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Review article

A systematic review and meta-analysis of the efficacy of intermittent theta burst stimulation (iTBS) on cognitive enhancement

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ABSTRACT

Intermittent theta-burst stimulation (iTBS) has been used to focally regulate excitability of neural cortex over the past decade – however there is little consensus on the generalizability of effects reported in individual studies. Many studies use small sample sizes (N < 30), and there is a considerable amount of methodological heterogeneity in application of the stimulation itself. This systematic meta-analysis aims to consolidate the extant literature and determine if up-regulatory theta-burst stimulation reliably enhances cognition through measurable behavior. Results show that iTBS – when compared to suitable control conditions — may enhance cognition when outlier studies are removed, but also that there is a significant amount of heterogeneity across studies. Significant contributors to between-study heterogeneity include location of stimulation and method of navigation to the stimulation site. Surprisingly, the type of cognitive domain investigated was not a significant contributor of heterogeneity. The findings of this meta-analysis demonstrate that standardization of iTBS is urgent and necessary to determine if neuroenhancement of particular cognitive faculties are reliable and robust, and measurable through observable behavior.

1. Introduction

The invention of non-invasive brain stimulation (NIBS) is potentially one of the most important advances in neuroscience. NIBS enables researchers to investigate the causal relationships between brain activity and behavior, without cost and risk associated with direct intracranial stimulation methods. Several protocols of NIBS exist and have been used not only as interventions in studies regarding the relationships between basic neurophysiology and cognition (for review, see Brunoni and Vanderhasselt, 2014; Simonsmeier et al., 2018), but also in the advancement of clinical neuroscience and the treatment of several neurological conditions, including Parkinson's disease (Goodwill et al., 2017), Alzheimer's disease (Hsu et al., 2015), dementia and mild cognitive impairment (MCI; Inagawa et al., 2019), schizophrenia (Rogasch et al., 2014; Sloan et al., 2020), and seizure disorders (Boon et al., 2018; Shafi et al., 2015). In particular, the theta burst magnetic stimulation protocols (TBS) are utilized to mimic the natural firing patterns of the brain to up- or down-regulate excitability of focal areas on the surface of the cortex with relatively high precision (Diamond et al., 1988; Peinemann et al., 2004; Rounis et al., 2005, 2006). The TBS protocols are advantageous because the stimulation can be applied relatively quickly (40–190 s), allowing for larger sample sizes from populations that may not be able to tolerate several minutes of stimulation, as is the case for repetitive transcranial magnetic stimulation (rTMS) protocols which can last up to 30 min (Maeda et al., 2000). Intermittent patterns of TBS (iTBS; 190 s of stimulation comprised of 3

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50 Hz pulses administered every 200 ms, and each burst repeated every 10 s, with 600 total pulses applied at 80% of a subject's active motor threshold (AMT)) tend to increase neural excitability and induce long-term potentiation (LTP) in targeted neural circuits, whereas continuous theta burst stimulation (cTBS; 40 s of stimulation with 3 50 Hz pulses administered every 200 ms uninterrupted, with 600 total pulses applied at 80% AMT) tends to decrease neural excitability and induce long-term depression (LTD) in targeted circuits (Huang et al., 2005).

Interest in facilitatory stimulation (including iTBS) in healthy human populations has grown throughout the past decade, specifically within government and private sectors because NIBS is a potentially useful and efficient method to enhance human cognition (Nelson and Tepe, 2015; Wexler, 2017). Due to this interest, a significant body of work has emerged regarding the ethical implications of neuroenhancement on cognition for healthy individuals, namely regarding safety, autonomy, justice, and authenticity. Regarding safety, the potential for long-term side effects and unknown side effects are of great concern (Bikson et al., 2016), especially considering that individuals who have access to commercial NIBS devices report that they over-use these devices (Wexler, 2016). However, in an additional study conducted by Jwa (2015), those users of commercial NIBS devices did not report misuse of the product and were aware of safety risks, but did stress the desire for explicit guidelines and regulations from researchers. Regarding autonomy, ethical concerns regarding the prevalence of use and social acceptance of this technology, having access to clear and concise information about the risks and benefits of NIBS are a current challenge facing the field, as the term non-invasiveness implies a sense of safety and the validity of consent comes into question for users when researchers are unsure of the full scope of possible risks of NIBS. Regarding justice, depending on the efficacy of brain stimulation enhancing cognition, ethical issues surrounding equitable distribution of this technology and ideological stances on neuroenhancement can contribute to inequality (Dijkstra and Schuijff, 2016). Finally, regarding the issue of authenticity post societal adoption of NIBS for cognitive enhancement, there are mounting concerns on how NIBS may have transfer effects, how it may impact personality, mood, and identity (Klein et al., 2016), and more work is required in this space to determine if non-invasive stimulation impacts these characteristics.

Despite growing interest in widespread adoption of neuroenhancement techniques, there are several caveats to interpreting recent studies utilizing iTBS protocols as having successfully enhanced human cognition. First, the iTBS protocol (Huang et al., 2005) was standardized to the human motor cortex of the dominant hand, and enhancement was operationalized as changes in cortical excitability (measured as motor-evoked potentials (MEPs)). Extending this protocol to areas outside of the dominant motor cortex has not been standardized within the field. While this has not impeded new experimental findings using the iTBS protocol, researchers need to be cautious in the interpretation of their results when targeting non-dominant motor and non-motor cortical areas.

Researchers should also take caution in how they measure behavior and cognition, especially if there are no secondary measurements to directly quantify neural excitability before and after stimulation to monitor cortical change (Miniussi and Thut, 2010; Sack and Linden, 2003). Second, there is a lack of consistency in how human subjects respond to facilitatory stimulation (López-Alonso et al., 2014). Subjects can be classified as 'responders' or 'non-responders' to NIBS, but the proportion of subjects who are classified in these categories is rarely reported in methods sections of published studies. Third, there is no standardization in the reporting of equipment such as coil diameter and manufacturer of the TMS equipment or stimulation parameters including motor threshold used for stimulation (resting motor threshold (RMT) vs. AMT). The effects of manipulating these parameters are largely unknown, and under-reporting is common. While these issues exist, it is important to assess the existing studies within this body of work to understand which reported parameters may be contributing to variation between study results, and how or if existing studies provide support for the hypothesis that iTBS generally enhances cognition.

In a review conducted by Wischnewski and Schutter (2015), the authors investigated the efficacy of theta-burst protocols on MEP size and duration. iTBS was found to be efficacious for up to a duration of 60 min, whereas cTBS was efficacious for 20–40 min, depending on the duration of stimulation. While insightful, the outcomes of their review are limited to interventions involving stimulation of primary motor cortices, and these results should not be extended to findings where stimulation is performed outside of the motor cortex. Another review conducted by Chung and colleagues (2016) investigated the efficacy of TBS on multiple measures of cortical excitability across time. Similar to Wischnewski and Schutter's (2015) findings, Chung et al. found cTBS was effective for reduction of MEP amplitudes for up to 60 min, peaking in efficacy at 5 min, and iTBS was found to be effective for the increase of MEP amplitudes for up to 30 min, remaining similarly effective at both early (5 min post-TBS) and mid (20–30 min post-TBS) time points.

At this time, no systematic review on the efficacy of iTBS for neuroenhancement has been conducted. Specifically, no systematic review has been done to assess whether or not iTBS enhances cognition through measurable behavior due to its ability to potentiate neural populations. In this case, enhancement of cognition refers to a myriad of behavioral measurements that determine improvement in a particular skill or aspect of cognition, specifically reaction time, accuracy, or performance enhancements. While this is limited in the scope of what cognition entails and the ways in which it can be measured, a meta-analysis of this scope is justified due to the lack of understanding in the field of how iTBS manipulations effect higher-order cognitive processes which exclude corticospinal excitability measures and are generally measured through behavioral response paradigms. A systematic review or meta-analysis on the efficacy of iTBS with measures of cognition as the variable of interest and location of stimulation, parameters of stimulation, and the type of cognitive phenomena studied as the primary covariates would allow researchers to fully utilize neurostimulation techniques while avoiding methodological pitfalls.

The primary objective of this systematic meta-analysis was to determine if iTBS – when compared with proper control conditions – reliably enhances cognitive functioning. We evaluated reported effect sizes across studies for a variety of measures of cognitive enhancement that are not merely measures of cortical and cortico-spinal excitability, which have been assessed in the aforementioned meta-analyses (Chung et al., 2016; Wischnewski and Schutter, 2015). Specific measures of cognitive enhancement evaluated here include behavioral measurements of performance, accuracy, and reaction time in healthy adults. The definition of accuracy in the context of this study is the degree to which the result of a measurement, calculation, or specification conforms to the correct value or a standard, whereas performance in this study is defined as an action, task, or operation, seen in terms of how successfully it was performed. Whereas these two terms are closely related, the distinction made between the two was when the measurement of interest was unrelated to error processes - and took the form of a singular score without a relationship between correct and incorrect performance (i.e. no ratios or percentages), and these measurements were enveloped in the term 'performance' for this study. A secondary objective of this meta-analysis was to determine the optimal and influential parameters which contribute to reliable effect sizes in studies of cognitive enhancement using iTBS. Specific parameters assessed include stimulation location, and stimulation protocols including: determination of motor threshold, determination of stimulation location, coil and stimulator features, and features of the control condition. We also investigated the distribution of effect sizes and assessed heterogeneity between studies using aforementioned parameters as factors in meta-analytic models. Additionally, indications of publication bias were also assessed through small sample bias methods, as well as p-curve analyses.

2. Methods

2.1. Protocol and registration

The meta-analysis adhered to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (Moher et al., 2009).

2.2. Search strategy

The types of studies included in our search were: meta-analyses, original research articles, systematic reviews, and randomized controlled trials. All sources must have been peer reviewed and have high standards of methodological rigor to ensure that outside sources of variance are not contributing to the effects found in each study. Methodological rigor in this meta-analysis disqualified studies that did not provide details regarding motor threshold, an insufficient control condition, had a protocol deviating from the Huang et al. (2005) recommendation (including Goldsworthy et al., 2012), measured motor threshold at the beginning of the experiment and not during each session (if multiple sessions of iTBS), and had stimulation sessions more than once per day with less than an hour between sessions.

Two independent reviewers (AP & SP) first examined each database (Google Scholar, PsychINFO, and MEDLINE through PubMed) and selected articles that contained the following topics/terms in their abstract or title: 1) iTBS, theta burst stimulation, TMS, or transcranial magnetic stimulation, 2) cognitive enhancement, neuroenhancement, or brain enhancement, and 3) healthy adults. All authors agreed on the terms and search conditions used for searching each database. MEDLINE and PsychINFO databases were searched, and an additional search was conducted using Google Scholar. The Google Scholar search included the following terms: "intermittent theta burst stimulation AND iTBS OR theta burst stimulation OR TMS, enhancement OR cognitive enhancement OR neuroenhancement OR brain enhancement, healthy adults". This search generated 1000 results, as that is the limit of Google Scholar's search query. The PsychINFO database search used the following conditions: Record types: dissertation, dissertation chapter, journal articles, peer reviewed journals; Methodology: Brain imaging, clinical trial, empirical study, experimental replication, literature review, meta-analysis, quantitative study, systematic review; Language: English; Age group: adulthood; Population: human; Timeframe: 2010–2020; Search terms: In the abstract, must contain: "theta burst stimulation OR iTBS OR intermittent theta burst stimulation AND transcranial magnetic stimulation OR TMS AND healthy adults AND cognitive enhancement OR neuroenhancement OR brain enhancement". This search query generated 399 results. For the MEDLINE database search, this used the same search terms as the PsychINFO search, however the publication type was changed to include: "clinical study OR clinical trial OR comparative study OR controlled clinical trial OR journal article OR meta-analysis OR randomized controlled trial OR systematic review or validation study". Limits for the MEDLINE search included no restrictions on gender, the age of the population studied must be 18 or above, the years of publication from January 2010 - April 2020, and language set to English for ease of reviewing for the reviewers. This search query generated 134 results. The final search query was performed April 14, 2020. In total, 1533 results were generated. After comparing the results of each query and checking for duplicates, 525 individual records were ready for initial review (see Fig. 1 for study selection outline). A search was conducted on the Web of Science platform to identify additional journal articles using the following search terms: "Theta burst stimulation" OR "iTBS" OR "iTBS" AND "Transcranial Magnetic Stimulation" OR "TMS" AND "healthy adults" AND "cognitive enhancement" OR "neuroenhancement" OR "brain enhancement" AND date of search = "2010–01–01/2020–04–14" AND document type = "Article" OR "Data Paper". This search did not yield any new articles not listed in other databases.

The articles contained within each database that met the following criterion were added into a Google Spreadsheet that was shared across reviewers (AP, SP, DCC, BM, JMR). Two independent reviewers (AP, SP) assessed all screened articles in their entirety, adding information to a shared spreadsheet that would allow for determination of eligibility for each article. If any article raised concerns about ambiguity for adhering to the criteria set forth by all reviewers (AP, SP, DCC, BM, JMR), it was flagged and discussed by all reviewers until 100% agreement was achieved. The information that was collected included the following: publication type, name of the journal, year of publication, mean and standard deviation of the studied sample, age range and gender of the studied sample, total sample size, experimental and control sample sizes, study design (between, mixed, or within-subjects), location of stimulated brain areas, stimulator and coil type, details of the control and experimental conditions, details of the motor thresholding process, percentage of motor threshold used for iTBS intensity, information about the type of cognitive task used, and the type of behavioral data collected.

2.3. Selection criteria and outcome measures

The population assessed included healthy adult subjects (aged 18 +) with no neurological illness or reported contraindications to TMS (see Table 1 for specific inclusion and exclusion criteria). The intervention examined was the application of iTBS offline in relation to cognitive tasks. Cognitive tasks needed to include behavioral measurements of sensation, perception, cognition, or action in order to satisfy the inclusion criteria. Studies needed to include a sufficient control condition, which included sham stimulation, active stimulation of a region not involved in the task at hand, use of a placebo coil, or a separate no-stimulation condition. Study outcomes were required to pertain to the enhancement of cognitive abilities, specifically using behavioral measurements of performance, accuracy, or reaction time. The study designs that were included within the meta-analysis included between and within subject designs that compared control conditions with stimulation conditions. Criteria for dates were set to articles published after 2010, as safety guidelines for TMS were amended to include the use of theta-burst stimulation in 2009 (Rossi et al., 2009).

2.4. Data extraction

Each article was assessed in full text by five independent reviewers (AP, SP, BM, DC, JMR) to determine study eligibility. During this time, reviewers wrote questions in a collaborative document if an article posed additional questions that could change the determination of eligibility of an article, and any prior articles assessed before such questions arose were reassessed with the adapted criterion. Reviewers provided 'yes', 'no', or 'maybe' inclusion judgements, including reasons for 'no' and 'maybe' judgments. Reviewers were blind to each other's analysis eligibility decisions until all reviewers completed assessing the studies. At this point, the reviewers met and determined whether each study should be included in the meta-analysis. The inter-rater reliability was 86.23%. Any study that did not have unanimous agreement between reviewers was discussed until a consensus was formed.

Data were pulled from reported behavioral measurements taken in each study. If information was insufficient to calculate and estimate effect sizes, authors of that study were contacted to access the appropriate statistical information to estimate the effect size. Of the 55 eligible studies, 9 authors needed to be contacted for further information. Of the 9 authors contacted, 5 authors responded and shared information necessary for effect size calculation and regarding clarifying questions about the methodology used for stimulation, and the rest (5 research findings in total) were excluded from quantitative analysis due to lack of reported data.

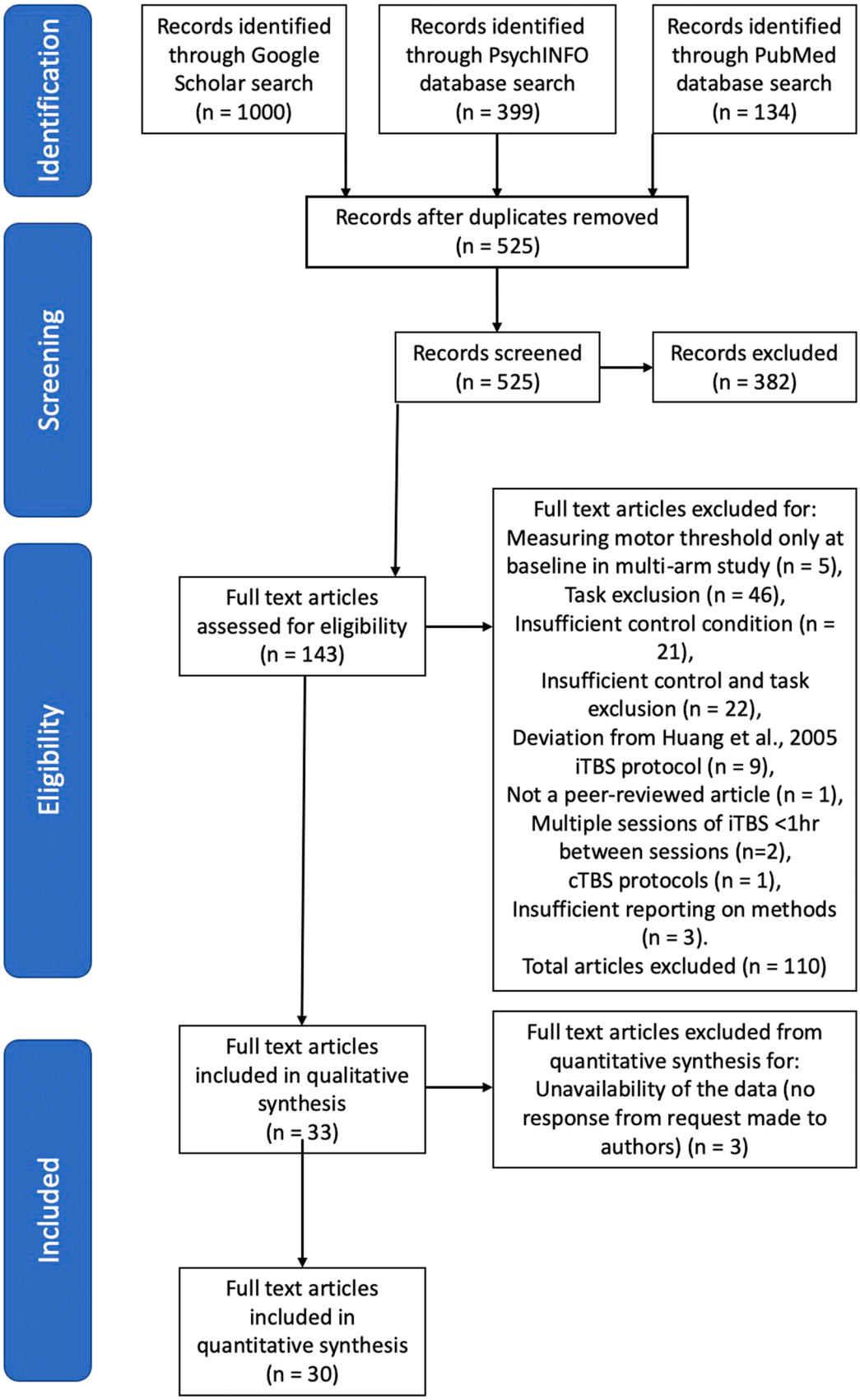

Fig. 1. PRISMA Flowchart. Assessment of articles outlined in the Search Strategy section, beginning with identification of articles, the screening and eligibility process, and the number of full-text articles included. Note that multiple studies or research findings can be extracted from a single article.

Table 1
PICOS Criteria for iTBS meta-analysis. This table describes the criteria required for a study to be eligible for inclusion in the meta-analysis, following PICOS (Participants, Interventions, Comparisons, Outcomes, and Study Design) guidelines.

	Inclusion	Exclusion
Participants	1. Healthy adult subjects age 18 or over 2. No neurological illness 3. No contraindications to TMS	1. Non-human subjects 2. Any kind of neurological illness or contraindication to TMS 3. Subjects under age 18
Interventions	1. iTBS following the Huang et al. (2005) protocol (3 50 Hz pulses applied every 10 s for 190 s, 600 total pulses) 2. Offline behavioral measurements 3. Cognitive tasks include behavioral measurements of sensation, perception, cognition, or action	1. iTBS administration deviating from Huang et al. (2005) protocol 2. Online measurements of cognition 3. Any other form of NIBS
Comparison	1. Sham condition (using placebo coil, reduction of stimulation intensity, coil rotation to point pulses away from cortex) 2. No stimulation condition 3. Active stimulation of a region not involved in the behavior measured	1. No comparison conditions 2. Active stimulation of regions involved in the measured behavior
Outcomes	1. Behavioral measurements of performance, reaction time, or accuracy	1. Cortico-spinal excitability measurements 2. fMRI, EEG, MEG, fNIRS measurements
Study Design	1. Post iTBS measurements compared to post-control measurements	1. Pre-post measurement studies with no control/ sham conditions
Data Reported	1. Data that enables the estimation and calculation of effect sizes between comparator conditions and iTBS stimulation conditions including mean and standard deviation / standard error and effect sizes	1. Unpublished data 2. Published studies without enough data to enable effect size calculations
Type of Publications	1. Peer-reviewed journal articles 2. Written in English 3. Written between 2010 and 2020	1. Non-English journal articles 2. Grey literature, non-peer reviewed articles, pre-prints, case studies, review articles 3. Written before 2010

TMS – transcranial magnetic stimulation; iTBS – intermittent theta burst stimulation; NIBS – non-invasive brain stimulation; fMRI – functional magnetic resonance imaging; EEG – electroencephalography; MEG – magnetoencephalography; fNIRS – functional near-infrared spectroscopy.

2.5. Meta-analysis

2.5.1. Calculating effect sizes

Effect size data and their respective standard errors, variances, and 95% confidence intervals were calculated by a single reviewer (AP), using standardized mean difference estimations of Cohen's d from reported means and standard deviations and tests of statistical significance. Hedges' g corrections were applied for small sample sizes ($N < 30$). 52 studies were included in the summative quantitative analysis. When standard deviations were not available but standard error was reported, the formula $SD = SE\sqrt{n}$, where n = sample size was used to calculate standard deviation (Higgins and Green, 2008). Meta-analyses were conducted in R (R version 4.0.3) and aided by Harrer and colleagues online guide and their "dmetar" R package (see Harrer et al., 2019a, 2019b for a complete guide on performing meta-analysis). Prediction intervals, which are 95% confidence intervals that, given the present data, predict the significance of an effect in a subsequent study were calculated for each meta-analysis.

The meta-analysis models utilized all had the Hartung-Knapp adjustment set because it estimates the variance with improved coverage (Hartung and Knapp, 2001a, 2001b; IntHout et al., 2014; Langan et al., 2019), especially when there is heterogeneity within the dataset, as we would expect given our a priori assumptions of the included studies. A Paule-Mandel estimator for tau heterogeneity and Q-profile confidence interval estimation was used due to its robust performance and lack of requirement for fulfilling effect size distribution assumptions (Paule and Mandel, 1982; Veroniki et al., 2016).

2.5.2. Data analysis

The primary objective of this systematic meta-analysis was to determine if facilitatory stimulation using the iTBS protocol – when compared with proper control conditions – reliably enhances cognitive functioning. Due to the exploratory nature of the research question and the lack of consensus in the field regarding the true effects of facilitatory stimulation across research paradigms, all analyses were approached in an exploratory manner. First, meta-analysis was conducted across every effect regardless of cognitive task or behavior measured to establish if iTBS versus a properly controlled condition had an overall effect. Subsequent subgroup meta-analyses were then conducted across cognitive domains. Cognitive domains were established by independent reviewers during the eligibility screening process, with less than 100% consensus warranting a group discussion until agreement could be reached to place a study within a particular subgroup category. If a cognitive domain did not have a sufficient number of studies to allow for feasible effect-size analysis or publication bias, then they are mentioned in the discussion as a future direction worthy of pursuing but for the purposes of this meta-analysis, did not have the sufficient statistical power to address our research question directly. The cognitive domains that were established included attention ($k = 5$), decision making ($k = 4$), emotion ($k = 4$), language ($k = 1$), memory ($k = 5$), motor skill ($k = 17$), perception ($k = 4$), social cognition ($k = 1$), and working memory ($k = 9$). Each study was limited to being placed in one category. Because each study had variation in how the dependent variables were measured and in the methodology employed, the standardized mean difference effect size measure was used to remove some of that variation and standardize measurements in the analysis.

Additional subgroup analyses were conducted to examine the impact of the chosen method of control, stimulation location, the type of measurement used, the percent of motor threshold used to set the iTBS settings, the use of active versus resting motor threshold, navigation to the stimulation location, and direction of current flow.

2.5.3. Test of heterogeneity

Between-study heterogeneity was assessed through the I^2 statistic of each model, with values of 25%, 50%, and 70% representing low, moderate, and substantial heterogeneity respectively. (Higgins et al., 2002). Due to the exploratory nature of the meta-analysis and the apparent heterogeneity in methodology utilized across studies (see Table 2 for a description of each study included in the meta-analysis), random-effects models were chosen for all analyses despite differing percentages of heterogeneity.

Outlier and influence analyses were conducted to determine which individual studies contributed substantial amounts of heterogeneity to the overall effect, and to determine extreme effect sizes that have a large influence on the pooled effect of the meta-analysis. Outlier analyses were conducted by first examining extreme effect sizes where confidence intervals of individual studies did not overlap with the confidence interval of the pooled effect using the "dmetar" R package. Inference analyses were implemented using the "dmetar" package via a "leave-one-out" method, in which a meta-analysis is performed and its effect size is recalculated when a single study is left out of the analysis

Table 2
Study Characteristics. Table depicting each study included in the quantitative analysis and characteristics of each study relevant to analysis, if reported.

Studies (no. of experiments)	Sample Size (n)	Gender Ratio	Mean Age ± SD (age range)	iTBS parameters (current flow)	Control Condition	Targeted Area (Nav. To location)	Cognitive Task	Study Design	Coil type (diameter), Stimulator
Bogdanov et al. (2018)	32*	35 F:30 M	24.52 ± 0.36 (19 – 32)	80% RMT	No Stim	Infero-lateral rPFC (Ind. MRI)	Motor Skill (Acc)	Between	Fig. 8 coil (70 mm), Magstim SuperRapid2
Cárdenas-Morales et al. (2011)	17	17 M	23.7 ± 2.6 (24 – 33)	90% AMT (AP)	No Stim	lM1 (Ind. Mapping)	Decision Making (RT)	Within	MCFB70 (97 mm), MagProX100
Che et al. (2019) (1)	20	12 F:8 M	26.45 ± 4.54	70% RMT	Rotated coil	ldmPFC (10–20 system)	Emotion (Score)	Within	Cool-B65 (75 mm)
Che et al. (2019) (2)	20	12 F:8 M	26.45 ± 4.54	70% RMT	Rotated Coil	ldmPFC (10–20 system)	Perception (Score)	Within	Cool-B65 (75 mm)
Chung et al. (2018) (1)	18	10 F:8 M	25.6 ± 7	75% RMT (PA)	Rotated Coil	ldmPFC (10–20 system)	Working Memory (Score)	Within	Cool-B65 (75 mm)
Chung et al. (2018) (2)	18	10 F:8 M	25.6 ± 7	75% RMT (PA)	Rotated Coil	ldmPFC (10–20 system)	Working Memory (Score)	Within	Cool-B65 (75 mm)
Crescentini et al. (2015)	14	8 F:6 M	22.07 ± 2.12	80% AMT (PA)	Rotated Coil	rIPL (Ant. Landmarks)	Decision Making (Acc.)	Within	Air-cooled Fig. 8 (70 mm), Magstim SuperRapid2
de Dreu et al. (2016)	36	36 M	25.16 ± 2 (20–28)	80% AMT	imTBS	rIFG (Ind MRI)	Decision Making (Score)	Within	Fig. 8 (70 mm), 3.5 T Magstim SuperRapid2
Debarnot et al. (2015)	20*	iTBS – 7 F:3 M; control 6 F:4 M	iTBS: 70.2 ± 5.5; control: 70.2 ± 4.8	80% AMT	Active control	lBA10 (Ind MRI)	Memory (Score)	Between	Fig. 8 (70 mm), Magstim SuperRapid
Deppermann et al. (2016)	42*	74 F:9 M	26.46 ± 8.47	80% MT (PA)	Rotated Coil	lDLPFC (10–20 system)	Emotion (RT)	Between	MCFB65 (75 mm), MagOption/ MagproX100
Duffy et al. (2019)	56	37 F:19 M	24.6 ± 5.3 (18–40)	80% AMT	Rotated Coil	rTPJ (Ind. MRI)	Social Cognition (Score)	Between	Cool-BCF65 (75 mm), MagProX100
Finkel et al. (2019)	14	7 F:7 M	27.3 (22–35)	80% AMT (AP)	Active Control	rS1 larynx (Ind. MRI)	Perception (Acc.)	Within	Fig. 8 (70 mm), Magstim Rapid2
Gan et al. (2019) (1)	22	14 F:8 M	(18–40)	80% RMT (AP)	Sham tDCS	lPPC (10–20 system)	Working Memory (Score)	Within	Circular (114 mm), MagProX100
Gan et al. (2019) (2)	22	14 F:8 M	(18–40)	80% RMT (AP)	Sham tDCS	lPPC (10–20 system)	Attention (Score)	Within	Circular (114 mm), MagProX100
Gan et al. (2019) (3)	22	14 F:8 M	(18–40)	80% RMT (AP)	Sham tDCS	lPPC (10–20 system	Emotion (RT)	Within	Circular (114 mm), MagProX100
Gheysen et al. (2017) (1)	67	8 F:7 M*	24.4 ± 3.1	80% AMT (AP)	No Stimulation	lCerebellum (Ind MRI)	Motor Skill (Acc)	Between	Fig. 8 Airfilm (70 mm), Magstim Rapid2
Gheysen et al. (2017) (2)	71	12 F:7 M*	24.6 ± 3.1	80% AMT (AP)	No Stimulation	rCerebellum (Ind MRI)	Motor Skill (Acc)	Between	Fig. 8 Airfilm (70 mm), Magstim Rapid2
Giboin et al. (2016)	10	10 M	26 ± 2	80% AMT (AP)	Rotated coil	lM1 Lower Limb (Ind Mapping)	Motor Skill (Score)	Within	MCB70 (97 mm), MagPro R30
He et al. (2013) (1)	60	30 F:30 M	20.1 (19–23)	80% RMT (AP)	Rotated Coil	lPPC (10–20 system)	Attention (RT)	Within	Nitrogen-cooled Fig. 8 (70 mm), YirudeCCY-I
He et al. (2013) (2)	60	30 F:30 M	20.1 (19–23)	80% RMT (AP)	Rotated Coil	rPPC(10–20 system)	Attention (RT)	Within	Nitrogen-cooled Fig. 8 (70 mm), YirudeCCY-I
He et al. (2013) (3)	60	30 F:30 M	20.1 (19–23)	80% RMT (PA)	Rotated Coil	lDLPFC (10–20 system)	Attention (RT)	Within	Nitrogen-cooled Fig. 8 (70 mm), YirudeCCY-I
He et al. (2013) (4)	60	30 F:30 M	20.1 (19–23)	80% RMT (PA)	Rotated Coil	rDLPFC (10–20 system)	Attention (RT)	Within	Nitrogen-cooled Fig. 8 (70 mm), YirudeCCY-I
Hoy et al. (2016) (1)	19	9 F:10 M	22.16 ± 2.93	80% RMT	Rotated Coil	lDLPFC (10–20 system)	Working Memory (score)	Within	Fig. 8 (70 mm) MagVenture R30/ X100
Hoy et al. (2016) (2)	19	9 F:10 M	22.16 ± 2.93	80% RMT	Rotated Coil	lDLPFC (10–20 system)	Working Memory (score)	Within	Fig. 8 (70 mm) MagVenture R30/ X100
Jelić et al. (2015) (1)	20*	12 F:18 M	26 ± 3	80% AMT (PA)	Placebo Coil	rM1 (Ind Mapping)	Motor Skill (Score)	Between	Fig. 8 (70 mm) Magstim Rapid
Jelić et al. (2015) (2)	20*	12 F:18 M	26 ± 3	80% AMT (PA)	Placebo Coil	rM1 (Ind Mapping)	Motor Skill (Score)	Between	Fig. 8 (70 mm) Magstim Rapid
	24*	20 F:16 M	26.2 ± 3.9		Rotated Coil			Between	

(continued on next page)

Table 2 (*continued*)

Studies (no. of experiments)	Sample Size (n)	Gender Ratio	Mean Age ± SD (age range)	iTBS parameters (current flow)	Control Condition	Targeted Area (Nav. To location)	Cognitive Task	Study Design	Coil type (diameter), Stimulator
Koch et al. (2020) (1)				80% AMT (AP)		rCerebellum (Ant Landmarks)	Motor Skill (Acc)		Fig. 8 (70 mm) Magstim Rapid
Koch et al. (2020) (2)	12	6 F:6 M	25.6 ± 2.9	80% AMT (AP)	Rotated Coil	rCerebellum (Ant Landmarks)	Motor Skill (Acc)	Within	Fig. 8 (70 mm), Magstim Rapid
Lee et al. (2013)	53*	40 F:42 M	32.9	80% RMT (PA)	Rotated Coil	lM1 (Ind. Mapping)	Motor Skill (Score)	Between	Fig. 8 coil (100 mm), MagPro RapidRate
López-Alonso et al. (2015)	56	6 F:50 M	20.51 ± 1.52	80% AMT (PA)	Non-Responder Participants	lM1 (Ind Mapping)	Motor Skill	Within	Fig. 8 (70 mm), Magstim SuperRapid
López-Alonso et al. (2018)	14*	16 F:12 M	27.21 ± 6.93	80% AMT	Sham tDCS	lM1 (Ind Mapping)	Motor Skill	Between	Fig. 8 (70 mm), Magstim SuperRapid
Mioli et al. (2018) (1)	28	16 F:12 M	26.68 ± 4.66	80% AMT	Rotated Coil	rPMv (Opto Electric NeuroNav)	Perception (Score)	Within	Fig. 8 (90 mm), DuoMagXT100
Mioli et al. (2018) (2)	28	16 F:12 M	26.68 ± 4.66	80% AMT	Rotated Coil	rIPL (Opto Electric NeuroNav)	Perception (Score)	Within	Fig. 8 (90 mm), DuoMagXT100
Mioli et al. (2018) (3)	28	16 F:12 M	26.68 ± 4.66	80% AMT	Rotated Coil	rPMv (Opto Electric NeuroNav)	Perception (Acc)	Within	Fig. 8 (90 mm), DuoMagXT100
Mioli et al. (2018) (4)	28	16 F:12 M	26.68 ± 4.66	80% AMT	Rotated Coil	rIPL (Opto Electric NeuroNav)	Perception (Acc)	Within	Fig. 8 (90 mm), DuoMagXT100
Notzon et al. (2018)	41	21 F:20 M	iTBS: 24.7 (19–29) Control: 27.2 (21–45)	80% RMT	Rotated Coil	rDLPFC (10–20 system)	Emotion (RT)	Between	Fig. 8 (70 mm), MagProX100 Option
Restle et al. (2012)	18	NA	26 ± 4.7	80% AMT	Active Control	lpIFG (Ind MRI)	Language (Acc)	Within	Fig. 8 (65 mm), MagProX100
Si et al. (2019)	24*	25 F:35 M	22.03 (18–26)	80% MT	Rotated Coil	FZ (10–20 System)	Decision Making (Score)	Between	Fig. 8 (70 mm), Magstim SuperRapid2
Stöckel et al. (2015)	24	14 F:10 M	iTBS: 28.1 ± 6.7 Control: 24.3 ± 5.1	80% AMT (PA)	Rotated Coil	lM1 (Ind Mapping)	Motor Skill	Between	Fig. 8 (70 mm) Magstim SuperRapid2
Stöckel et al. (2016) (1)	24*	13 F:11 M	iTBS: 24.4 ± 5.9 Control: 24.4 ± 5	80% AMT (PA)	Rotated Coil	rM1 (Ind Mapping)	Motor Skill (Score)	Between	Fig. 8 (70 mm), Magstim SuperRapid2
Stöckel et al. (2016) (2)	24*	14 F:10 M	iTBS: 26.2 ± 5.6 Control: 24.4 ± 5	80% AMT (PA)	Rotated Coil	lM1 (Ind Mapping)	Motor Skill (Score)	Between	Fig. 8 (70 mm), Magstim SuperRapid2
Turriziani et al. (2012) (1)	20*	78 F:22 M	(20–35)	80% AMT	Rotated Coil	rDLPFC (10–20 system)	Memory (Acc)	Mixed	Fig. 8 (70 mm), Magstim SuperRapid
Turriziani et al. (2012) (2)	20*	78 F:22 M	(20–35)	80% AMT	Rotated Coil	lDLPFC (10–20 system)	Memory (Acc)	Mixed	Fig. 8 (70 mm), Magstim SuperRapid
Vidal-Piñeiro et al., 2014 (1)	22	NA	71.75 ± 6.81 (61–80)	80% AMT	Placebo Coil	lIFG (Ind MRI)	Memory (Acc)	Between	Fig. 8, MagProX100
Vidal-Piñeiro et al., 2014 (2)	22	NA	71.75 ± 6.81 (61–80)	80% AMT	Placebo Coil	lIFG (Ind MRI)	Memory (Acc)	Between	Fig. 8, MagProX100
Viejo-sobera et al. (2017) (1)	24*	26 F:10 M	29.22 ± 9.7	80% AMT	Rotated Coil	lDLFPC (Ind MRI)	Working Memory (Acc)	Between	Fig. 8 (70 mm), Magstim SuperRapid2
Viejo-sobera et al. (2017) (2)	24*	26 F:10 M	29.22 ± 9.7	80% AMT	Rotated Coil	lDLPFC (Ind MRI)	Working Memory (Score)	Between	Fig. 8 (70 mm), Magstim SuperRapid2
Viejo-sobera et al. (2017) (3)	24*	26 F:10 M	29.22 ± 9.7	80% AMT	Rotated Coil	lDLPFC (Ind MRI)	Working Memory (Score)	Between	Fig. 8 (70 mm), Magstim SuperRapid2
Viejo-sobera et al. (2017) (4)	24*	26 F:10 M	29.22 ± 9.7	80% AMT	Rotated Coil	lDLPFC (Ind MRI)	Working Memory	Between	Fig. 8 (70 mm), Magstim SuperRapid2
Wilkinson et al. (2010)	16	10 F:6 M	iTBS: 27.63 ± 4.44	80% AMT (PA)	Rotated Coil	lM1 (Ind Mapping)	Motor Skill	Between	Fig. 8 (70 mm), Magstim Rapid

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Table 2 (*continued*)

Studies (no. of experiments)	Sample Size (n)	Gender Ratio	Mean Age ± SD (age range)	iTBS parameters (current flow)	Control Condition	Targeted Area (Nav. To location)	Cognitive Task	Study Design	Coil type (diameter), Stimulator
			Control: 27.63 ± 4.44						

* indicates a subset of the total recruited subjects; RMT – resting motor threshold; AMT – active motor threshold; MT – unspecified motor threshold; AP – anterior-posterior; PA – posterior-anterior; rPFC – right prefrontal cortex; lM1 – left primary motor cortex; ldmPFC – left dorsomedial prefrontal cortex; rIPL – right inferior parietal lobe; rIFG – right inferior frontal gyrus; lBA10 – left Brodmann's area 10; lDLPFC – left dorsolateral prefrontal cortex; rTPJ – right temporoparietal junction; rS1 – right primary somatosensory cortex; lPPC – left posterior parietal cortex; rPPC – right posterior parietal cortex; rDLPFC – right dorsolateral prefrontal cortex; rM1 – right primary motor cortex; rPMv – right ventral premotor cortex; lpIFG – left posterior inferior frontal gyrus; FZ – electrode location FZ (10–20 system).

(Viechtbauer and Cheung, 2010). Studies that were determined to be both outliers and have an unusually high influence on the effect size were removed from further analysis (see Baujat et al., 2002 for practical application of outlier analyses in meta-analysis). However, a sensitivity analysis was conducted and is included in the supplementary material.

Graphical displays of heterogeneity (GOSH) plots were generated to explore heterogeneity in the effect size data (Olkin, Dahabreh, and Trikalinos, 2012). GOSH plots fit a meta-analysis model to all possible subsets of included studies using the "metafor" R package (Viechtbauer and Cheung, 2010). Each of these models is then plotted, displaying the pooled effect size and between-study heterogeneity in which patterns and subgroups can be identified from the distribution of the data. The GOSH analyses did not influence our intention to pursue subgroup analyses; we intended to conduct exploratory analysis to determine which covariates, if any, had an influence on the heterogeneity of effect sizes or the effect sizes themselves. The particular covariates investigated included: study type (construct), control condition, stimulation location, dependent measure, percent of motor threshold used, AMT or RMT used, navigation to stimulation location, study design, and direction of current flow.

Further investigations into study heterogeneity and influence of subgroups on effect sizes were implemented by exploratory multiple meta-regression. Multiple meta-regression allows for the investigation of interactions and additive effects within a meta-regression model (Borenstein et al., 2011). This method allows the ability to combine and test all possible model predictor combinations and determines which predictors are the most important overall by comparing each model's corrected AIC value (Akaike Information Criterion; Akaike, 1974), creating an estimate for each predictor, and generating an estimate of predictor importance which ranges from 0 to 1 in value (Burnham and Anderson, 2002; Lindberg et al., 2015; Harrer et al., 2019a, 2019b). Multi-model inference was appropriate to use in this context due to the unknown nature of how each of our predictors influence the overall effect, as suggested by Higgins and Thompson for more robust models (Higgins and Thompson, 2004), and permutation tests were used to confirm the findings of the multiple meta-regression (Higgins and Thompson, 2004; Good, 2013; Viechtbauer et al., 2015).

2.5.4. Publication bias

Publication bias was investigated through both p-curve methods and small sample bias methods. P-curve methods investigate the likelihood of publication bias occurring due to significance levels and p-hacking (Simonsohn et al., 2014), whereas small-sample bias methods investigate the likelihood of publication bias occurring when small-sampled studies that have very large effects are published, leaving small-sampled studies whose effects are small and non-significant to contribute to the 'file-drawer' problem (Dickersin, 2005). Publication bias influences the pooled effect, and thus can contribute to a poor estimation of the true effect size of a given intervention in meta-analyses. Both of these methods were used to determine if any amount of publication bias exists regardless of theoretical assumptions.

2.5.5. Risk-of-bias assessment

A risk-of-bias assessment was conducted by four independent reviewers (AP, BM, DC, & SP) to assess the internal validity of the included studies in the meta-analysis. Reviewers were paired (AP & BM, and DC & SP) and independently assessed half of the studies included in the meta-analysis according to Cochrane ROB 2 tool's domains, which include: 1) bias arising from the randomization process, 2) bias due to deviations from intended interventions, 3) bias due to missing outcome data, 4) bias in the measurement of the outcome, and 5) bias in selection of the reported result (Sterne et al., 2019). Each domain was rated as having low bias, some concerns of bias, or high bias. Alongside each ranking, reviewers provided documentation and reasoning for their rating. If disagreement arose between the reviewers, the reviewers discussed and resolved any issues or questions until agreement was at 100% between all reviewers. Each study was assessed on the outcome of these domains - having all domains categorized as low risk of bias was judged as having low risk of bias overall, whereas a single rating of some concerns in any domain category would qualify that study as having some concerns toward bias, and similarly judge for having high risk of bias. Assessments were made from all available information relating to each study, including the journal articles, supplementary information, and personal correspondences with authors.

3. Results

3.1. Selection of studies

After duplicate removal from the set of studies generated through electronic query of journal article databases and the web, a total of 525 studies underwent initial review. Abstracts and titles were screened against the aforementioned selection criteria, and a total of 382 articles were removed for not meeting the inclusion criteria. Of the 143 articles that underwent full-text screening of eligibility, 5 were removed for not meeting the methodological standards of establishing motor threshold or a baseline measurement prior to iTBS, 46 were removed for not meeting the task requirements, 21 were removed for having insufficient control conditions, 22 were removed for both having insufficient control conditions and not meeting the task requirements, 9 were removed for not adhering to the Huang et al. (2005) iTBS protocol, 1 was removed for being a conference abstract and not being a peer-reviewed journal article, 2 were removed for applying iTBS within an hour of having received a first dose of iTBS, which may impact cortical excitability (Tse et al., 2018), 1 was excluded for being an inhibitory protocol and 3 were excluded for having insufficient details reported in their methodology. This left 33 articles (55 total studies, as many articles contributed more than one eligible research finding) to be included within the qualitative synthesis of studies, and finally 50 research findings from those articles were included in the quantitative assessment of the meta-analysis (see Fig. 1 for the PRISMA flowchart of article assessment). The 55 research findings included in the qualitative synthesis reflect the total number of research findings deemed eligible, and the 50 research findings included

in the quantitative synthesis of results reflect all the studies (n = 30 full text articles) that provided sufficient data to estimate effect sizes.

3.2. Synthesized findings

3.2.1. iTBS versus control

Fig. 2 provides a summary of the effect sizes across all studies, regardless of cognitive domain or methodological parameters. The effect of iTBS is small compared to control conditions and is non-significant (pooled SMD = 0.17, 95% CI [−0.07, 0.41], $p = 0.17$). Additionally, the prediction interval was non-significant (95% CI [−1.34, 1.67]). Heterogeneity of the studies was determined to be significant (tau^2 = 0.54, 95% CI [0.31, 0.99]; I^2 = 75.3%, 95% CI [67.6%, 81.2%]; Q = 198.58, $p < 0.0001$).

Outlier and influence analyses were conducted to determine which studies contribute significantly to the heterogeneity and size of the pooled effect. Further influence analyses using GOSH plots to identify naturally occurring clusters in the data. Confidence interval boundary outlier analyses tagged 8 studies as having potentially significant influence on the effect size. K-means algorithm, DBSCAN (density-based spatial clustering of applications with noise) algorithm, and a Gaussian Mixture Model found 5, 25, and 6 studies respectively which significantly influenced the effect size. The three studies that overlapped between the outlier analysis and the influence analyses were removed from subsequent analyses. An updated meta-analysis was conducted with the following studies removed: Koch et al. (2020) (2), Turriziani et al. (2012) (1), and López-Alonso, 3) et al. (2015) (see Table 2 for study characteristics). The updated meta-analysis (k = 47) revealed a significant effect (SMD = 0.21, 95% CI [0.003, 0.42], $p = 0.047$), however the prediction interval maintained no significant effects would be produced in future studies on the basis of the data present (95% CI [−1.01, 1.44]). Heterogeneity measures indicate a sizeable decrease in the outlier-reduced model compared to the full model ($tau^2 = 0.36$, 95% CI [0.18, 0.71]; I^2 = 68.3%, 95% CI [57.2%, 76.5%]; Q = 145.09, $p < 0.001$). This indicates that overall, when iTBS is compared to control conditions, there may be very small significant effects. However, this may be dependent on the context of the study conducted, as heterogeneity measures indicate a moderate to substantial presence of heterogeneity. This warrants further investigation using subgroup analyses to determine the specific variables and contexts in which studies using iTBS compared to control may have significant effect sizes. Fig. 3.

3.2.2. Subgroup analyses: cognitive domain

Cognitive domain covariates included attention (k = 5), decision-making (k = 4), emotion, (k = 4), language (k = 1), memory (k = 4), motor skill (k = 15), perception (k = 4), social cognition (k = 1), and working memory (k = 9). The factor of cognitive domain was not found to have significant differences between groups (Q = 8.07, $p = 0.43$). None of the subgroups were found to significantly influence effect size (see Fig. 4).

3.2.3. Subgroup analyses: study design

The experimental design was also taken into account as a factor for subgroup analyses. Covariates included between subject design (k = 25), mixed design (k = 1), and within subject design (k = 21). No significant differences were found between groups (Q = 2.97, $p = 0.23$), and no groups significantly contributed to overall effect size.

3.2.4. Subgroup analyses: control conditions

The type of control condition used in each iTBS study was included as a factor for contributions to between-study heterogeneity. The control conditions used were active control (k = 3), intermediate theta burst stimulation (imTBS; k = 1), non-responding control populations (k = 3), no stimulation condition (k = 4), placebo coil (k = 4), rotation of the coil away from cortex (k = 29), and sham transcranial direct current stimulation (sham tDCS; k = 4). Marginally significant differences were found between groups (Q = 11.89, $p = 0.06$), however none of the subgroups of the control conditions were found to significantly influence effect size. This could be because the control condition of rotation with the coil included many more studies than other covariates.

3.2.5. Subgroup analyses: stimulation location

Location of non-control stimulation was included as a factor for contributions to between-study heterogeneity. The location subgroups included FZ (k = 1), larynx sensory cortex (k = 1), left BA10 (k = 1), left cerebellum (k = 1), left dorsolateral prefrontal cortex (DLPFC; k = 9), left dorsomedial prefrontal cortex (dmPFC; k = 4), left inferior frontal gyrus (IFG; k = 2), left primary motor cortex (M1; k = 8), left posterior inferior frontal gyrus (pIFG; k = 1), left posterior parietal cortex (PPC; k = 4), lower limb motor cortex (k = 1), right cerebellum (k = 2), right DLPFC (k = 2), right IFG (k = 1), right inferior parietal lobule (IPL; k = 2), right M1 (k = 3), right inferolateral PFC (k = 1), right ventral premotor cortex (PMv; k = 1), right PPC (k = 1), right temporoparietal junction (TPJ; k = 1). Significant differences were found between groups for location of stimulation (Q = 46.53, $p = 0.0004$; see Fig. 5). Locations FZ and larynx sensory cortex, and left BA10 were found to significantly influence effect size (FZ: SMD = 1.02, 95% CI [0.17, 1.87]; larynx S1: SMD = 0.87, 95% CI [0.30, 1.45]; lBA10: SMD = 3.43, 95% CI [2.06, 4.81]), however each of these location subgroups only had one study contribution to that location and should not be considered to generalize to future studies or the population.

3.2.6. Subgroup analyses: measurement variable

The measurement variable used was included as a factor for contributions of between-study heterogeneity. The measurement variable subgroups included studies that measured reaction time (k = 8), accuracy (k = 15), and performance (k = 24). No differences were found across subgroups (Q = 0.32, $p = 0.85$; see Fig. 7). No significant differences in effect size were found for any of the groups.

3.2.7. Subgroup analyses: AMT versus RMT

The motor thresholding technique used to set iTBS intensity was investigated to determine if between-group differences exist for active motor threshold versus resting motor threshold. The subgroups included studies that used AMT (k = 29), unspecified MT (k = 2), and RMT (k = 16). No differences were found between subgroups (Q = 2.07, $p = 0.35$). No significant differences in effect size were found for any of the groups.

3.2.8. Subgroup analyses: navigation to stimulation location

Navigation to stimulation location was included in subgroup analyses to determine if any differences existed between subgroups due to navigation techniques. The conditions included using the 10–20 system (k = 17), individual mapping of the cortex (k = 12), individualized MRI scans (k = 14), measured distance from primary motor cortex (k = 1), neuronavigation using anatomical landmarks (k = 1), and opto-electric neuronavigation (k = 2). Significant differences were found between groups (Q = 14.12, $p = 0.01$; see Fig. 6). Measured distance methods of navigation had a significant influence on effect size (SMD – 1.21, 95% CI [0.34, 2.08]), however this finding should be taken with caution and not extended to generalize to population effects because only one research finding was contributed to that subgroup. Individual mapping contributed the most heterogeneity to the distribution of effect sizes (Q = 59.32, $tau^2 = 0.52$), followed by individualized MRI (Q = 39.22, $tau^2 = 0.67$) and use of the 10–20 system (Q = 20.49, $tau^2 = 0.12$). Heterogeneity measures could not be calculated for the other conditions as their sample sizes were too small.

3.2.9. Subgroup analyses: current flow

The orientation of the coil and the direction of the flow of current were investigated with subgroup analyses. The subgroups included

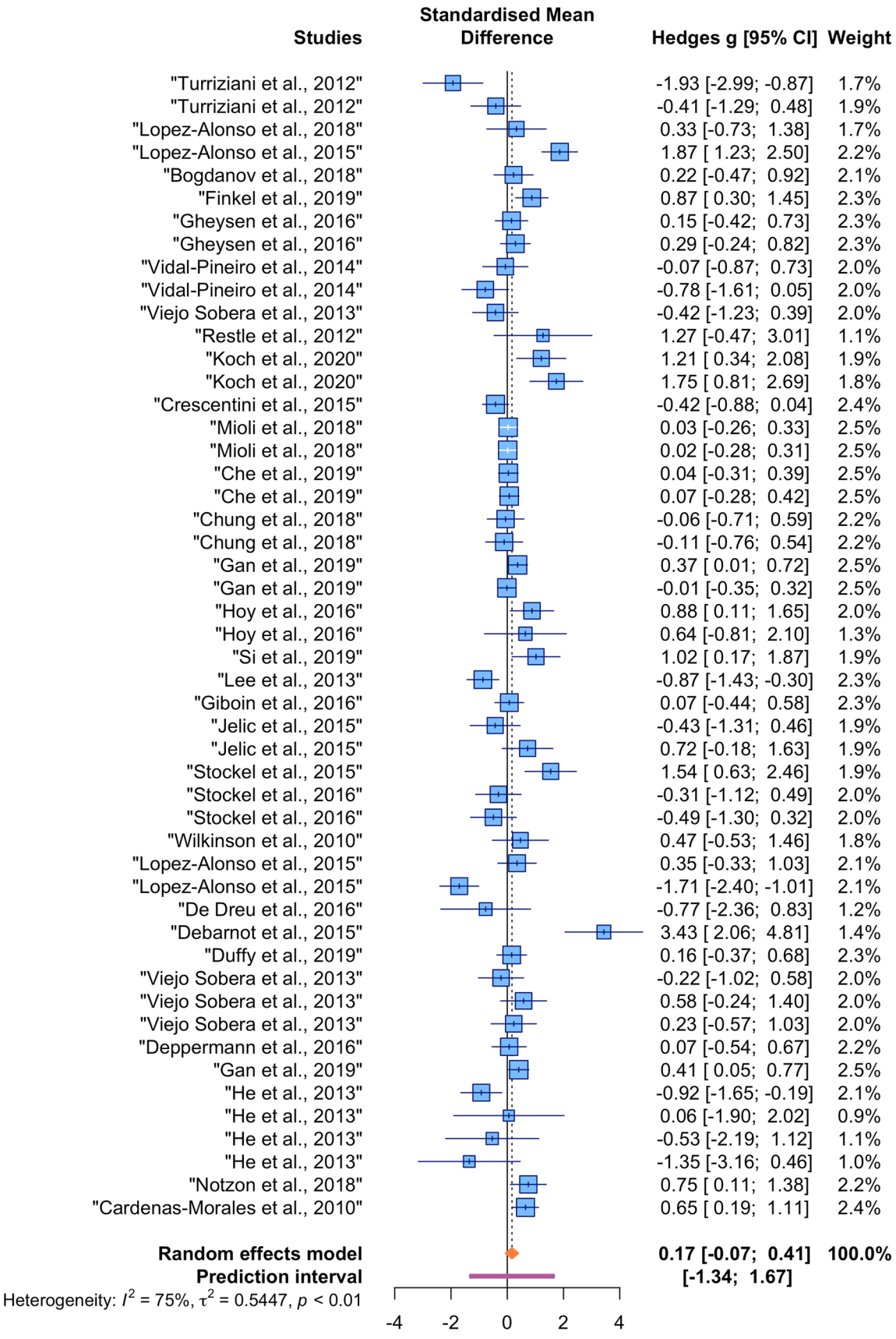

Fig. 2. iTBS versus Control. Forest plot of Hedges' g pooled effect size for iTBS versus control conditions across all studies.

anterior-posterior current flow (AP; k = 11), posterior-anterior current flow (PA; k = 15), and unknown current flow (k = 21). No differences between subgroups were found (Q = 0.68, $p = 0.71$). No current flow subgroups had a significant impact on effect size.

3.3. Multiple meta-regression

The multi-model inference method suggests that study design (importance value = 0.73), sham condition (importance value = 0.58), and current flow (importance value = 0.32) were the most important predictors to consider in a multiple meta-regression model (see Fig. 7). The top 5 models out of all possible combinations from the 8 chosen covariates were compared to each other using ANOVA comparisons, and the model with the lowest AIC value was interpreted. Interaction terms were included in all models. The meta-regression model that performed best included the control condition and study design covariates that were modeled with an interaction. The permutation test (run with 1000 iterations) indicated a marginally significant trend ($F(11,38) = 1.94$, $p = 0.09$) and marginal interaction effects: for no stimulation control condition and within study designs (estimate = 2.87, SE = 1.37, $p = 0.05$, 95% CI [0.09, 5.65]; for coil rotation control condition and within study designs (estimate = 2.24, SE = 1.16, $p = 0.07$, 95% CI [−0.09, 4.59]). This indicates that within study designs (which generally tend to have less between-subjects variance due to the nature of the design) paired with specific kinds of control conditions (no stimulation and coil rotation away from cortex) tend to result in larger positive effect sizes.

3.4. Publication bias

Publication bias results included the full model (not outlier reduced) to determine the full scope of publication bias if it exists. While we do not have any a priori reasons to believe that publication bias exists in this subsection of neuroscience (see Chung et al., 2016 for recent assessment of publication bias in iTBS studies on MEP and cortical excitability measurements), in psychology and science generally, it is an understood assumption that research studies are only published when significant effects are found. Emphasis has been placed on the p-value rather than the overall effect of an intervention to determine the meaningfulness of an experimental result. Dubbed the 'file-drawer' problem, publication of small-sampled studies with large and significant effects, but not small-sampled studies with small or non-significant effects, can increase the pooled effect of a given intervention (Dickersin, 2005). Recently alternative methods for reporting informative statistics have been suggested (Dirnagl, 2019; Halsey, 2019), and it remains important to evaluate the possibility of 'file-drawer' publication bias in studies using the iTBS protocol occurring due to non-publication according to this significance standard.

Small sample bias methods were utilized to assess publication bias, which are able to determine if small studies with small effect sizes are missing (Borenstein et al., 2011). The assumptions required to run these analyses include 1) large studies are likely to be published regardless of significance, 2) moderately sized studies with insignificant findings are at greater risk of not being published but are more represented in the literature as compared to small studies, and 3) small studies are at the greatest risk of not being published because of non-significant findings and thus should have the largest proportion of missing values.

Publication bias was not present in the overall evaluation (see Fig. 8). While the plot is slightly asymmetrical, which may visually indicate publication bias, an Egger's test of the intercept which quantifies funnel plot asymmetry was found to be non-significant (0.29, 95% CI [−1.02, 1.60], $p = 0.66$).

P-curve methods of analysis were also used to determine publication bias. This method assumes that publication bias is generated by p-hacking and/or exploratory forms of data analysis until findings become significant. Fig. 9 displays the observed p-curve versus null effects and sufficient power. We found that of the total 50 studies included, 16 presented significant findings. The evidential value, or the true effect size, was found to be present, indicating that these findings are not the product of publication bias and p-hacking. Were p-hacking present, the graph in Fig. 9 would be inverted, with a higher percentage of findings being located closer to p = 0.05. This bodes well for researchers utilizing iTBS, signaling that the significant effects found in these studies are likely the result of finding a true effect.

3.5. Risk-of-bias assessment

Results from the risk-of-bias assessment are presented in Fig. 10, and are weighted by their contribution to effect sizes. One set of independent reviewers had an overall agreement rating of 94.6% (SP & DCC), and the other set of independent reviewers had an overall agreement rating of 79.1% (AP & BM). All disagreements surrounding ratings for the risk of bias domain were resolved through discussion between all reviewers until 100% agreement was achieved.

Bias arising from the randomization process did not appear to significantly impact the results obtained from the meta-analysis. Some studies did present concerns, specifically related to not including information related to the randomization process or blindness of the participants to the applied TBS interventions, or having pseudorandomized assignment to protocols, which is not a proper substitute for complete randomization. Bias due to deviations from the intended interventions presented mostly low risk, however a few studies did present some concerns. The set of results from Gan and colleagues (2019) had some concerns in this domain due to subjects being asked if they felt the assigned intervention effect improved the outcome, with some participants within the sham condition answering that they did feel their abilities improved post-stimulation. While the results were always compared to subject baseline in this case, and there was no consistent agreement on which forms of stimulation were perceived as improving their abilities, it is unlikely that there was an effect on the trial itself, but reviewers felt this warranted some concern. The results of the meta-analysis were likely not impacted due to bias in missing outcome data or bias in the measurement of the outcome, due to reports of low bias across all studies. There was a significant impact found regarding bias in the selection of the reported result. Many studies presented some concern, and some presented high concern. This was due largely to many studies not explicitly stating or having a pre-specified analysis plan. Overall, there are some concerns related to risk of bias, specifically due to the randomization process, deviations from intended interventions, and in the selection of the overall results. Aggregated ratings for each of the studies in each domain are included in the supplementary material.

4. Discussion

4.1. Conclusions of iTBS efficacy

The primary aim of this meta-analysis was to determine if facilitatory brain stimulation experiments — following the protocol set by Huang and colleagues (2005) — have shown reliable and effective results in cognitive enhancement for healthy adults after a single session of iTBS. Secondary aims were to determine which factors may contribute to heterogeneity in the effects of iTBS on cognition between studies, and if certain factors were predictive of effect size outcomes. Meta-analytic approaches until this point have confirmed that iTBS enhances motor cortex excitability and facilitates MEPs (Chung et al., 2016), but questions regarding how facilitatory theta burst stimulation affects behavior which is mediated through higher-order cognition have until now remained unanswered.

Our findings indicate that in an outlier-reduced model, there is an indication that iTBS has a small positive effect on measures of cognitive enhancement compared to control conditions, indicating that facilitatory stimulation may indeed be effective. However, substantial

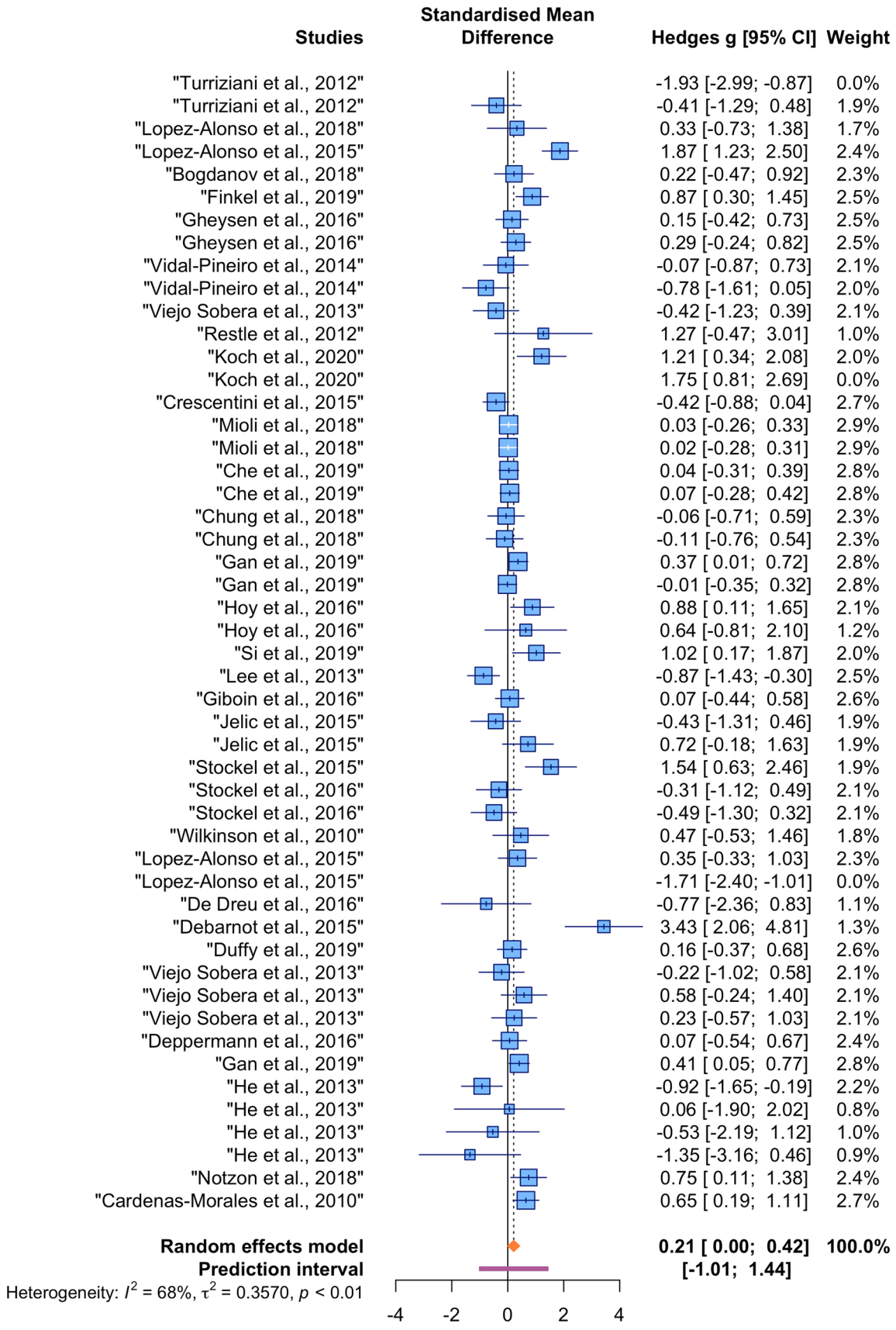

Fig. 3. iTBS versus Control – Outlier-reduced Model. Forest plot of outlier-extracted meta-analysis comparing iTBS versus control conditions.

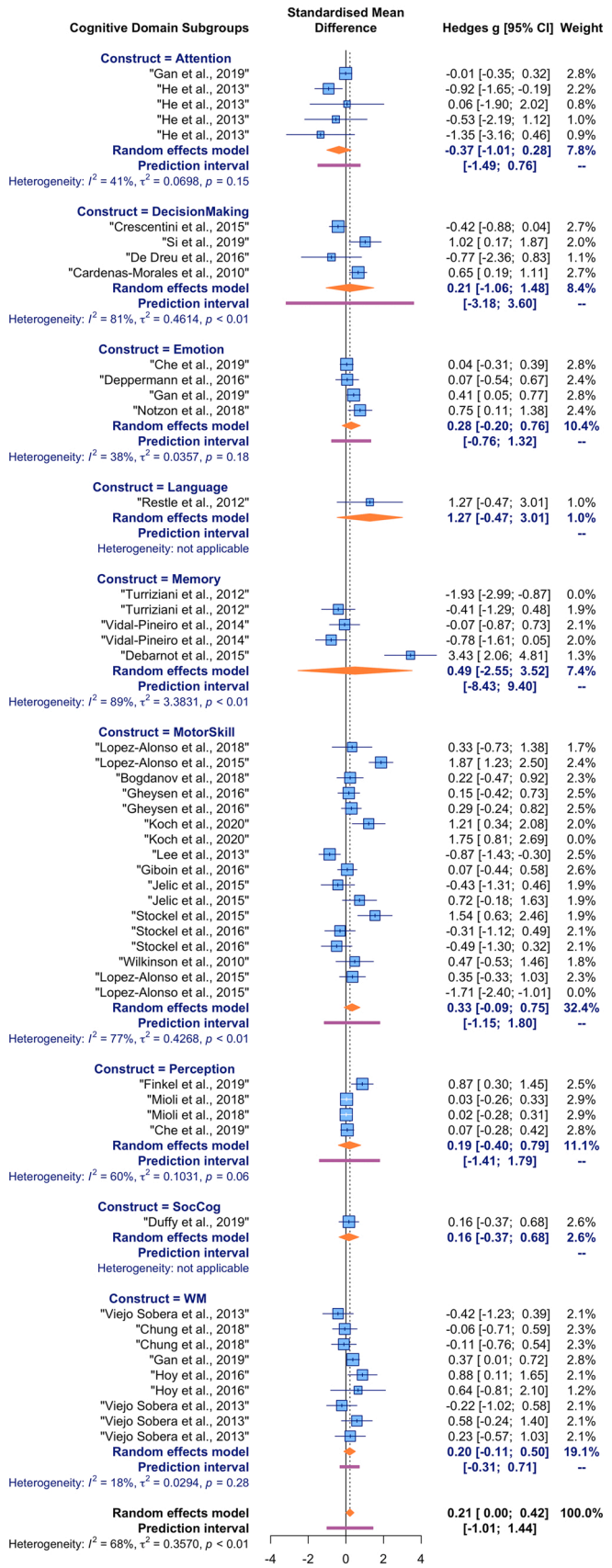

Fig. 4. iTBS versus Control: Cognitive Domain Subgroups. Forest plot distinguishing pooled effects for each cognitive domain of iTBS versus control conditions.

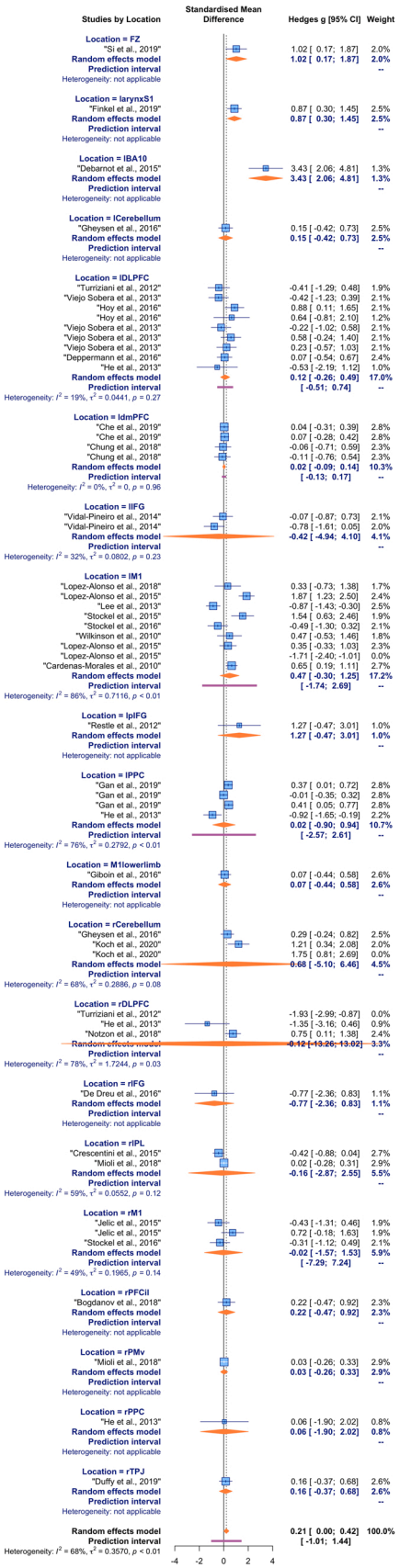

Fig. 5. iTBS versus Control: Stimulation Location Subgroups. Forest plot of location subgroups.

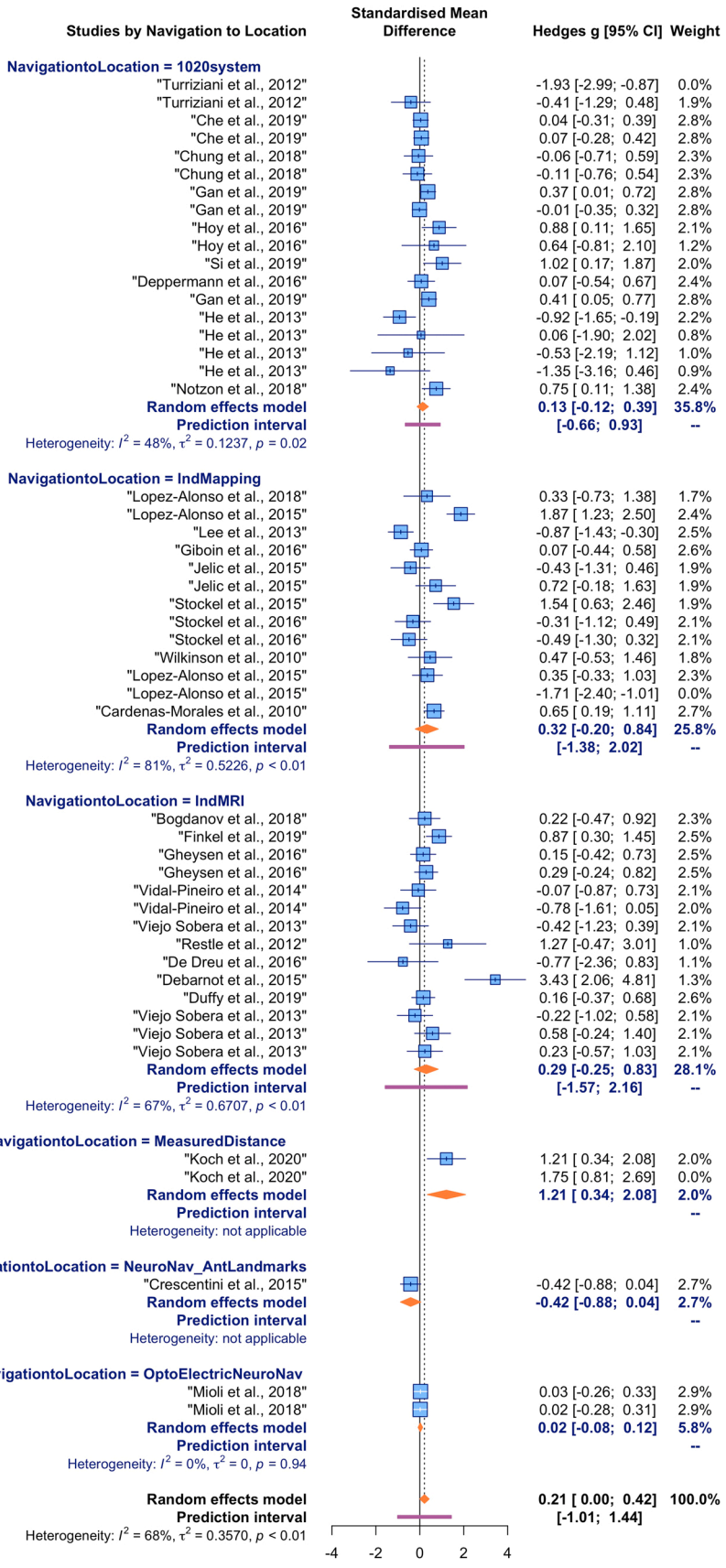

Fig. 6. iTBS versus Control: Navigation to Location Subgroups. Forest plot of effect sizes grouped by navigation to location factor.

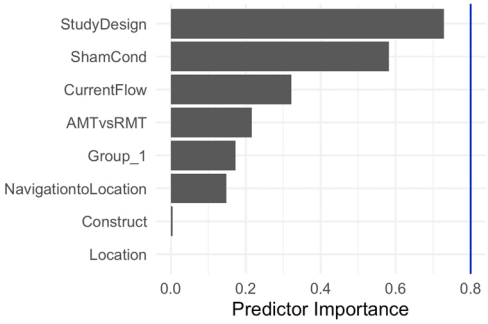

Fig. 7. Multimodel Inference. Graphical representation of multimodel inference analysis categorizing all predefined predictors by their importance with respect to effect size.

heterogeneity in effect sizes was present across these studies, indicating variability in the effect of iTBS on cognitive tasks. This variability arises from a number of researcher decisions which must be made when implementing TMS studies, such as the specific cognitive domain in question, the measurement variable for that cognitive domain, the motor thresholding strategy, TMS current flow, study design, the target of stimulation, type of control condition, and the method for navigation to the stimulation site. Subgroup analyses on these factors revealed three factors which contribute significantly to this heterogeneity— summarized below. Based on the results of these subgroup analyses, we conclude with a list of recommendations for future studies using the iTBS protocol as a causal method for investigating cognitive enhancement.

4.2. Factors that influence iTBS efficacy, conclusions from subgroup analyses

Subgroup analyses on a number of factors were run to determine the distribution of heterogeneity among effect sizes, and to determine which factors influence effect size for iTBS experiments of cognitive enhancement. These results should be referenced by researchers using the iTBS protocol to understand how experimental parameters can influence study outcomes. Notably, the specific brain region targeted, the method for navigating to the targeted brain region, and the type of control condition used were found to be influential factors for the effects of iTBS interventions on cognitive enhancement. Of the factors investigated, meta-regression analyses determined that study design and control condition were the two most important parameters in predicting effect size.

4.2.1. Cognitive domain

Grouping studies based on cognitive domain revealed no significant between-group differences, and no group contributed significantly to the distribution of effect sizes. This signals that there may be no differences in the efficacy of iTBS across cognitive domains. However, an alternative explanation is that the heterogeneity of studies between cognitive domains may be so disparate and the number of studies so small within each domain that the efficacy of iTBS is not accurately captured by the meta-analytic model. Some cognitive domains (social cognition and language) had only one research contribution, which does not allow for accurate estimations on how studies in these domains may or may not differ from cognitive domains with more published works.

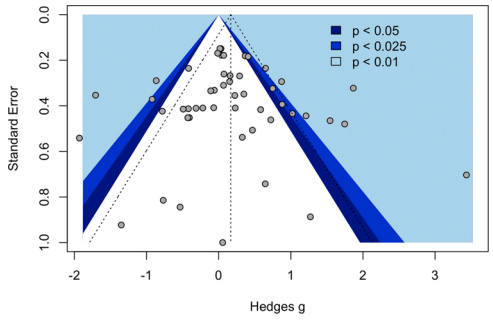

Fig. 8. Small Sample Bias Funnel Plot. Funnel plot of the studies included in the overall meta-analysis. Larger studies, which have an inherently smaller standard error are plotted on top of the y-axis, and the x-axis shows the effect size of each study. The shaded areas indicate levels of significance, with many studies reporting non-significant findings.

4.2.2. Control condition

Marginal differences were found between groups based on the type of control condition used, however no single group was found to significantly influence effect size. These results are to be interpreted with caution, as most studies implemented coil rotation away from the cortex as their control method (k = 29), while other control methods were used in a smaller number of studies, making interpretation of the individual impacts of other control methods on effect size difficult. In practice, our finding that there are differences between sham conditions demonstrates that the methods researchers use to control for stimulation may be lacking. If there were no differences between control groups, this would indicate that each method of controlling for stimulation acts as a control in the same way - this does not seem to be the case based on present findings. However, this does indicate that there may be reason to include a variety of control conditions in future iTBS studies. Recent work has investigated the effectiveness of sham conditions in TMS studies more broadly (Duecker and Sack, 2015), arguing that multiple control conditions should be utilized due to suboptimal performance of singular sham conditions as effective controls.

4.2.3. Target stimulation location

It may seem intuitive that target stimulation location is an important factor in iTBS studies – different regions of the brain may respond differently when provided with targeted facilitatory stimulation, and different cognitive tasks are associated with different brain regions. The findings of this meta-analysis related to target location do not support this intuition that particular target regions are more susceptible to the effects of iTBS on cognitive enhancement than other regions. On the contrary, it seems that iTBS effects may generally translate across target regions. However, target stimulation location is an important factor in the magnitude of the subsequent effect size of the measured behavior. Further investigation into how stimulation affects behavior, cortical excitability, and brain activity using simultaneous EEG, fMRI, or fNIRS technology could elucidate how different regions of the brain respond to stimulation at different time points.

4.2.4. Navigation to stimulation sites

Significant differences found between groups with different methods

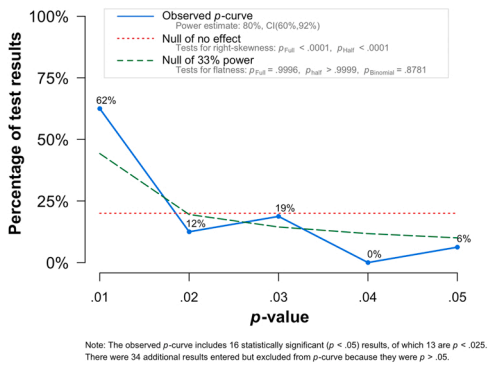

Fig. 9. P-Curve Analysis. P-curve of significant findings included in the meta-analysis.

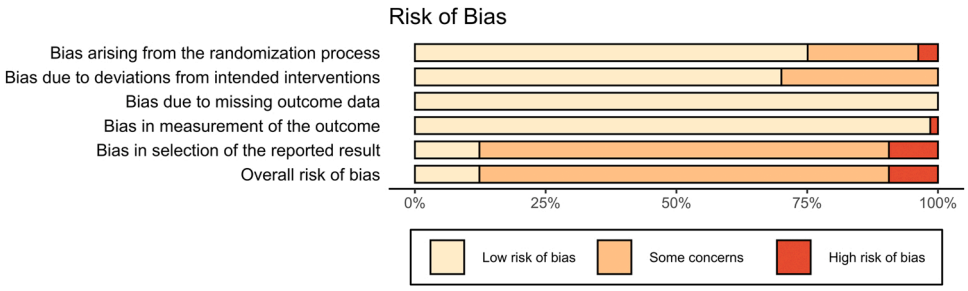

Fig. 10. Risk of Bias summary. Author's judgements for each risk of bias criterion across all included studies.

for navigating to stimulation location indicates that this is an important factor to consider when conducting iTBS studies. While no groups had a significant impact on effect size, we would expect differences to naturally arise due to the preciseness of each technique. For example, the 10–20 system is not as precise as individualized MRI or motor cortex mapping methods. One study has shown that the error of coil placement when using the 10–20 system can extend up to two centimeters in three dimensions, and approximately 10% of individuals had coil placement that bordered on functionally distinct areas (Herwig et al., 2003). Another study cited the 10–20 system as being the least-accurate targeting system when compared to fMRI-guided neuronavigation, probabilistic neuronavigation, and TMS-mapping methods for stimulation of the motor cortex (Sparing et al., 2008). This prior evidence is not to suggest that the 10–20 system should be thrown out, but we suggest other mapping approaches should be investigated in tandem to determine how exactly navigation to a stimulation location generates the effect of interest.

4.2.5. *Meta regression - study design and control condition*

Significant and marginal interactions with positive effect sizes were found for studies utilizing no-stimulation control conditions and coil-rotation control conditions with within-subjects experimental designs, as compared to an active stimulation control condition with between-subject experimental designs. Although within-subject studies have less inherent variability due to the nature of the design, these interactions were puzzling. We believe this finding may support placebo effects when subjects are not naïve to TMS. It is relatively easy for a participant to determine if a sham condition is being used, especially in no-stimulation conditions and in coil rotation conditions due to perceivable differences in the sensory aspects of stimulation (Rossi et al., 2009). Active control conditions may be indistinguishable from non-control conditions, however research regarding blindness of subjects or experimenters across control conditions remains sparse. Many experimental researchers do not report these data, however small systematic analyses have been conducted regarding clinical outcomes (Berlim et al., 2013; Broadbent et al., 2011). The lack of placebo effect with sham stimulation is a well-known issue in the field (Davis et al., 2013; Loo et al., 2000). The use of active controls, non-responder populations, and alternative forms of sham stimulation that are less likely to be correctly identified as control conditions, while problematic in their own ways (Duecker and Sack, 2015), are useful when working with subjects who are not naïve to stimulation.

4.3. *Limitations of the current meta-analysis*

It may be called into question whether studies which used disparate methodologies and measures can be compared within a single meta-analysis. Collapsing studies into a generalized cognitive domain category or measured behaviors can certainly muddy effects, especially considering that these findings were independent from one another, and it is likely that each researcher used different methods to investigate their variable of interest. While this is a sensible critique, the increasing use of and reliance on iTBS as an intervention to investigate cognitive enhancement renders the need to consolidate and evaluate these findings with a high degree of clarity and methodological rigor — as done here. Some of the variability across study subgroups from this aggregation was accounted for by using random-effects meta-analytic modeling, and this variability was further investigated by performing subgroup analyses and meta-regression, which can evaluate interactions between predictors. This does not account for all variability across studies; however, we believe these findings are novel contributions to the field – specifically for determining important factors that contribute to variability between studies and which parameters of iTBS influence effect sizes.

It should be noted that individuals themselves could be highly variable in their responses to iTBS, as some subjects do not have the expected facilitation of MEPs to iTBS (Hinder et al., 2014). A recent meta-analysis on subject response to NIBS found that factors that influence corticospinal excitability include genetic variation – specifically the BDNF genotype – age differences between older and younger adults, menstrual cycle variation, skull thickness and brain morphology (Pellegrini et al., 2018). These particular factors were out of the scope of the present meta-analysis due to low reporting of BDNF polymorphism, two studies having investigated older adults (Debarnot et al., 2015; Vidal-Pineiro et al., 2014), no studies reporting menstrual cycle characteristics of their samples, and no availability of data regarding brain structure and skull structure.

A related limitation of this meta-analysis was the exclusion of additional cortical excitability measurements, namely modulation of MEP and EEG transcranial evoked potential (TEP) amplitudes after stimulation. While we do consider cortico-spinal and cortical excitability measurements to be a component of cognitive processing and note that these are indeed measurements related to cognitive enhancement, the focus of this meta-analysis was to investigate behavioral measurements that were not direct indices of cortical excitability. Recent meta-analyses have already investigated the influence of iTBS on cortico-spinal and cortical excitability (Wischnewski and Schutter, 2015; Chung et al., 2016). Additionally, EEG-based studies were excluded, as there were not enough studies with post-iTBS EEG measurements with proper controls, making quantitative assessment infeasible.

This meta-analysis also excluded studies that utilized pre-post measurements when conducting iTBS interventions without additional control conditions. These studies use each individual subject's performance pre-iTBS as a measure of behavior at baseline, which is a valid way to control for subject-dependent variability. However, these pre-post studies require the estimation and calculation of the standardized mean gain, which is an effect size that should not be combined with the standardized mean difference which is the measure that was compared in this meta-analysis. To evaluate the efficacy of iTBS on cognitive enhancement for pre-post test methodologies would require conducting an additional protocol and separate meta-analysis. Therefore, evaluating the efficacy of pre-post iTBS procedures on cognitive enhancement was outside of the scope of the current meta-analysis. Future investigation should be conducted with these data, as the use of pre-iTBS baseline

measurements as a way to control for variability could help reduce heterogeneity in meta-analytic models.

The lack of standardization in the field for reporting many iTBS parameters created some difficulty in conducting this meta-analysis, which was reflected in the risk-of-bias assessments. Many studies did not include detailed information on the randomization processes in their study, or report if the subjects and administrators of TBS were blinded. It is increasingly important, especially considering the results from this meta-analysis surrounding control conditions, to try to mitigate any effects of knowledge of stimulation through use of either multiple control conditions or a proper sham condition that can simulate the physical sensations of being stimulated. The results regarding significant amount of bias related to the selection of reported results was heavily influenced by lack of an explicit pre-specified analysis plan before data were collected and available to analyze; this is something that would only improve the chances of understanding the true effect of iTBS on cognition, and should become standard in the field. Further, nine published studies did not provide adequate information to calculate effect sizes. In these instances, outreach to authors was necessary so as to include as many research findings as possible. But this outreach was not always successful. In addition to published articles not providing sufficient information for effect size estimation, many studies did not report parameters that would aid meta-analytic modeling, including coil dimensions ($k = 2$), coil and stimulator manufacturer ($k = 4$), method for calculating motor threshold ($k = 2$), and coil orientation ($k = 25$).

4.4. Specific recommendations for future iTBS research

The findings from this meta-analysis should be used to inform future studies utilizing iTBS in efforts to enhance particular aspects of cognition. These findings provide a consensus on the state of the field regarding the efficacy of iTBS interventions to cognitive measures, beyond cortical excitability. Moreover, both the findings and limitations of this meta-analysis have resulted in a list of recommendations for researchers conducting future studies using the iTBS protocol as a causal method for investigating cognitive enhancement.

Based on the current findings, we suggest the following prescriptions for future research using iTBS to enhance cognition. Researchers should use strict methodological rigor and careful attention when determining: the location of stimulation, the type of control condition to be used, and how navigation to the stimulated location is chosen. These factors were found to contribute to differences between studies. The location of stimulation and the type of navigation used should also be backed by prior literature – and ideally multiple control conditions should be implemented in experimental designs to account for potential placebo effects and variability across control conditions. This will aid future research by advancing our knowledge regarding the inadequacies of particular sham and control methods.

Authors contributing to the field of non-invasive brain stimulation should utilize effect size calculations in the statistical packages used to analyze their data, and report those statistics, even if the findings are not significant. Further, authors should make their data readily available to researchers who are attempting to conduct systematic reviews. Researchers should report the following methodological parameters: details of the control condition used, the location stimulated and how navigation to this location was determined, motor threshold determination and parameters of motor threshold used for theta burst stimulation (% output of stimulator, and whether resting or active motor threshold was used), coil orientation and the direction of current flow, and coil specifications and stimulator manufacturer.

We encourage researchers to report sham-blindness measures using both within-subjects and between-subjects designs. This can easily be adopted by asking participants what condition they perceived to be in post-stimulation. Additionally, we recommend that researchers using NIBS protocols pre-register their studies and report pre-specified analyses plans before assessing the iTBS interventions on outcomes. Reporting the aforementioned parameters enables successful replication of studies, which in turn enables the determination of a true effect regarding the enhancement of cognition after intervention with the iTBS protocol.

These recommendations may be relevant for any study using iTBS to modulate cognition, including academic and clinical research. In response to recent reports demonstrating noninferiority of iTBS to rTMS for the treatment of pharmacoresistant major depressive disorder (Blumberger et al., 2018), and suggested potential applications in other patient populations (Hanlon et al., 2017; Philip et al., 2019; Petrosino et al., 2020), it is pertinent to address experimental rigor and reporting. Similar concerns have been reported about TMS studies using patient populations, including small sample sizes, under-reporting methodological details, and inadequate sham and control conditions (Serafini et al., 2015), making meta-analytic review difficult (Martin et al., 2016, 2017). While the meta-analysis described here only examines healthy control populations, and thus the results may not be extended to conclusions about efficacy in patient populations, our recommendations for methodology and reporting are relevant across all fields using non-invasive iTBS. These recommendations will allow for rigorous meta-analytic review of iTBS efficacy for cognitive enhancement.

An important area for future TBS research involves the inclusion of simultaneous neural recording through the use of EEG or MEG to determine how stimulation of regions outside of the motor cortex impacts cortical excitability of those regions, whether we can assume that iTBS facilitates neural activity across the entire cortex, and for determining if and how inter-individual variability plays a role in cortical excitability across the cortex.

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Contributions of authors

AP and RB conceptualized the review, AP conducted the analyses, AP, SP, DCC, and BM conducted the codification of bias and AP, SP, DCC, BM, and JMR contributed to the codification of studies; All authors contributed to the writing of the manuscript.

Data Availability

I have shared my link to the dataset and code in the attach files step (iTBS meta-analysis dataset (Original data) (OSF)).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2022.104587.

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