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Large-scale analysis of interindividual variability in theta-burst stimulation data: Results from the 'Big TMS Data Collaboration'

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ABSTRACT

Background: Many studies have attempted to identify the sources of interindividual variability in response to theta-burst stimulation (TBS). However, these studies have been limited by small sample sizes, leading to conflicting results.

Objective/Hypothesis: This study brought together over 60 TMS researchers to form the 'Big TMS Data Collaboration', and create the largest known sample of individual participant TBS data to date. The goal was to enable a more comprehensive evaluation of factors driving TBS response variability.

Methods: 118 corresponding authors of TMS studies were emailed and asked to provide deidentified individual TMS data. Mixed-effects regression investigated a range of individual and study level variables for their contribution to iTBS and cTBS response variability.

Results: 430 healthy participants' TBS data was pooled across 22 studies (mean age = 41.9; range = 17–82; females = 217). Baseline MEP amplitude, age, target muscle, and time of day significantly predicted iTBS-induced plasticity. Baseline MEP amplitude and timepoint after TBS significantly predicted cTBS-induced plasticity.

Conclusions: This is the largest known study of interindividual variability in TBS. Our findings indicate that a significant portion of variability can be attributed to the methods used to measure the modulatory effects of TBS. We provide specific methodological recommendations in order to control and mitigate these sources of variability.

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Abbreviations and nomenclature

TMS	transcranial magnetic stimulation
MEP	motor evoked potential
iTBS	intermittent theta-burst stimulation
cTBS	continuous theta-burst stimulation
DV	dependent variable
IV	independent variable
Normalised MEP	DV for main regression analyses (conditioned MEP amplitude expressed as a percentage of the baseline MEP amplitude)
TS	test stimulus (pulses used to collect pre/post MEPs for TBS protocols, i.e. 120% RMT or 1 mV method)
RMT	resting motor threshold
AMT	active motor threshold
Pulse waveform	pulses used to collect pre/post MEPs (i.e. monophasic or biphasic)

Introduction

Repetitive transcranial magnetic stimulation (rTMS) protocols are widely used to induce plasticity in the human brain [1]. Such protocols are used experimentally, to assess the brain's response to modulation [2,3], and also clinically, to treat neuropsychiatric disorders such as major depressive disorder [4,5] and obsessive compulsive disorder [6]. One form of rTMS, theta-burst stimulation (TBS) holds particular promise in the induction of brain plasticity given that it requires lower stimulus intensities and shorter stimulation times than previous rTMS protocols [7]. At present however, the effects of TBS are highly variable across participants [8,9], limiting its utility as a clinical and experimental tool. Several studies have investigated interindividual variability in response to TBS [8,10–14]. However, these single site studies have been limited by small sample sizes, preventing a thorough evaluation of the sources of TBS variability. The current paper describes an approach that brings together over 60 TMS researchers to form the 'Big TMS Data Collaboration' (Supplementary file 1), where we share individual participant TMS data across studies to increase sample size and statistical power. Similar to other neuroscience consortia, which have long been common in neuroimaging [15,16], we form this collaboration in the hope that large-scale analyses will allow us to answer questions that have not been able to be answered with single-site research. Here in the first instance, we investigate factors accounting for interindividual variability in response to TBS.

Methods

This project was deemed exempt from ethical review by the Deakin University Human Research Ethics Committee because it involved only the use of pre-existing, non-identifiable or re-identifiable data. All primary studies had been approved by local institutional review boards, and all participants had provided informed consent.

Article identification strategy

The present TBS analysis comes from a larger project also collecting single and paired-pulse TMS data and input-output (I/O) curve data. A systematic search for all of these data was conducted in PubMed in February 2017. A search for each TMS protocol was conducted separately using the combination of synonyms of the following terms: intermittent theta-burst stimulation; continuous theta-burst stimulation; short-interval intracortical inhibition; intracortical facilitation; input-output curve; stimulus-response curve; and transcranial magnetic stimulation. The full search syntax is provided in Supplementary file 2. Given our aim of collecting individual participant data from corresponding authors, it was unrealistic to collect data from all previous TMS studies implementing these protocols. Rather, we set a goal of collecting at least 10 studies' individual participant data per TMS protocol. The initial search was limited to studies published between January 1, 2014 and December 31, 2016, as we reasoned that there was a higher likelihood of obtaining data from more recent studies. For iTBS and I/O curve data, the search was expanded to include studies from 2013, and studies from 2012 to 2013 for cTBS, because we could not initially collect enough individual participant data to meet our goal.

Inclusion criteria were: studies using a figure-of-eight coil and studies measuring TMS responses from intrinsic hand muscles. Exclusion criteria were: non-human subjects, and TBS applied to a brain region other than the M1 representation from which motor evoked potentials (MEPs) were collected.

Titles of all articles identified by the search were exported to a spreadsheet for iTBS, cTBS, SICI, ICF, and I/O curve data separately. To avoid bias in study selection, we then ran a random number generator to identify the studies from which we would attempt to collect individual participant data. If an article met inclusion criteria, the corresponding author of the study was emailed and asked for participants' age, gender, motor threshold (MT), and baseline and conditioned MEP amplitudes. We screened studies and emailed authors in blocks of 20 studies at a time until we reached our goal of at least 10 studies per protocol. Corresponding authors were asked to de-identify data prior to sending, and the template spreadsheet was sent with numbers pre-filled 1-x along a 'Participant ID' column. Formal collection ceased in August 2017. Unpublished data, and other TMS data not identified within our search, were also included through informal communication with colleagues or corresponding authors. These data were subject to inclusion/exclusion criteria, but were not constrained by publication date.

Variables of interest and data used for present TBS analyses

All participants' data were collected from studies, yet only healthy participant data were analysed within the present paper. For each individual, conditioned MEP amplitudes (i.e. post-TBS MEPs) were normalised to the baseline MEP amplitude using the equation: (conditioned MEP amplitude/baseline MEP amplitude) x 100 [9,13,17]. A value of 100% represents no change, values < 100% represent suppression, and values > 100% indicate facilitation, of MEP amplitudes following TBS. This value is referred to as 'normalised MEP' henceforth, and was used as the dependent variable (DV) for all main analyses. Note that some previous studies have used a 'percentage of change' value to quantify TBS effects (conditioned MEP amplitude - baseline MEP amplitude)/(baseline MEP amplitude) x 100 [3,14]. However, this value and normalised MEP give the exact same output for regression analysis (Supplementary file 3).

For the main analyses investigating IVs predicting iTBS and cTBS-induced plasticity, as per the results of Chung et al. [18], who demonstrated changes in MEP amplitudes at early (<5 min), mid (20–30 min), and late (50–60 min) post TBS, we analysed MEP amplitudes up to 60 min post-TBS. A grand average normalised MEP amplitude was then created for each participant by averaging normalised data across all (0–60 min) timepoints [9,14].

Subsequent analyses investigated TBS-induced plasticity at different timepoints (see 'Additional analyses' section).

The following independent variables (IVs) were analysed for their influence on interindividual variability in TBS data: age, gender, baseline MEP amplitude, TMS machine delivering TBS, target muscle, M1 hemisphere, TBS intensity, test stimulus (TS) intensity, pulse waveform, the use/absence of neuronavigation, MT (monophasic RMT, monophasic AMT, biphasic RMT and biphasic AMT), time of day, and the number of baseline MEPs collected. For time of day, we grouped data into morning (7am–11.59am), afternoon (12pm–2.59pm), and evening (3pm–7pm) groups. These times were defined based upon an effort to make the study/participant numbers approximately equal between groups. For the number of MEPs collected, the uneven distribution of the data did not allow this to be analysed as a continuous variable, therefore we split the dataset into a low number of MEPs collected (<20), or a high number of MEPs collected (≥20), based on the median value (20). We collected handedness data for nine studies, yet there were only four left handers, therefore this IV could not be analysed statistically.

Studies used either a Magstim Rapid TMS machine, a Nexstim NBS TMS, or a MagPro TMS machine to deliver TBS. We could not determine the specific MagPro model used in all studies, therefore these machines were grouped based on the brand. For the comparison of TS intensities, most studies either used 120% of RMT or a percentage of maximum stimulator output evoking a 1 mV MEP, thus a comparison was made between these intensities. Two studies used neither method [19,20] and were therefore excluded from this comparison.

Three studies used I/O curves to measure corticospinal excitability pre and post TBS [21–23]. Here, to maintain uniformity and increase statistical power, we included data elicited by the 120% of RMT stimulus intensity within the I/O curves. We were not able to obtain baseline MEP amplitude data from one study [24]. To ensure that this study's data were not excluded from any regression analysis (i.e. listwise deletion) including baseline MEP amplitude as a IV, we imputed these missing values based on a Gaussian normal regression model in Stata 15.0 [25,26]. For studies that tested the effect of external interventions on TMS outcomes (e.g. exercise - McDonnell et al. [27]), only control/baseline data were analysed.

We verified the accuracy of the data sent to us by comparing the results to group mean data in the corresponding published paper. In cases of discrepancies, corresponding authors were contacted for clarification. In instances where accuracy could not be verified, the study was excluded. See Fig. 1 for adapted PRISMA flowchart [28].

All statistical analyses were conducted using Stata 15.0 (StataCorp, USA). First, normalised MEP data were checked for outliers using histograms and descriptive statistics. A number of outliers were detected, therefore values falling outside of the 2nd and 98th percentiles (for iTBS and cTBS protocols separately) were winsorized [29,30]. See Supplementary file 4 for histograms prior to winsorization.

Variability analysis

Prior to our main analyses investigating IVs predicting interindivdual variability in response to TBS, we sought to characterise the variability of the data across our collected sample. As per the method of Brown et al. [31], we calculated intraclass correlation coefficient (ICC), standard deviation (SD), and coefficient of variation (CV) [32] values to assess within participant, within study, and between study variability of TBS data. Within participant ICCs were calculated using the normalised MEP value across TBS timepoints. Note that this differs to previous studies' evaluations of within participant variability/reliability, which have used within-participant responses to TBS across separate sessions [33,34]. Within study values were calculated using the normalised MEP of participants within each study, and between study values were calculated using the mean normalised MEP value of each study [31]. ICC values < 0.50 were considered low; values 0.50–0.75 considered moderate; and >0.75 considered high [35]. High 'within participant' ICC values reflect smaller normalised MEP variance within participants (i.e. across TBS timepoints) relative to larger variance within study (i.e. between participants), while high 'within study' ICC values represent smaller within, relative to larger between, study variance [36].

Main regression analysis

Main analyses investigated IVs predicting iTBS and cTBS-induced plasticity. Here, we used mixed-effects linear regression using a 'one-step' model as described by Riley et al. [37], using 'study ID' as a random factor. This preserves the nesting of participants within studies, given that it is inappropriate to simply analyse individual-participant data as if they all came from a single study [37]. We used forward-stepwise regression in two stages for each TMS protocol [38]. We chose this method because we had a large set of potential predictors, and we wanted to identify IVs that had a remaining independent relationship with the DV.

Stage 1 regressions analysed the variance in normalised MEP explained by each IV separately, while controlling for the age and gender of participants. Age and gender were included in all stage 1 models given that these are individual characteristics for which we had data for all participants. IVs with p-values < 0.10 were added to the regression model in stage 2, while IVs with p-values > 0.10 were dropped.

The stage 2 starting regression model comprised of all IVs that were $p < 0.10$ in stage 1. Consecutive regressions then iterated through IVs that were dropped in stage 1, to see whether these IVs now obtained a p-value < 0.10 controlling for IVs in the starting stage 2 model. Thus, the final regression model comprised of IVs that obtained a p-value < 0.10 in predicting TBS-induced plasticity in either stage 1 or 2 regressions.

IVs were omitted from regression analyses for three possible reasons. First, an IV was omitted if it was not comprised of at least three studies within each IV level, given that unreliable estimates may have resulted from a smaller number of studies per level. For example, the IV 'M1 hemisphere' was included only if both left and right hemisphere data were present across at least three studies. Second, an IV was omitted if its inclusion led to a substantial reduction in the overall sample size of the regression analysis for that DV, due to that IV only being measured in a subset of studies. We defined a 'substantial reduction of the regression sample size' as cases where two or more studies were excluded from the regression analysis. Third, an IV was omitted because of collinearity, which occurred if two types of MTs were included in the same regression model. To avoid this, if two or more types of MTs had a p-value < 0.10 in stage 1 regressions, for stage 2 we included only the MT that was the strongest predictor of normalised MEP.

Given the presence of non-linearity and non-normality, robust variance estimates were used for all regressions. Adjusted marginal means (just 'marginal means' henceforth) estimated the mean normalised MEP amplitude adjusted/controlled for all other variables in the regression model, allowing for an interpretable estimate of TBS-induced plasticity [39].

Post-hoc analyses

Where sufficient data, post-hoc analyses were run on IVs that were omitted from the main regression analyses for any of the three

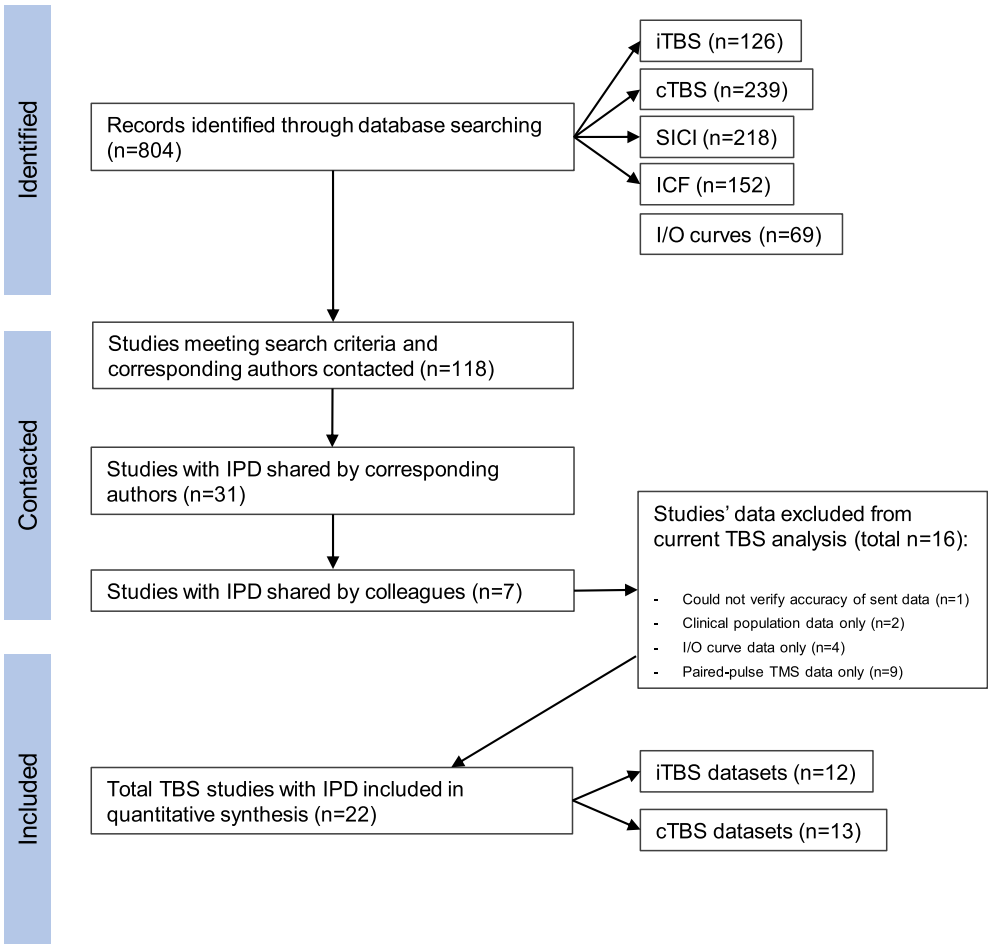

Fig. 1. PRISMA flowchart. Adapted from Liberati et al. (2009). Note that some studies employed both TBS protocols, resulting in more datasets than studies. IPD = individual participant data.

aforementioned reasons. Next, given the appearance of bimodal groupings of age (see Figs. 4 and 7), we also analysed normalised MEP with age split into a younger and older group, based on median age (iTBS = 50 years; cTBS = 30 years). Lastly, scatterplots indicated possible non-linear relationships between normalised MEP and age and also baseline MEP amplitude. Therefore, we re-analysed these relationships using quadratic and cubic regression models [40]. All post-hoc analyses controlled for all other IVs in the final regression model.

Additional analyses

A number of additional analyses were performed to further explore the data. First, we sought to determine the effect of time on TBS-induced plasticity. To do this, we created the IV 'timepoint', and grouped data into 10 min intervals post-TBS (i.e. data collected 0–10 min post TBS; 10–20 min, etc.), up until the point at which fewer than three studies collected data in that time interval (as per our criteria for the necessary number of studies per level in the main regression analyses). For example, only one iTBS study [3] collected MEPs > 30 min post-TBS, thus our last time interval for iTBS was 20–30 min. There were two exceptions to this: first, we had sufficient data to split the first time interval into 0–5 min and 5–10 min post-TBS; and second, only two studies collected MEPs 40–50 min post cTBS, thus we grouped these data into a time interval of 40–60 min (4 studies). To analyse the effect of time, we re-ran our final iTBS and cTBS regression analyses while additionally including the 'timepoint' IV. Post-hoc analyses compared normalised MEP data between each of the timepoints, and also to 100 (no TBS-induced plasticity).

Next, given evidence that TBS-induced effects may be strongest at early timepoints [17,18], and the results of the above timepoint analysis demonstrating that plasticity was only present 0–10 min following cTBS, we sought to determine whether the results of our main analyses may have differed if data were analysed within this earlier time interval where plasticity was strongest. To do this, we repeated our main regression analyses whilst only including normalised MEP data from 0 to 10 min following TBS.

Lastly, we investigated whether 70% RMT and 80% AMT TS intensity methods might deliver TBS at different machine output intensities, given these methods have previously shown to result in differences in TBS-induced plasticity [41]. To do this, we used the marginal means of biphasic RMT and biphasic AMT as computed in our companion paper [42], and then multiplied these values by 0.7 (i.e., 70% of biphasic RMT) and 0.8 (i.e., 80% of biphasic AMT), respectively.

Results

Individual participant data from 22 TBS studies (Table 1) and 430 healthy participants (mean age = 41.9; SE = 1.02;

Table 1
Characteristics of included studies.

Study	Author/s	Participants	TBS protocol/s
1	Barhoun (unp.)	13 healthy (5F, 22.1 ± 3.0 y)	cTBS
2	Di Lazzaro et al. (2008) [79]	12 stroke patients (5F, 69.4 ± 9.5 y), 12 controls (2F, 63.2 ± 5.3 y)	iTBS & cTBS
3	Di Lazzaro et al. (2011) [80]	10 healthy (7F, 26.6 ± 4.1 y)	iTBS & cTBS
4	Dickins et al. (2015) [81]	20 younger (10F, 22.9 ± 2.5 y) and 20 older participants (10F, 70.2 ± 3.1 y)	iTBS
5	Dileone et al. (2016) [2]	16 healthy (10F, 23.2 ± 3.8 y)	iTBS
6	Do et al. (2018) [74]	20 healthy (14F, 26.5 ± 3.1 y)	cTBS
7	Fried et al. (2017) [33]	28 type 2 diabetes patients (12F, 65.8 ± 7.7 y), 22 AD patients (13F, 69.6 ± 7.4 y), 26 healthy (13F, 62.9 ± 8.9 y)	iTBS
8	Goldsworthy et al. (2016) [21]	18 healthy (10F, 22.1 ± 4.4 y)	iTBS
9	Gomes-Osman (unp.)	17 healthy (10F, 30.0 ± 12.9 y)	iTBS
10	Jannati et al. (2017) [12]	30 healthy (3F, 36.0 ± 14.4 y)	cTBS
11	Koch et al. (2016) [75]	40 AD patients (17F, 71.0 ± 6.4 y) and 24 healthy (12F, 69.3 ± 2.3 y)	iTBS & cTBS
12	Lee et al. (2014) [76]	18 healthy (12F, 73.8 ± 5.1 y)	cTBS
13	McDonnell et al. (2013) [27]	25 healthy (9F, 26.8 ± 8.1 y)	cTBS
14	Morris (unp.)	15 healthy (9F, 25 ± 2.7 y)	iTBS
15	Munneke et al. (2013) [24]	10 ALS patients (10 M, 57.8 ± 1.8 y) and 10 controls (0F, 49.0 ± 3.6 y)	cTBS
16	Nettekoven et al. (2014) [22]	16 healthy (9F, 27.0 ± 3.0 y)	iTBS
17	Opie et al. (2013) [77]	13 sleep apnoea patients (2F, 42.6 ± 10.2 y), 11 controls (2F, 43.0 ± 10.3 y)	cTBS
18	Puri et al. (2016) [19]	33 healthy (21F, 66.0 ± 4.8 y)	iTBS
19	Singh et al. (2016) [20]	10 healthy (6F, 25.4 ± 4.0 y)	cTBS
20	Vallence et al. (2015) [46]	18 healthy (10F, 23.1 ± 4.0 y)	cTBS
21	Vernet et al. (2014) [78]	10 healthy (5F, 33.0 ± 18.0 y)	cTBS
22	Young-Bernier et al. (2014) [67]	20 younger (13F, 22.3 ± 3.2 y) and 18 older healthy (9F, 70.1 ± 5.6 y)	iTBS

Note: age mean and standard deviation are shown. Abbreviations: F = females; y = years old; GAD = generalised anxiety disorder; AD = Alzheimer's disease; ALS = amyotrophic lateral sclerosis; MDD = major depressive disorder.

range = 17–82; males = 213) were included in the present analysis (Fig. 1).

Fig. 2 shows the distribution of normalised MEP data for each protocol. 67.9% of participants (180 of 265) demonstrated iTBS-induced facilitation and 65.4% of participants (138 of 211) demonstrated cTBS-induced suppression of MEP amplitudes. There was no evidence of bimodal groupings for 'responders' and 'non-responders' to TBS, as per previous suggestions [13,43].

Variability analysis

Table 2 shows variability for iTBS and cTBS data. ICCs demonstrated low to moderate reliability of normalised MEP within participants, reflecting some grouping of participant data across repeated TBS timepoints. However, within study reliability was almost non-existent for both iTBS and cTBS normalised MEP, demonstrating very little grouping of study data (relative to the entire sample of data). This is also reflected by CVs, showing that while variability is relatively low between studies, there is high variability within studies.

iTBS regression analysis

The final iTBS regression model demonstrated that baseline MEP amplitude and target muscle were significantly associated with changes in iTBS-induced plasticity (Table 3 and Fig. 3). See Supplementary file 5 for results of all stage 1 and 2 iTBS regressions.

Note that two iTBS studies used biphasic pulses to collect pre and post TBS MEPs [3,44], yet we could not control for pulse waveform in the iTBS regression model due to insufficient data (Fig. 3). Thus, we also re-ran the final regression analysis with these studies excluded. In this case, TMS machine and neuronavigation use were significant predictors of iTBS normalised MEP: Magstim Rapid marginal mean (studies = 6; N = 169) = 119.43; SE = 1.14 vs. MagPro marginal mean (studies = 4; N = 53) = 129.97; SE = 3.72; p = 0.014. Neuronavigation used marginal mean (studies = 3; N =

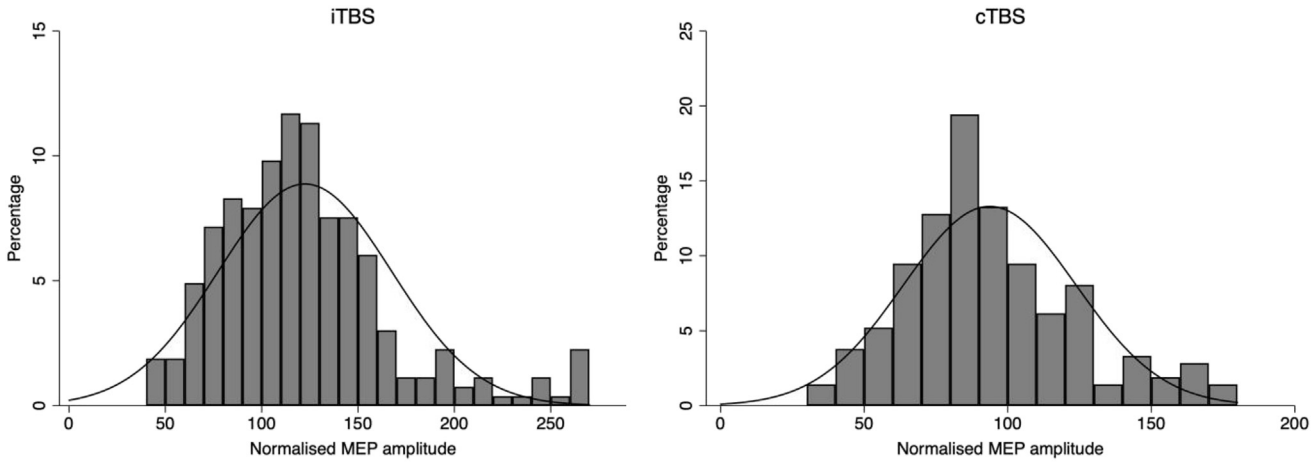

Fig. 2. Distribution plots. Histograms show distribution of normalised MEP data for iTBS and cTBS protocols. Y-axis shows the percentage of responses within each normalised MEP bin of 10 along the X-axis.

Table 2
Variability of iTBS and cTBS data. ICC = intraclass correlation coefficient; SD = standard deviation; CV = coefficient of variation %.

	ICC within participants	ICC within studies	SD within studies	SD between studies	CV (%) within studies	CV (%) between studies
iTBS	0.53	0.00	43.08	15.28	34.61	12.04
cTBS	0.34	0.04	27.02	12.19	30.31	13.49

Table 3
Final iTBS regression model. B-values for continuous IVs show the amount of increase in normalised MEP, for a one unit increase in the IV, after adjusting for all other variables in the model. i.e. a 1 unit increase in age (i.e. 1 year) resulted in a 0.18% reduction in iTBS-induced facilitation. For categorical IVs, the B-value shows the difference between the IV levels in normalised MEP. e.g. the APB muscle demonstrated 16.41% less iTBS-induced facilitation than the FDI muscle (see Fig. 5 for all IV levels). Bold denotes significance ($p < 0.05$). Participants = 265; studies = 12.

IV	B	SE	95% CIs			ß	p
Age	−0.18	0.10	−0.38	–	0.02	−0.09	0.071
Baseline MEP	−10.93	2.73	−16.27	–	−5.58	−0.23	**<0.001**
Machine	5.63	5.91	−5.95	–	17.20	0.13	0.341
Muscle	−16.41	4.61	−25.44	–	−7.38	−0.37	**<0.001**
TBS intensity	4.94	6.09	−6.98	–	16.87	0.11	0.417
Neuronavigation use	−9.41	5.93	2.21	–	-21.02	−0.21	0.113

71) = 114.82; SE = 3.51 vs. Neuronavigation not used marginal mean (studies = 7; N = 151) = 125.30; SE = 1.97; p = 0.039. The significance of other other IVs was unchanged.

Fig. 4 presents bivariate relationships for continuous IVs age and baseline MEP, which were both included in the final iTBS regression model.

Fig. 5 shows the iTBS normalised MEP marginal means for IVs included in the final regression model. Overall, there was significant iTBS-induced facilitation of MEP amplitudes across this sample (orange bar).

iTBS post-hoc analyses

With age split into younger and older groups based on the median value, there was slightly greater iTBS-induced facilitation for younger (marginal mean = 126.04; SE = 2.63), compared to older adults (marginal mean = 119.02; SE = 2.92), as in the main analysis. However, this was again non-significant (p = 0.115).

Although no significant linear relationship was found in the main regression (nor split by group, as above), there was a significant cubic relationship between iTBS normalised MEP and age (p = 0.038) (Fig. 4). Further, in addition to a linear relationship

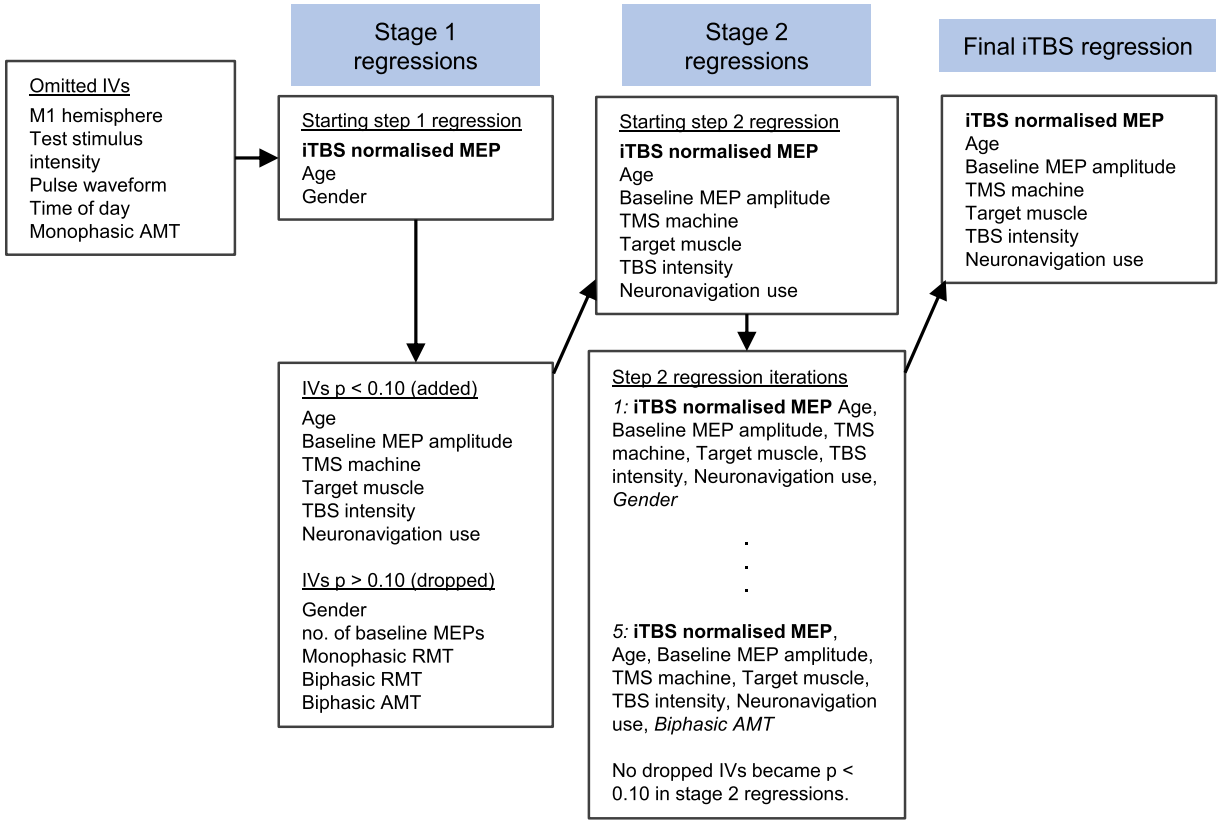

Fig. 3. Regression flowchart for iTBS. Figure shows the method employed to arrive at the final regression model, demonstrating IVs accounting for interindividual variability in iTBS normalised MEP. IVs were omitted if they did not include at least three studies within each IV level, or their inclusion led to a substantial reduction in regression sample size (see Methods). Stage 1 regressions analysed the variance in normalised MEP explained by each IV separately, while controlling for age and gender. IVs were dropped from the model if they did not obtain a p-value < 0.10. Stage 2 regressions again iterated through IVs that were dropped in stage 1, to see whether these IVs now obtained a p-value < 0.10 controlling for IVs in the starting stage 2 model. Thus, the final regression model comprised of IVs that obtained a p-value < 0.10 in predicting iTBS-induced plasticity in either stage 1 or 2 regressions. See Table 3 for results.

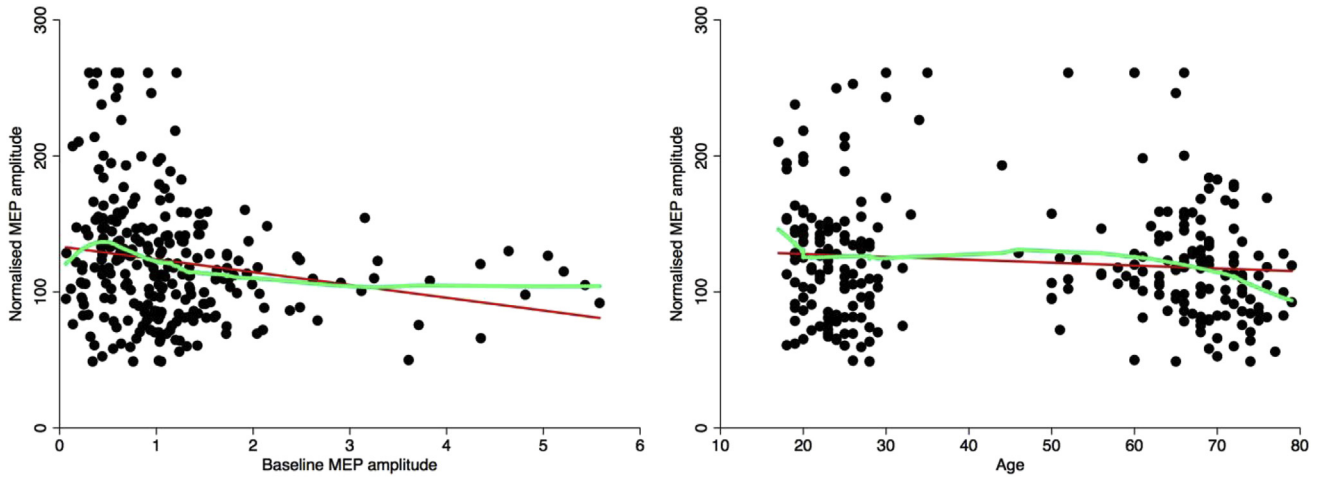

Fig. 4. Relationships between normalised MEP amplitude and continuous IVs in final iTBS regression model. Our main analyses using linear regression showed that baseline MEP was a significant predictor of iTBS normalised MEP, while age did not reach significance (Table 3). However, post-hoc analyses demonstrated a significant cubic relationship for age, and a significant quadratic relationship for baseline MEP amplitude. These bivariate scatterplots are presented to give an indication of relationships only. See regression analyses for results controlling for all IVs in final model. Green line fits a smoothed 'lowess' curve through data (smoothing level = 0.8 - default).

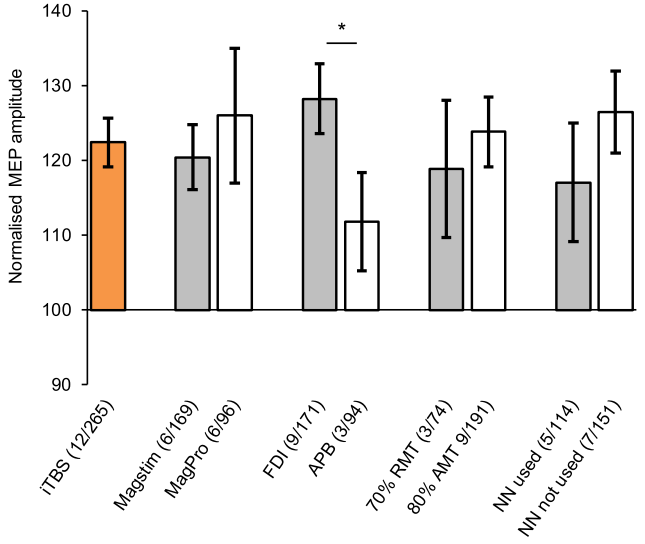

Fig. 5. Marginal means for iTBS normalised MEP amplitude. Marginal means provide an estimate of normalised MEP, adjusted for all variables in the final regression model. Orange bar shows the overall marginal mean for iTBS. Grey and white bars show marginal means for each level of the IVs TMS machine, target muscle, TBS intensity, and neuronavigation (NN) use, which were each included in the final model. * denotes a significant difference between levels ($p < 0.05$). All samples showed significant facilitation from 100 (all $p < 0.001$). Error bars show 95% confidence intervals. Brackets show (studies/participants). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

(Table 3), there was a significant quadratic relationship between iTBS normalised MEP and baseline MEP amplitude ($p < 0.001$) (Fig. 4).

Time of day significantly predicted iTBS-induced plasticity ($\chi^2 = 7.46$; df = 2; $p = 0.024$). Post-hoc pairwise comparisons showed that there was a significant difference between morning and afternoon groups (marginal mean morning = 132.96; SE 3.94, studies = 4; N = 32; marginal mean afternoon = 122.17; SE = 2.61, studies = 6; N = 50; $p = 0.008$), but no differences between these groups and the evening group (125.78; SE = 8.95, studies = 6; N = 24).

cTBS regression analysis

The final regression model (Fig. 6) demonstrated that baseline MEP amplitude was significantly negatively associated with cTBS normalised MEP (Table 4). See Supplementary file 6 for results of all stage 1 and 2 cTBS regressions.

Fig. 7 shows bivariate relationships for continuous IVs baseline MEP and age, which were included in the final cTBS regression model.

Fig. 8 (blue bar) shows that there was significant cTBS-induced suppression of MEPs across this sample ($p = 0.018$). With age split into younger and older groups based on the median value, there was slightly greater cTBS-induced suppression for younger adults, yet this was non-significant ($p = 0.194$) (Fig. 8). Although TS intensity and pulse waveform did not reach our p-value threshold (<0.10) for inclusion in the final regression model, we present these results given the debate on the influence of these IVs on TBS-induced plasticity [33,45] (Fig. 8). While there were moderate effect sizes for these IVs, neither were significant (pulse waveform $p = 0.174$; TS intensity $p = 0.186$). Interestingly, our companion paper, investigating single and paired-pulse TMS, showed reduced MEP amplitudes and increased MEP variability for the 120% RMT TS intensity method in comparison to the 1 mV method [42]. There were insufficient data to evaluate whether these two IVs also showed the same trends in iTBS data.

cTBS post-hoc analyses

Controlling for all variables included in the final model, biphasic AMT just fell short of out threshold for significance in predicting cTBS normalised MEP (B = −0.44; SE 0.23; ß = −0.17; $p = 0.057$; studies 8; N = 132). Time of day did not significantly predict cTBS-induced plasticity ($\chi^2 = 1.44$; df = 2; $p = 0.488$).

In addition to a linear relationship (Table 4), there were significant quadratic ($p = 0.014$) and cubic ($p < 0.001$) relationships between cTBS normalised MEP and baseline MEP amplitude (Fig. 7).

Additional analyses

Fig. 9 shows the effect of time on iTBS and cTBS effects. iTBS-induced plasticity was significant at all timepoints (up to 30 min

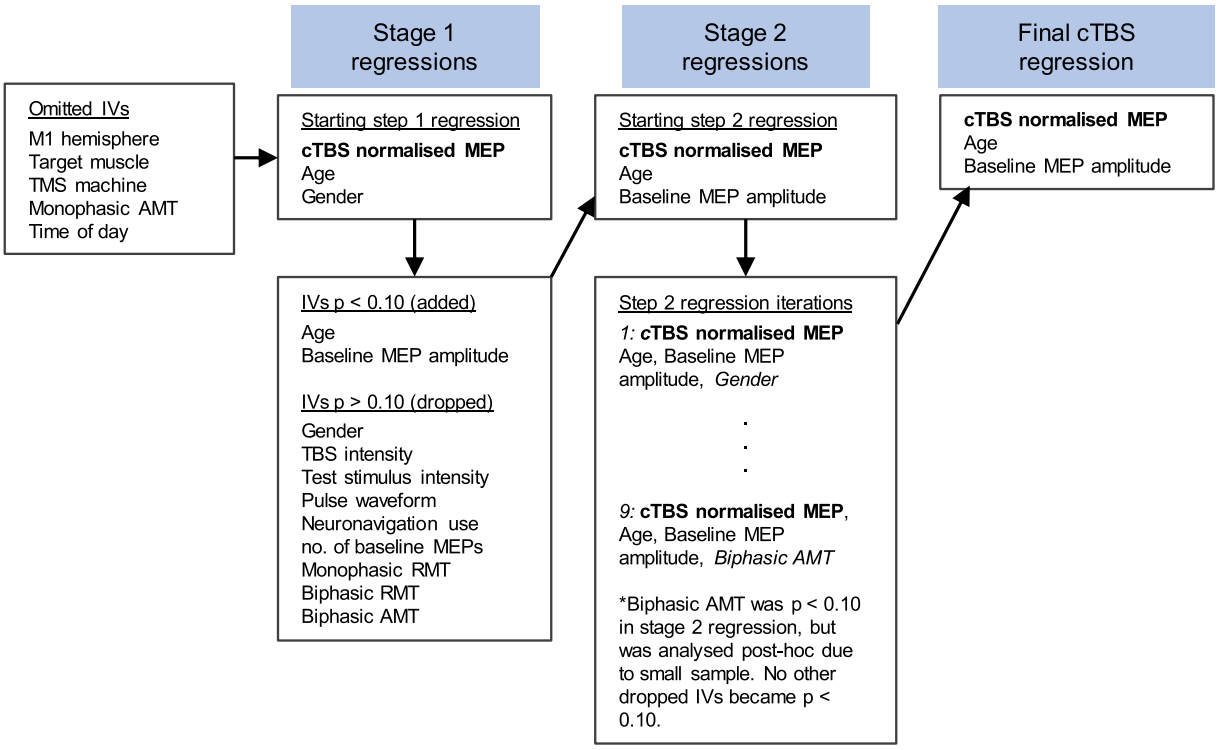

Fig. 6. Regression flowchart for cTBS. Figure shows the method employed to arrive at a final model, demonstrating IVs accounting for interindividual variability in cTBS normalised MEP. See Methods and Fig. 3 caption for further explanation of method.

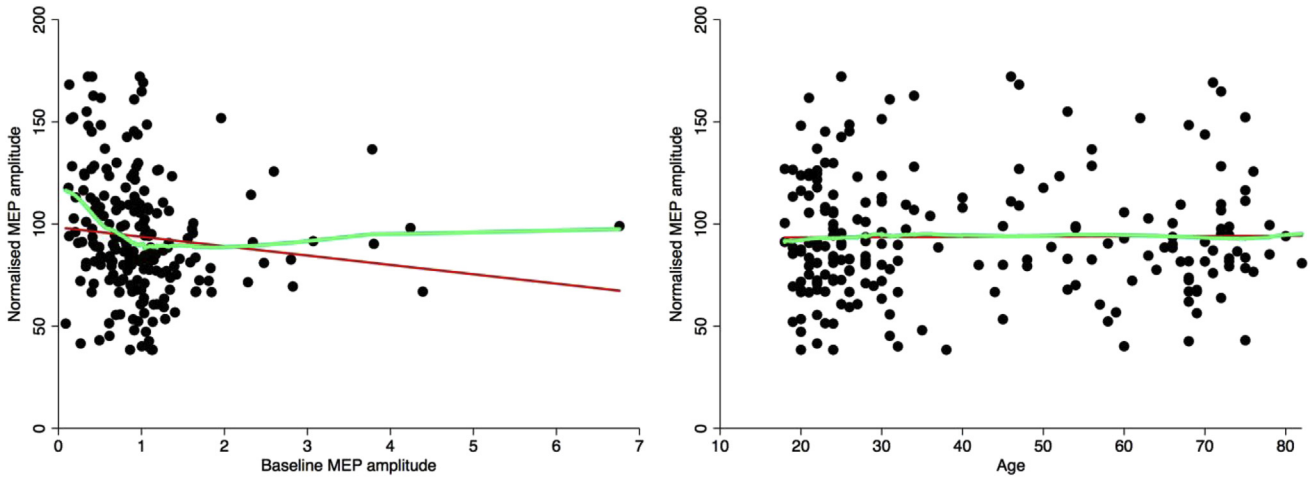

Fig. 7. Relationships between normalised MEP amplitude and continuous IVs in final cTBS regression model. Our main linear regression analyses showed that baseline MEP, but not age was a significant predictor of cTBS normalised MEP (Table 4). Post-hoc analyses also demonstrated significant cubic and quadratic relationships for baseline MEP amplitude. Green line fits a smoothed 'lowess' curve through data. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

post-iTBS), and there was no significant difference in plasticity across the timepoints ($\chi^2 = 4.56$; df = 3; p = 0.207). In contrast, cTBS-induced plasticity was only significant at 0–5 min and 5–10 min timepoints, and regression demonstrated a significant difference in plasticity across the timepoints ($\chi^2 = 26.70$; df = 5; p < 0.001) (see Fig. 9 for pos-hoc pairwise comparisons).

Our additional regression analyses including only ≤10 min post-TBS data demonstrated very similar results, with the exact same IVs being included in these iTBS and cTBS models as in the main regression analyses (due to obtaining a p-value < 0.10 in either stage 1 or 2 regressions) (Supplementary file 7).

Finally, there was only a small difference between the TMS machine output % used for the two TBS intensities: 70% of biphasic RMT = 33.93% versus 80% of biphasic AMT = 35.24%.

Discussion

This study pooled data from 22 studies to investigate factors contributing to interindividual variability in response to TBS. Our initial variability analysis largely agreed with previous research by demonstrating moderate levels of within participant reliability [14,33,34,46], yet much larger variability of between participant

Table 4
Final cTBS regression model. For every 1 mV increase in baseline MEP, there was on average a 5.32% reduction in cTBS normalised MEP (greater suppression). Bold denotes significance ($p < 0.05$). Participants = 211; studies = 13.

IV	B	SE	95% CIs			ß	p
Age	0.13	0.12	−0.01	–	0.36	0.09	0.246
Baseline MEP	−5.32	1.59	−8.44	–	−2.20	−0.14	**0.001**

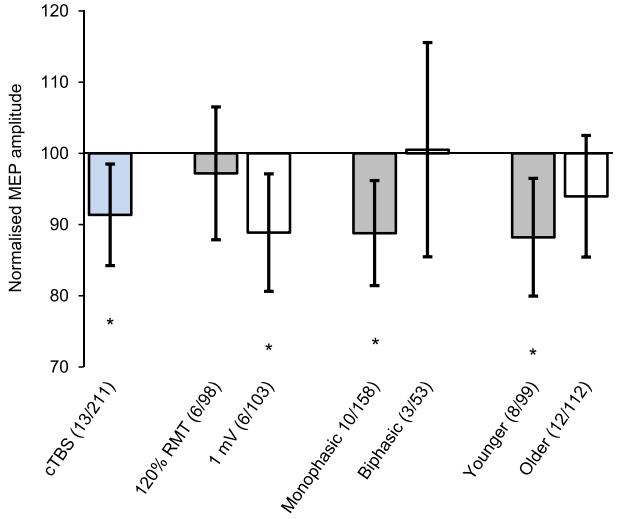

Fig. 8. Marginal means for cTBS normalised MEP amplitude. Blue bar shows the overall marginal mean for cTBS. Grey and white bars show marginal means for each level of the IVs TS intensity, pulse waveform, and age group. These IVs were not included in the final regression model, but demonstrated moderate effect sizes between levels. * denotes a significant difference from 100 (suppression) ($p < 0.05$). Error bars show 95% confidence intervals. Brackets show (studies/participants). Slight discrepancy in age group N is due to a number of participants aged at the median value (30). These were placed into the 'older' group. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

responses to TBS [11,13,46]. In attempting to identify the sources of this variability, we demonstrated that baseline MEP amplitude, target muscle, age, time of day, and TBS timepoint significantly predicted response to TBS. This indicates that a significant portion of variability can be attributed not only to TBS-induced plasticity itself, but also to the methods used to measure it, and highlights the need for greater standardisation in the methods used to measure TBS-induced plasticity.

Baseline MEP amplitude predicts TBS response

The clearest result from this study was the negative relationship between baseline MEP amplitude and normalised MEP, with smaller baseline MEP amplitudes related to larger relative MEPs amplitudes following TBS. However, post-hoc analyses demonstrated that this effect was not linear (also see Figs. 4 and 7). We suggest a number of possible reasons for these patterns of response.

Regression to the mean

Regression to the mean is the statistical phenomenon by which an initial extreme measurement is more likely to be closer to the mean if measured for a second time, and should be considered when designing experimental studies [47–49]. For example, a large reduction in an extremely high blood pressure measurement in a drug trial at follow up does not necessarily demonstrate an effect of the intervention, because it is likely that any extreme initial measurement was partly attributable to chance [47,48]. High trial-to-trial MEP variability means that baseline MEP values are susceptible to chance, especially if relatively few MEPs are collected [32,50,51]. This suggests that a portion of interindividual variability in TBS response might be attributable to regression to the mean after the collection of baseline MEPs that may not accurately reflect the individual's typical level of corticospinal excitability.

Extreme baseline MEP values could also be partly attributable to an initial state of MEP hyperexcitability during TMS sessions [52,53]. Thus, depending on the time taken to carry out procedures such as finding motor hotspot and measuring MT, one participant's

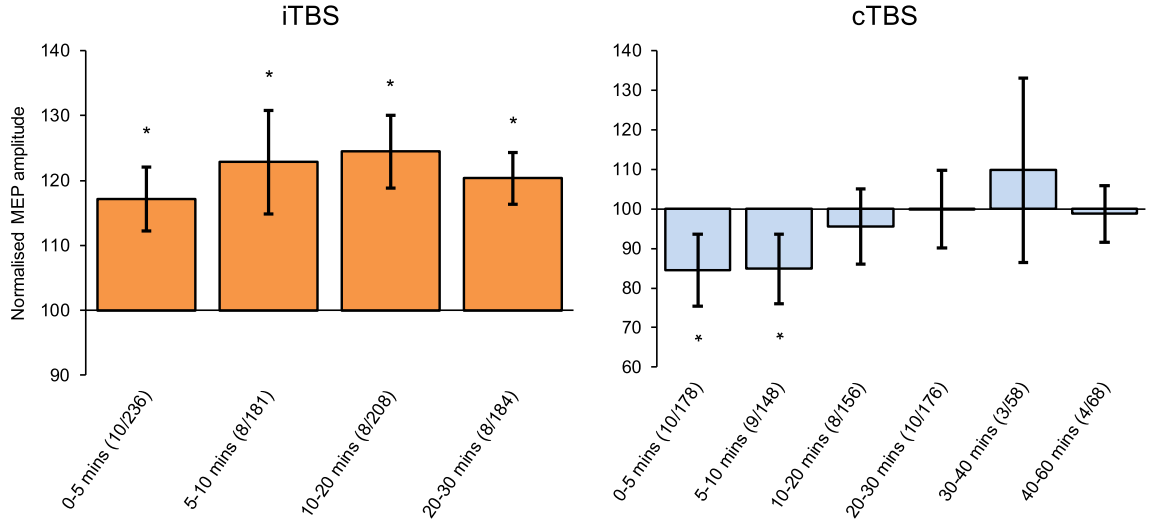

Fig. 9. TBS-induced plasticity across different timepoints. iTBS normalised MEP amplitude was significantly different from 100 at each timepoint (* denotes $p < 0.05$) and there were no significant differences between timepoints. cTBS plasticity was only significant at 0–5 and 5–10 min timepoints. 0–5 min and 5–10 min timepoints demonstrated significantly greater cTBS plasticity than all other timepoints, except for the 30–40 min timepoint ($p = 0.10$ and $p = 0.08$, respectively). No other pairwise comparisons were significant for cTBS. Error bars show 95% confidence intervals. Brackets show (studies/participants).

baseline MEPs could be collected within a state of hyperexcitability, while another's could be collected in a relatively steady state.

Floor and ceiling effects

Floor and ceiling effects occur when increases in TMS inputs at low or high intensities fail to produce changes in MEP amplitude due to a lack of activation (floor), or maximal activation (ceiling) of neurons that comprise the MEP [54,55]. While single-pulse (pre/post) TMS intensities are individualised, usually to 120% RMT or a 1 mV value, there can be substantial variability in relation to where these stimulus intensities occur in relation to each individual's input/output curve [21,56,57]. In other words, these individualised stimulus intensities can still be relatively low or high between individuals. This can bias estimates of TBS plasticity between individuals, with a floor effect more likely in the former individuals, and a ceiling effect more likely in the latter individuals [21]. These effects could partly explain the non-linear relationships for baseline MEP in the present data, where TBS-induced plasticity first increased, and then decreased, in response to higher baseline MEP amplitudes (Figs. 4 and 7). While speculative, this pattern could reflect a lower susceptibility to floor and ceiling effects for participants with baseline MEP amplitudes in the intermediate range (i.e. ~0.5–1.5 mV).

Interindividual variability in the neural circuits activated by the TMS pulse

The observed relationships to baseline MEP amplitude could also be explained by individual differences in the neural circuits activated by the TMS pulse assessing TBS plasticity. These differences may occur due to interindividual variability in the anatomy of the motor cortex, and variability in relative stimulus intensities between participants (as above) [58,59]. Studies using input/output curves have shown that iTBS-induced plasticity may be best detected at low stimulus intensities relative to an individual's MT, whereas cTBS-induced plasticity may be best detected at high relative intensities, because these intensities might better assess the components of neural circuitry that are differentially acted upon by iTBS and cTBS [21,22]. If we assume that those with low baseline MEP amplitudes received TMS pulses at relatively low intensities, this would agree with the present data, where low baseline MEP amplitudes resulted in greater iTBS effects yet ameliorated cTBS effects (Figs. 4 and 7). However, this is speculative, and we could not test this further because we did not possess sufficient I/O curve data, as in the aforementioned studies [21,22].

Target muscle

We demonstrated greater iTBS-induced facilitation for the FDI than the APB muscle. This result does not seem to be caused by significant differences in the size and location of the muscle representations within the M1 [60]. Thus, this may be due to technical reasons. Studies have shown that optimal current directions for evoking MEPs vary between different intrinsic hand muscles [60,61]. Specifically, Pascual-Leone et al. [60], showed that the optimal current direction for evoking MEPs from the FDI muscle was at a greater angle antero-laterally than for the APB. Thus, the use of a fixed coil orientation of 45° with respect to the mid-sagittal line (as done in all iTBS studies in present analysis) may better activate cortico-cortical circuits connected to FDI corticospinal neurons, than those connected to APB corticospinal neurons. Notably, this may apply to repetitive pulses, and also to the single pulses used to measure the response. This requires further investigation, ideally using a repeated-measures design, and neuronavigated TMS.

Effect of timepoint on TBS-induced plasticity

Our timepoint analysis on iTBS data agreed with a prior meta-analysis, with induced plasticity lasting at least 30 min [18]. Longer duration analyses were prevented by the small number of iTBS studies collecting data after this timepoint. In contrast, while Chung et al. [18], showed that cTBS suppression was significant at mid (20–30 min) and late (50–60 min) timepoints, our analyses demonstrated this effect for only 10 min. However it should be noted that when Chung et al. [18], only included studies that used the standard 600 pulse cTBS protocol (as with all studies in present analysis), cTBS suppression was non-significant at the late timepoint [18]. Thus, while our results also show the greatest cTBS effects at early timepoints [18,62,63], our results differ to prior literature in that our effects do not last beyond 10 min. Although our study has the advantage of controlling for participant and study covariates, unlike Chung et al. [18], it is open to sampling bias due to only including a fraction of the cTBS literature. For instance, if we exclude one study from the present analysis that demonstrated the reversal of the typical cTBS effect [12], cTBS suppression becomes significant up to 20 min post-stimulation. Therefore, it is possible that sampling error can account for the aforementioned discrepancies in cTBS results. The collection of additional individual participant data in the future is required to answer this question.

Effect of age on TBS-induced plasticity

Previous TMS studies have demonstrated attenuated plasticity for older adults [64–66]. However, the influence of age on *TBS plasticity* has been mixed [67,68]. Linear and grouped analyses demonstrated small (non-significant) effects for attenuated iTBS and cTBS-induced plasticity with age (Tables 3 and 4). However, further analysis demonstrated a significant non-linear effect for iTBS. The curved pattern of response shows that very young participants exhibited increased iTBS-induced facilitation, which stabilised in middle age, before a steady drop-off in facilitation for older adults (Fig. 4). However, there were few child/adolescent participants (minimum age = 17 years) and middle-aged participants included in the sample (just four participants aged 35–50). A more staged approach, testing across the lifespan (e.g. Freitas et al. [68]), appears to be justified in the future.

Limitations

A number of limitations should be acknowledged. First, we did not have data for various factors that have been demonstrated to contribute to variability in TBS responses, such as genotype [69], direct and indirect-wave recruitment profile [70], nor did we have participants' MRI data [71]. Second, our approach pools data from different studies, and therefore does not have the precision of a repeated-measures design [72]. Next, the effects demonstrated are limited to the studies and participants within the present sample, and are therefore open to sampling error. Also, of the eight studies that used neuronavigation, none reported the coordinates of the motor hotspot, nor coil shift data from the motor hotspot. Thus, differences in coil position may have accounted for some unobserved intraindividual variability in TMS outcomes. Lastly, our findings may be influenced by publication bias, which has been previously demonstrated in a meta-analysis of TBS studies [18].

Recommendations

We first propose some steps to counter the significant relationships observed between baseline MEP amplitude and response to TBS. To avoid regression to the mean caused by chance

occurrences of high or low MEP amplitudes, we recommend that investigators: 1) collect a sufficient number (20–30) of MEPs in their TMS blocks [50,51]; 2) avoid possible initial states of hyperexcitability within TMS sessions [52,53]; and 3) include baseline MEP amplitude as a covariate in statistical analyses. To avoid possible floor and ceiling effects, it has been suggested that researchers could use the machine intensity evoking an MEP amplitude of 50% of a participants' maximum MEP value [21,57]. However, Goldsworthy et al. [21], showed that this intensity also produced high levels of interindividual variability and did not demonstrate either iTBS or cTBS-induced plasticity at the group level. Authors suggested that this may be due to the still substantial between-participant differences in the neural circuits activated by the TMS pulse (as discussed above). This is a complex issue, therefore we recommend focused research into the most appropriate stimulus intensity/intensities to probe TBS-induced plasticity, given that this may substantially reduce the high between-participant (versus between-study) variability observed in the present study. Until a more time-efficient solution, we recommend the collection of input-output curves to evaluate TBS-induced plasticity across a range of intensities [21,46]. However, these can be more complex to calculate and interpret, thus we recommend a consensus on the specific input/output curve methods and analyses that should be employed to enable comparison of outcomes across studies [73]. In addition, we suggest that where neuronavigation can be used, researchers should report the coordinates of the motor hotspot, and report or analyse the impact of shifts from the motor hotspot for individual participants. Next, grouped (i.e. young vs. old), or linear, analyses may not be sufficient to uncover more fine-grained relationships between age and TBS plasticity, especially with very young or very old participants. Thus, non-linear relationships across the lifespan should be considered. Lastly, we recommend the use of the FDI muscle over the APB muscle to better detect iTBS-induced plasticity.

Conclusions

This study pooled data from 22 studies to demonstrate a number of readily controllable factors that can reduce interindividual variability in TBS-induced plasticity. Our findings demonstrate that a significant portion of variability may be attributable not only to brain plasticity, but also to the methods used to measure it. We make specific methodological recommendations that we hope will reduce interindividual variability and increase the standardisation of the methods used to evaluate TBS-induced plasticity. These findings justify the benefit of this collaborative approach to TMS research, which we are currently expanding through the construction of an individual participant TMS data repository at www.bigtmsdata.com. We welcome investigators to contribute to this database in order to solve these important questions that cannot be easily answered with single-site research.

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CRediT authorship contribution statement

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2020.07.018.

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