) 1.63
Leyman et al., (2009) 10Hz RDLPFC 0.63 (-0.22, 1.49) 1.94
Lowe et al., (2014) cTBS LDLPFC 0.36 (-0.25, 0.97) 3.22
Muggleton et al., (2010) exp1 10Hz rFEF 1.85 (0.73, 2.97) 1.23
Muggleton et al., (2010) exp2 10Hz rFEF 1.67 (0.59, 2.76) 1.30
Obeso et al., (2013) cTBS rIFG 0.62 (-0.14, 1.38) 2.34
Vanderhasselt et al., (2006) 10Hz LDLPFC 0.37 (-0.16, 0.90) 3.86
Vanderhasselt et al., (2007) 10Hz LDLPFC 0.59 (-0.04, 1.23) 3.05
Verbruggen et al., (2010) cTBS pre-SMA 0.16 (-0.50, 0.81) 2.91
Verbruggen et al., (2010) cTBS rIFG 0.70 (0.03, 1.38) 2.79
Verbruggen et al., (2010) cTBS rIFJ 0.74 (0.07, 1.41) 2.80
Wagner et al., (2006) 20Hz LDLPFC -0.11 (-0.78, 0.56) 2.80
Watanabe et al., (2015) QPS- pre-SMA 0.38 (-0.55, 1.32) 1.69
Watanabe et al., (2015) QPS+ pre-SMA 0.42 (-0.51, 1.36) 1.68
Zandbelt et al., (2013) 1Hz rIFC -0.47 (-1.17, 0.23) 2.65
Zandbelt et al., (2013) 1Hz SMA -0.36 (-0.94, 0.21) 3.49
Overall 0.30 (0.17, 0.43) 100.00
NOTE: Weights are from random effects analysis
-2
0
2
$Q_{40} = 53.91,\ p = .070,\ I^2 = 25.8\%,\ Tau^2 = 0.047$

Figure 2 (a)

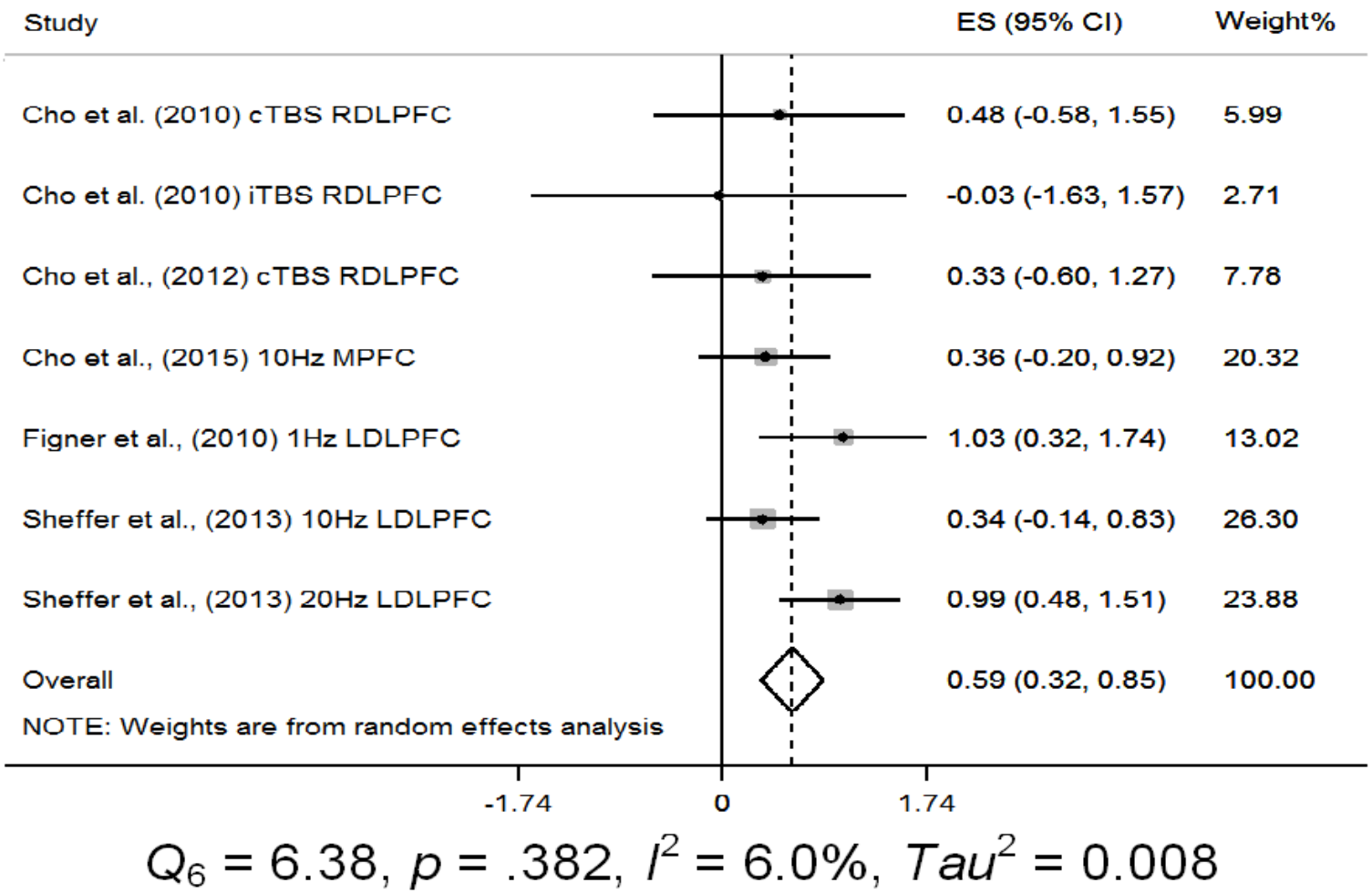
Study
ES (95% CI)
Weight%
Cho et al. (2010) cTBS RDLPFC
0.48 (-0.58, 1.55)
5.99
Cho et al. (2010) iTBS RDLPFC
-0.03 (-1.63, 1.57)
2.71
Cho et al., (2012) cTBS RDLPFC
0.33 (-0.60, 1.27)
7.78
Cho et al., (2015) 10Hz MPFC
0.36 (-0.20, 0.92)
20.32
Figner et al., (2010) 1Hz LDLPFC
1.03 (0.32, 1.74)
13.02
Sheffer et al., (2013) 10Hz LDLPFC
0.34 (-0.14, 0.83)
26.30
Sheffer et al., (2013) 20Hz LDLPFC
0.99 (0.48, 1.51)
23.88
Overall
0.59 (0.32, 0.85)
100.00
NOTE: Weights are from random effects analysis
-1.74
0
1.74
$Q_6 = 6.38,\ p = .382,\ I^2 = 6.0\%,\ Tau^2 = 0.008$

Figure 2 (b)

Table 1 Characteristics of eligible studies

Study/Country	study design	age of participants (mean± SD; range)	N[c], sex ratio (M/F)	target area	rTMS protocol (frequency, intensity, paradigm, number of pulses)	sham method	tasks	outcome measure
Motor impulsivity								
Bermpohl et al., (2005)/ Brazil	CCRT	38.3± 13.9	11, 5/6	RDLPFC LDLPFC	1Hz, 60%MSO (104-187%rMT, mean 151%rMT), off-line, 600	OC stimulation	affective GNG	false alarm rates
Chambers et al., (2006)/ Australia	CCRT	18-27	16, 8/8	rIFG right MFG right AG	1Hz, 92%dMT, off-line, 900	Coil oriented away from the scalp	SST	SSRT
Chambers et al., (2007)/ Australia	CCRT	19-46	16, NA	rIFG, right dPM, lIFG, left dPM	1Hz, 92%rMT in average, off-line, 1200	coil oriented away from the scalp	SST	SSRT
Chen et al., (2009)/ Taiwan	CCRT	25.7; 21-35	7, 7/2	left pre-SMA	10Hz, 60%MSO, online, 960	Vertex stimulation	SST	SSRT
Dambacher et al., (2014)/ Netherlands	CCRT	27±7.27	11, NA	right SFG, right MFG, right AI, right pre-SMA	cTBS, 100%AMT, off-line, 600	sham coil	GNG SST	false alarm rates in GNG; false alarm rates in inhibition trials of SST

Esterman et al., (2015)/ USA	CCRT	20.4 ± 2.4; RFEF(19.43 ± 1.70); LFEF (21.50 ± 2.79)	14, (RFEF: 10/4, 14, LFEF: 5/9)	RFEF, LFEF	1Hz, 110%RMT, off-line, 480	coil oriented 180° away from the scalp	GNG	commission error
Grossheinrich et al., (2009) / Germany	RCRT[b]	20-35	12, 5/7	LDLPFC	iTBS, 80% AMT, off-line, 600	imTBS	GNG	commission error
exp1:					cTBS, 80%AMT, off-line, 600,			
exp2:		22-38	12, 4/8	MPFC	iTBS, 80% AMT, off-line, 600	imTBS	GNG	commission error
					cTBS, 80%AMT, off-line, 600,			
Huang et al., (2004)/ Taiwan	RCRT[b]	27.0± 4.7; 20-37	24, 12/12	LDLPFC	5Hz, 100%RMT, offline, 1600	Tilt coil at 90°	GNG	Percentage of shortening choice reaction time
Hwang et al., (2010)/ South Korea	RCRT[b]	23.53± 2.12	17, 17/0	LDLPFC	10Hz, 90%MT, off-line, 900	Tilt coil at 90°	Conners' CPT (GNG)	mean commission errors
Kim et al., (2012)/ South Korea	RCT[b]	63.13± 4.90	16, 0/16	LDLPFC	10Hz, 30%MSO, off-line, 780 (5 sessions, 3900 in total)	Tilt coil at 90°	modified Stroop	reaction time of incongruent condition
Lee et al., (2016) / Taiwan	CCRT	23±2	24, 18/6	right pre-SMA	cTBS, 40%MSO, off-line, 600	Tilt coil at 90°	conditional SST	SSRT
				rIFG				
Leyman et al., (2009)/	RCRT[b]	21.1± 1.45; 19-24	18, 0/18	LDLPFC	10Hz, 110%RMT, off-line, 1560	Tilt coil at 90°	NAP	NAP scores
Belgium		24± 2.33; 20-30	22, 0/22	RDLPFC	10Hz, 110RMT, off-line, 1560	Tilt coil at 90°	NAP	NAP scores

Lowe et al., (2014)/ Canada	CCRT	21.10±1.86	21, 0/21	LDLPFC	cTBS, 80%RMT, off-line, 600	Tilt coil at 90°	Stroop GNG SST	interference time d' sensitivity proportion of incorrect responses on stop trials
Muggleton et al., (2010)/ Taiwan exp1	RCRT[b]	25.7; 21-35	9, 7/2	rFEF	10Hz, 65%MSO, online, 960	sham coil	SST	SSRT
exp2		22.9; 20-27	9, 5/4	rFEF	10Hz, 65%MSO, online, 960	no stimulation	modified SST	SSRT
Obeso et al., (2013)/ Spain	CCRT	35.40±7.7; 24-44	16, 7/9	rIFG	cTBS, 80%AMT, off-line, 600	Tilt coil at 90° at M1	modified SST	SSRT
Upton et al., (2010)[a]/ Australia	CCRT	26± 3.4; 18-39	14, NA	RDLPFC LDLPFC	1Hz, 110%RMT, off-line, 900	Tilt coil at 90°	SST	NA
Vanderhasselt et al., (2006)/ Belgium	CCRT	23± 4.4; 18-60	28, 0/28	LDLPFC	10Hz, 110%MT, off-line, 1560	Tilt coil at 90°	computeris ed Stroop	reaction time of incongruent condition
Vanderhasselt et al., (2007)/ Belgium	CCRT	24± 2.6; 18-25	20, 0/20	LDLPFC	10Hz, 110%MT, off-line, 1560	Tilt coil at 90°	computeris ed Stroop	reaction time of incongruent condition (high expectancy)
Verbruggen et al., (2010)/ UK	CCRT	25.9; 20-38	18, 9/9	rIFG rIFJ right pre-SMA	cTBS, 70% distance-adjusted MT, off-line, unknown	coil oriented away from the scalp	SST	SSRT
Wagner et al., (2006)/ Switzerland	RCRT[b]	22.3±2.1; 19-26	17, 17/0	LDLPFC	20Hz, 100%RMT, off-line, 1600	Tilt coil at 90°	Stroop	interference time
Watanabe et al.,	CCRT	28-44	10, NA	right pre-	QPS, 90%AMT,	Sham coil	SST	SSRT

(2015)/ Japan				SMA	off-line, 1440			
Zandbelt et al., (2013)/ Neitherlands	CCRT	24.1; 20-38	24, 12/12	rIFG SMA	1 Hz,(special), 90% RMT, for 6 Hz and 110%RMT, for 1Hz, off-line, 600 6Hz,(pulses), 600 1Hz,(pulses)	Sham coil at right superior parietal lobe	stop-signal anticipation task	SSRT
Temporal impulsivity								
Cho et al., (2010)/ Canada	CCRT	22.4±4.3; 18-29	7, 3/4	RDLPFC	iTBS, 80%AMT, off-line, 600 cTBS, 80%AMT, off-line, 600	Tilt coil at 90°	computerised DDT	k-value
Cho et al., (2012)/ Canada	CCRT	22.6±2.7; 18-27	8, 4/4	RDLPFC	cTBS, 80%AMT, off-line, 600	Tilt coil at 90°	computerised DDT	k-value
Cho et al., (2015)/ Canada	CCRT	22.1±2.9; 18-27	24, 13/11	MPFC	10Hz, 80%AMT, off-line, 150	vertex stimulation	computerised DDT	k-value
Figner et al., (2010)/ USA/Switzerland	RCT[b]	19-33	52, 52/0	LDLPFC RDLPFC	1Hz, 54%MSO, off-line, 900	Sham coil	choice task	preference reversals
Sheffer et al., (2013)/ USA	CCRT	41.3±10.4; 19-55	66, 40/26	LDLPFC	20Hz, 110%MT, off-line, 900 10 Hz, 110%MT, off-line, 900	sham coil	DDT	Ln(k-value)
Reflection impulsivity								
Knoch et al., (2006)/ Switzerland	RCT[b]	23.8; 21-31	27, 27/0	RDLPFC LDLPFC	1Hz, 100%MT, off-line, 900	not reported	Risk Task	total points earned

[a] not included in meta-analysis; [b] no randomisation method reported; [c] number of participants start of study

AG, angular gyrus; AI, anterior insula; AMT, active motor threshold; CCRT, counterbalanced crossover trial; cTBS, continuous theta burst ;stimulation; DDT, delayed discounting task; dMT, distance-adjusted motor threshold; dPM, dorsal premotor cortex; LFEF, left frontal eye field; GNG, Go/No-Go; imTBS, intermediate theta burst stimulation; iTBS, intermittent theta burst stimulation; LDLPFC, left dorsolateral prefrontal cortex; lIFG, left inferior frontal gyrus; M1, primary motor cortex; MFG, middle frontal gyrus; MPFC, medial prefrontal cortex; MSO, maximum stimulator output; MT, motor threshold; NA, not available; OC, occipital cortex; RCRT, randomised crossover trial; RCT, randomised controlled trial; RDLPFC, right dorsolateral prefrontal cortex; rFEF, right frontal eye field; rIFG, right inferior frontal gyrus; rIFJ, right inferior frontal junction; RMT, resting motor threshold; rTMS, repetitive transcranial magnetic stimulation; SFG, superior frontal gyrus; SMA, supplementary motor area; SSRT, stop signal reaction time; SST, Stop-signal task; Stroop, Stroop interference colour task, TBS, theta burst stimulation

Table 2 Subgroup analyses

	Pooled effect size			Between-study heterogeneity		
	k	Effect size (Hedges' *g*)	95% CI	*Q* test	I^2	*p* value
Motor impulsivity						
Total	41	0.30***	0.17-0.43	53.91	25.8%	0.070
Effect of stimulation						
Inhibitory	27	0.27***	0.13-0.41	26.75	2.8%	0.423
Excitatory	14	0.36*	0.06-0.65	27.04	51.9%	0.012
rTMS type						
Conventional rTMS	26	0.26**	0.07-0.45	45.59	45.2%	0.007
TBS	15	0.39***	0.20-0.58	6.49	0.0%	0.952
Stimulation site						
LDLPFC	11	0.26**	0.07-0.46	5.62	0.0%	0.846
rIFG	7	0.42**	0.11-0.73	8.69	31.0%	0.192
rFEF	3	1.30***	0.58-2.03	3.77	46.9%	0.152
mPFC	2	0.61*	0.03-1.19	0.10	0.0%	0.755
RDLPFC	4	0.24	-0.18-0.66	1.17	0.0%	0.761
SMA	3	-0.09	-0.47-0.28	0.17	0.0%	0.683
right Pre-SMA	5	0.29	-0.05-0.62	0.27	0.0%	0.991
Stimulation effect x site						
Inhibitory at LDLPFC	3	0.38	-0.01-0.78	0.27	0.0%	0.875
Excitatory at LDLPFC	8	0.23*	0.00-0.45	4.88	0.0%	0.675
Type of the task used						
GNG	14	0.24*	0.05-0.42	13.13	1.0%	0.438
SST	21	0.32**	0.10-0.55	36.70	45.5%	0.013
Stroop	4	0.35*	0.02-0.68	2.87	0.0%	0.412
Temporal impulsivity						
Total	7	0.59***	0.32-0.85	6.38	6.0%	0.382
Effect of stimulation						
Inhibitory	3	0.71**	0.21-1.21	1.57	0.0%	0.457
Excitatory	4	0.54**	0.16-0.92	4.52	33.6%	0.211
rTMS type						
Conventional rTMS	4	0.65**	0.28-1.03	5.37	44.1%	0.147
TBS	3	0.33	-0.31-0.97	0.27	0.0%	0.872
Stimulation site						
LDLPFC	3	0.76**	0.29-1.22	4.15	51.8%	0.126
RDLPFC	3	0.33	-0.31-0.97	0.27	0.0%	0.872

CI, confidence interval; GNG, Go/No-Go; LDLPFC, left dorsolateral prefrontal cortex; mPFC, medial prefrontal cortex; RDLPFC, right dorsolateral prefrontal cortex; rFEF, right frontal eye field; rIFG, right inferior frontal gyrus; rTMS, repetitive transcranial magnetic stimulation; SMA, supplementary motor area; SST, Stop-signal task; Stroop, Stroop interference colour task, TBS, theta burst stimulation; * $p < .05$, ** $p < .01$, *** $p < .001$

Table S1: search syntax

AMED (Allied and Complementary Medicine) 1985 to February 2017		
#	**Searches**	**Results**
1	(impulsiv* or self-regulation or inhibitory control or impulse control or delay* discounting or response inhibition or information sampling or stop signal or temporal discounting or inhibition or go-no-go).mp. [mp=abstract, heading words, title]	320
2	("transcranial magnetic stimulation" or TMS or TBS or "theta burst stimulation").mp. [mp=abstract, heading words, title]	335
3	**1 and 2**	**39**

OVID: Embase 1980 to 2017 Week 08		
#	**Searches**	**Results**
1	(impulsiv* or "self-regulation" or "inhibitory control" or "impulse control" or "delay* discounting" or "response inhibition" or "information sampling" or "stop signal" or "temporal discounting" or "stroop" or "inhibition" or "go-no-go").kw.	48718
2	("TMS" or "transcranial magnetic stimulation" or "theta burst stimulation" or "TBS").kw.	7698
3	1 and 2	784
4	limit 3 to (human and embase and (conference abstract or conference paper or conference proceeding or journal or report or short survey) and adult <18 to 64 years>)	**94**

OVID MEDLINE(R) 1946 to February Week 2 2017		
#	**Searches**	**Results**
1	(impulsiv* or self-regulation or inhibitory control or impulse control or delay* discounting or response inhibition or information sampling or stop signal or temporal discounting or inhibition or go-no-go).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	742364
2	("TMS" or "transcranial magnetic stimulation" or "theta burst stimulation" or "TBS").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier,	16256

	synonyms]	
3	1 and 2	2639
4	limit 3 to (humans and "all adult (19 plus years)")	**2030**

OVID: PsycINFO 1806 to February Week 2 2017		
#	**Searches**	**Results**
1	(impulsiv* or "self-regulation" or "inhibitory control" or "impulse control" or "delay* discounting" or "response inhibition" or "information sampling" or "stop signal" or "temporal discounting" or "stroop" or "inhibition" or "go-no-go").mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]	113070
2	("TMS" or "transcranial magnetic stimulation" or "theta burst stimulation" or "TBS").mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]	8961
3	1 and 2	1625
4	limit 3 to (human and adulthood <18+ years> and "300 adulthood <age 18 yrs and older>" and human)	**1260**

Table S2. The component and overall quality ratings of the reviewed studies								
Study	**Selection bias**	**Study design**	**Confounders**	**Blinding**	**Data collection method**	**Withdrawals and dropouts**	**Overall**	**Adverse effect**
Cho et al. (2010)	+	+++	+++	+++	+++	+++	Moderate	Not mentioned
Bermpohl et al., (2005)	+	+++	+++	++	+++	+++	Moderate	Not mentioned
Chambers et al., (2006)	+	+++	+++	+++	+++	+++	Moderate	Not mentioned
Chambers et al., (2007)	+	+++	+++	+++	+++	+++	Moderate	Not mentioned
Chen et al., (2009)	+	+++	+++	+++	+++	+++	Moderate	Not mentioned
Cho et al. (2012)	+	+++	+++	+++	+++	+++	Moderate	No significant discomfort
Cho et al. (2015)	+	+++	+++	+++	+++	+++	Moderate	Not mentioned
Dambacher et al. (2014)	+	+++	+++	+++	+++	++	Moderate	uncomfortable facial twitches (n =1)
Esterman et al., (2015)	+	+++	+++	++	+++	+++	Moderate	Not mentioned

Figner et al., (2010)	+	+++	+++	+++	+++	+++	Moderate	No participant experienced serious adverse effects or reported any scalp pain, neck pain, or headaches
Grossheinrich et al., (2009)	+	+++	+++	+++	+++	+++	Moderate	headache and muscle twitching during stimulation and nausea and lightheadedness after stimulation (n=1), sweating and feeling dizzy after stimulation(n=1), nausea after stimulation(n=1)
Huang et al., (2004)	+	+++	+++	+++	+++	+++	Moderate	No subjective or objective ad-verse effects were observed in any subject during stimulation

Hwang et al., (2010)	+	+++	+++	+++	+++	+++	Moderate	no adverse event occurred
Kim et al., (2012)	+	+++	+++	+++	+++	+++	Moderate	Not mentioned
Knoch et al., (2006)	+	+++	+++	+++	+++	+++	Moderate	no adverse side effects
Lee et al., (2016)	+	+++	+++	+++	+++	+++	Moderate	Not mentioned
Leyman et al., (2009)	+	+++	+++	++	+++	+++	Moderate	Not mentioned
Leyman et al., (2009)	+	+++	+++	++	+++	+++	Moderate	Not mentioned
Lowe et al., (2014)	+	+++	+++	+++	+++	+++	Moderate	Not mentioned
Muggleton et al., (2010) exp1	+	+++	+++	+++	+++	+++	Moderate	Not mentioned
Obeso et al., (2013)	+	+++	+++	+++	+++	+++	Moderate	No participants reported major adverse effects
Sheffer et al., (2013)	++	+++	+++	++	+++	+	Moderate	Not mentioned
Upton et al., (2010)	+	+++	+++	++	+++	+++	Moderate	Not mentioned

Vanderhasselt et al., (2006)	+	+++	+++	+++	+++	+++	Moderate	Not mentioned
Vanderhasselt et al., (2007)	+	+++	+++	+++	+++	+++	Moderate	Not mentioned
Verbruggen et al., (2010)	+	+++	+++	++	+++	+++	Moderate	No adverse effects
Wagner et al., (2006)	+	+++	+++	++	+++	+++	Moderate	mild headaches (n=3)
Watanabe et al., (2015)	+	+++	+++	++	+++	+++	Moderate	Not mentioned
Zandbelt et al.,(2013)	+	+++	+++	+++	+++	+++	Moderate	no adverse side effects
+ = weak, ++ = moderate, +++ = strong								

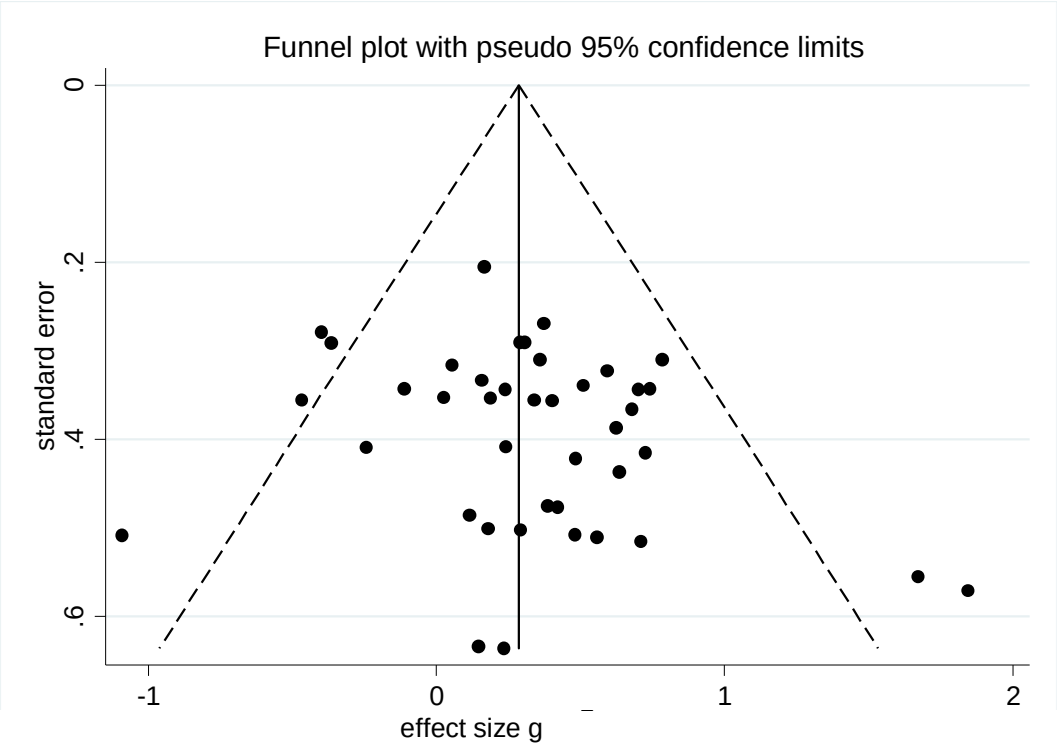

Figure S2a. Funnel plot of the motor impulsivity trials in the meta-analysis.

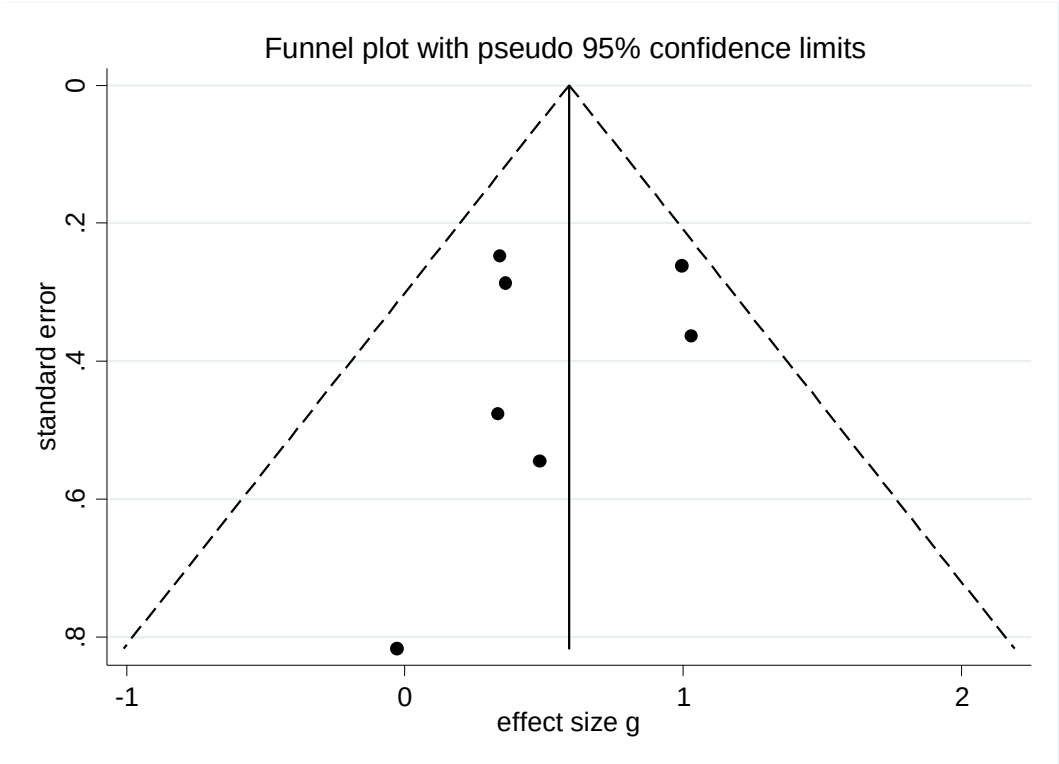

Figure S2b. Funnel plot of the temporal impulsivity trials in the meta-analysis.