1 Large-scale analysis of interindividual variability in single and paired- 2 pulse TMS data: results from the 'Big TMS Data Collaboration'

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Abstract

Objective: Interindividual variability of single and paired-pulse TMS data has limited the clinical and experimental applicability of these methods. This study brought together over 60 TMS researchers to create the largest known sample of individual participant single and paired-pulse TMS data to date, enabling a more comprehensive evaluation of factors driving response variability.

Methods: 118 corresponding authors provided deidentified individual TMS data. Mixed-effects regression investigated a range of individual and study level variables for their contribution to variability in response to single and pp TMS data.

Results: 687 healthy participant's TMS data was pooled across 35 studies. Target muscle, pulse waveform, neuronavigation use, and TMS machine significantly predicted an individual's single pulse TMS amplitude. Baseline MEP amplitude, M1 hemisphere, and biphasic AMT significantly predicted SICI response. Baseline MEP amplitude, test stimulus intensity, interstimulus interval, monophasic RMT, monophasic AMT, and biphasic RMT significantly predicted ICF response. Age, M1 hemisphere, and TMS machine significantly predicted motor threshold.

Conclusions: This large-scale analysis has identified a number of factors influencing participants' responses to single and paired pulse TMS. We provide specific recommendations to increase the standardisation of TMS methods within and across laboratories, thereby minimising interindividual variability in single and pp TMS data.

1 **Abbreviations and nomenclature**

2 TMS: Transcranial magnetic stimulation

3 MEP: motor evoked potential

4 pp: paired-pulse

5 SICI: short-interval intracortical inhibition

6 ICF: intracortical facilitation

7 IV: independent variable

8 DV: dependent variable

9 Normalised MEP: DV for SICI and ICF analyses (conditioned MEP amplitude expressed as a
10 percentage of the baseline MEP amplitude)

11 CS: conditioning stimulus (initial pulse for paired-pulse TMS protocols)

12 TS: test stimulus (second pulse for pp TMS protocols, or unconditioned / baseline MEPs for
13 pp protocol)

14 ISI: interstimulus interval

15 RMT: resting motor threshold

16 AMT: active motor threshold

17 Pulse waveform: monophasic or biphasic pulse waveforms

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20 **Highlights**

21 • 687 healthy participant's TMS data was pooled across 35 studies

22 • Significant relationships between age and resting motor threshold

23 • Significant relationships between baseline MEP amplitude and

24 SICI/ICF

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1. Introduction

Single and paired-pulse (pp) TMS protocols are used to measure neural excitability within the primary motor cortex (M1) (Hallett 2000). However, these measures of M1 excitability have been shown to vary significantly between individuals (Iskan et al. 2016, Orth et al. 2003). A lack of understanding of the factors driving this variability has restricted greater application of single and pp TMS as a clinical and experimental tool (Iskan et al. 2016). Many studies have investigated this issue, yet there are conflicting findings in relation to the role of individual factors such as age (Cahn et al. 2003, Peinemann et al. 2001) and gender (Cahn et al. 2003, Shibuya et al. 2016), and also methodological factors such as the stimulus intensity used (Cosentino et al. 2018, Ibáñez et al. 2020, Ilić et al. 2002), and the hemisphere stimulated (Ilic et al. 2004, Maeda et al. 2002). Some of these conflicting findings are likely caused by small sample sizes inherent to most single-site studies (Fried et al. 2017a, Gilbert et al. 2005). To attempt to overcome this limitation, we recently formed the ‘Big TMS Data collaboration’ (Supplementary file 1) to combine individual participant TMS data across multiple studies. In the first instance, we used mixed-model regression to analyse data across 22 distinct datasets and demonstrate the variables driving interindividual variability in response to theta-burst stimulation (TBS) (Corp et al. 2020). Here we employ the same method, combining data from 35 TMS studies, to investigate the factors accounting for interindividual variability in response to single and pp TMS. The collation of multiple data-sets allowed us to more thoroughly examine sources of variability demonstrated by previous single and pp TMS studies, such as age, gender, and baseline MEP

1 amplitude (Cahn et al. 2003, Shibuya et al. 2016, Strube et al. 2015), and also
2 to further explore the possible influence of less examined variables on single
3 and pp response, such as TMS machine, target muscle, and neuronavigation.

4

5 **2. Methods**

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

11

12 *2.1 Article identification strategy*

13 This analysis comes from a larger project collecting individual participant
14 single and pp TMS data, input-output (I/O) curve data, and TBS data.
15 Systematic search procedures are described in detail our companion paper
16 (Corp et al. 2020), and the full search syntax is provided in Supplementary file
17 2. Inclusion criteria were: studies using a figure-of-eight coil; studies
18 measuring TMS responses from intrinsic hand muscles of humans; and
19 studies that collected baseline and conditioned MEP amplitudes. If an article
20 met inclusion criteria, the corresponding authors of studies were emailed to
21 ask for participants' age, gender, motor threshold, and baseline and
22 conditioned MEP amplitudes. Corresponding authors were asked to deidentify
23 data prior to sending. A number of other studies were also included via
24 informal data sharing with colleagues (Corp et al. 2020).

25

1 2.2 *Variables of interest and data used for present analyses*

2 Only healthy participant data were analysed within the present paper. To
 3 investigate interindividual variability for single pulse MEP amplitude, we used
 4 baseline MEP responses collected at 120% of RMT as our dependent
 5 variable (DV), collected across TBS, paired-pulse, and I/O curve datasets.
 6 This intensity was chosen as the DV because it was the most commonly used
 7 single-pulse TMS intensity, enabling comparison across multiple studies (see
 8 Results, Table 3). We were not able to collect sufficient input/output curve
 9 data to analyse MEP amplitudes across a range of TS intensities. For SICI
 10 and ICF, each individual's mean conditioned MEP amplitude was normalised
 11 to their mean baseline MEP amplitude ('normalised MEP') using the equation:
 12 (conditioned MEP amplitude / baseline MEP amplitude) x 100 (Amandusson
 13 et al. 2017, Di Lazzaro et al. 2006), where a value of 100% represents no
 14 change in conditioned MEP amplitudes. Note that the use of a 'normalised
 15 MEP' value or a percentage of change value (Fried et al. 2017b) (0% = no
 16 change in conditioned MEPs) provide the exact same results after regression
 17 analyses (Corp et al. 2020).

18
 19 Because MT is extensively used as a measure of corticospinal excitability
 20 (Fried et al. 2017a, Kammer et al. 2001), we also investigated interindividual
 21 variability for four types of MT for which we had data: monophasic RMT,
 22 monophasic AMT, biphasic RMT and biphasic AMT. In addition to these four
 23 MTs being used as DVs (as above), MT may also predict single and pp TMS
 24 outcomes (Amandusson et al. 2017, Chen et al. 1998), thus these four MTs
 25 were also used as independent variables (IV) for our analyses of factors

1 predicting single pulse MEP amplitude, and pp normalised MEP. Other IVs
2 investigated were: age, gender, target muscle, M1 hemisphere, conditioning
3 stimulus (CS) intensity, test stimulus (TS) intensity, pulse waveform (i.e.
4 monophasic or biphasic), inter-stimulus interval (ISI), baseline MEP
5 amplitude, the use/absence of neuronavigation, and TMS machine (Corp et
6 al. 2020). Studies used either a Magstim 200² TMS machine, a Magstim
7 Rapid TMS machine, a Nexstim NBS TMS, or a MagPro TMS machine. We
8 could not determine the specific MagPro model used in all studies, therefore
9 these machines were grouped based on the brand. We controlled for pulse
10 waveform in regression analyses to ensure that the effect of TMS machine
11 was not due the differential use of monophasic or biphasic pulses. For TS
12 intensity, studies used either 120% of RMT or a machine stimulus output
13 evoking an MEP amplitude of 0.5 mV, 0.5 - 1 mV, 1 mV MEP, or 0.5 - 1.5 mV.
14 To increase statistical power, we grouped these intensities into machine
15 stimulus output evoking an MEP amplitude of 0.5 - 1.5 mV. Three studies did
16 not use a TS intensity evoking 0.5 - 1.5 mV or 120% of RMT (Corp et al.
17 2015, Puri et al. 2016, Singh et al. 2016), and were therefore excluded from
18 this comparison. We were not able to obtain baseline MEP amplitude data
19 from one study (Munneke et al. 2013), thus these values were imputed as per
20 the method of Corp et al. (2020). For studies that tested the effect of external
21 interventions on TMS outcomes (e.g. exercise Singh et al. (2016)), only
22 control/baseline data were analysed. We collected handedness data for 21
23 studies, yet there were only nine left handers represented across five studies,
24 therefore this IV could not be analysed statistically.

25

1 We verified the accuracy of the data sent to us by comparing the results to
2 group mean data in the corresponding published paper. In cases where we
3 could not verify based on this group mean data, corresponding authors were
4 contacted for clarification. In instances where data could not be verified, the
5 study was excluded (n = 1).

6

7 All statistical analyses were conducted using Stata 13.0 (StataCorp, USA).

8 First, data were checked for outliers using histograms and descriptive
9 statistics. A number of outliers were detected in single and pp MEP data,
10 therefore values falling outside of the 2nd and 98th percentiles were winsorized
11 (Field 2009, Tukey 1962). Histograms prior to outlier winsorization are
12 provided in Supplementary file 3.

13

14 2.3 *Variability analyses*

15 Prior to our main analyses investigating IVs predicting interindividual
16 variability in single and pp TMS responses, we sought to characterise the
17 variability of the data across our collected sample. As per the method of
18 Brown et al. (2017), we calculated intraclass correlation coefficient (ICC),
19 standard deviation (SD), and coefficient of variation (CV) (Brasil-Neto et al.
20 1992) values to assess within study, and between study variability of single
21 and pp TMS data. Within study SDs and CVs were calculated using the mean
22 MEP amplitude (or MT) of participants, and between study SDs and CVs were
23 calculated using the mean MEP amplitude (or MT) of each study (Brown et al.
24 2017). ICC values < 0.50 were considered low; values 0.50 – 0.75 considered
25 moderate; and > 0.75 considered high (Portney and Watkins 2009). High

1 'within study' ICC values reflect smaller variance within studies relative to
2 larger variance between studies (Kline 2000).

3
4 Only one study (Beynel et al. 2014) assessed participants' corticospinal
5 excitability at multiple time-points, restricting an analysis of within-participant
6 reliability over time. Yet, with the corresponding authors' permission, we
7 provide these (unpublished) data in Supplementary file 4.

8

9 *2.4 Main regression analysis*

10 Our main analyses investigated IVs predicting the aforementioned single, pp,
11 and MT data. To do this, we employed the same regression analyses as
12 described in detail in Corp et al. (2020). Briefly here, we used mixed-effects
13 linear regression using a 'one-step' model as described by Riley et al. (2010),
14 using 'study ID' as a random factor. Some data contained multiple entries by
15 the same participants due to studies collecting multiple data-points across
16 certain measures, such as ISI (e.g., 2 ms and 4 ms) (Croarkin et al. 2013).
17 Thus, in these regressions we also included a random factor of 'participant ID'
18 to maintain the nesting of these data-points within individual participants.

19

20 We used forward-stepwise regression in two stages for each TMS protocol
21 (Bendel and Afifi 1977). Stage 1 regressions analysed the variance explained
22 in the DV by each IV separately, while controlling for the age and gender of
23 participants. IVs with p-values < 0.10 were added to the regression model in
24 stage 2, while IVs with p-values > 0.10 were dropped (Corp et al. 2020). The
25 stage 2 starting regression model comprised of all IVs that were $p < 0.10$ in

1 stage 1. Consecutive regressions then iterated through IVs that were dropped
2 in stage 1, to see whether these IVs now obtained a p-value < 0.10 controlling
3 for IVs in the starting stage 2 model. Thus, the final regression model
4 comprised of IVs that obtained a p-value < 0.10 in predicting the DV in either
5 stage 1 or 2 regressions (Corp et al. 2020).

6
7 IVs were omitted from regression analyses for three possible reasons. First,
8 an IV was omitted if it was not comprised of at least three studies within each
9 IV level, given that unreliable estimates may have resulted from a smaller
10 number of studies per level (Corp et al. 2020). For example, the IV 'ISI' was
11 included only if all ISIs for which we had data (e.g. for SICl: 2 ms, 2.5 ms, 3
12 ms, and 4 ms) were used in at least three separate studies. Where some, but
13 not all, levels of a given IV were represented across three or more studies, we
14 compared these levels post-hoc (see below). Second, an IV was omitted if its
15 inclusion led to a substantial reduction in the overall sample size of the
16 regression analysis for that DV, due to that IV only being measured in a
17 subset of studies. We defined a 'substantial reduction of the regression
18 sample size' as cases where two or more studies were excluded from the
19 regression analysis. Third, an IV was omitted because of collinearity, which
20 occurred if two types of MTs were included in the same regression model. To
21 avoid this, if two or more types of MTs had a p-value < 0.10 in stage 1
22 regressions, for stage 2 we included only the MT that was the strongest
23 predictor of normalised MEP for that particular regression analysis.

24

1 Given the presence of non-linearity and non-normality, robust variance
2 estimates were used for all regressions (Gaubard and Korn 1996). Adjusted
3 marginal means (just ‘marginal means’ henceforth) estimated the mean
4 normalised MEP amplitude adjusted/controlled for all other variables in the
5 regression model (Williams 2012). This allowed an interpretable estimate of
6 the mean across the sample, and also for each level of categorical IVs (e.g.
7 the levels ‘left’ and ‘right’ for the IV ‘M1 hemisphere’) (Williams 2012).

8

9 2.5 *Post-hoc analyses*

10 Where sufficient data, post-hoc analyses were run on IVs that were omitted
11 from the main regression analyses for any of the three aforementioned
12 reasons. In relation to reason three for omission (i.e. collinearity), different
13 types of MT were always analysed in separate regression models, to assess
14 their independent relationship to normalised MEP. Next, post-hoc pairwise
15 comparisons were performed on significant IVs that had 3 or more levels
16 (given that results from IVs with only 2 levels can be interpreted from the main
17 regression output). Given their exploratory nature, these pairwise analyses
18 were not corrected for multiple comparisons. Finally, scatterplots indicated
19 possible non-linear relationships between normalised MEP and some
20 continuous variables (e.g. age). Therefore, we re-analysed all (continuous
21 variable) relationships that were included in the final regression model, or
22 were significant in post-hoc analyses, using quadratic and cubic regression
23 models (Davidson and MacKinnon 1993). All post-hoc analyses controlled for
24 all other IVs in the final regression model.

25

1 2.6 Additional analyses

2 A number of additional analyses were performed to further explore the data.
 3 Marginal means following single pulse regression analysis indicated that
 4 120% RMT MEP data did not reach 1 mV in amplitude. Therefore, we then
 5 assessed whether these MEP amplitudes were significantly lower in
 6 comparison to MEP amplitudes collected using the 1 mV method (i.e. stimulus
 7 intensity required to evoke a 1 mV MEP amplitude). To do this, we performed
 8 two-stage mixed-effects linear regression analysis, as above, including TS
 9 intensity (with levels of 120 RMT method and 1 mV method) as an IV. Given
 10 that controlling for other IVs may cause unwanted influence on 1 mV values,
 11 which were already adjusted by TMS operators to attain a 1 mV amplitude
 12 regardless of age, gender etc., we also repeated this analysis without the
 13 inclusion of these IVs (i.e. including only the TS intensity IV, and 'study ID'
 14 and 'Participant ID' as a random factors). This analysis did not include the
 15 imputed data of Munneke et al. (2013).

16
 17 We then assessed a possible difference in MEP amplitude *variance* between
 18 these TS intensity methods. Here we used the same method as in our
 19 'variability analysis', calculating SD and CV values of single pulse MEP
 20 amplitudes, yet split the sample to analyse SD and CV separately for studies
 21 that used the 120% RMT method, and the 1 mV method. Significance
 22 between the TS intensity methods was assessed using Levene's robust test
 23 for equality of variances (Levene 1961). While lower variance may be
 24 expected for the 1mV method, given that operators specifically set the

1 machine intensity to evoke a 1mV amplitude, we still thought it valuable to
 2 quantify these (possible) differences.
 3
 4 Lastly, we analysed correlations between the four types of MT. Because
 5 different studies use different methods for obtaining MTs and therefore vary in
 6 their average MT values, we normalised MTs to z-values within study, then
 7 performed Pearson's correlation analyses on these z-values across the
 8 sample. This gives similar results to correlating MT values within studies, then
 9 taking the average of these correlations (Supplementary file 5).

10

11 **3. Results**

12 See Corp et al. (2020) for the PRISMA flowchart describing our initial
 13 systematic search. In total, 38 studies contributed individual participant data.
 14 Three studies were removed because they either included clinical populations
 15 only (2) (Kuppuswamy et al. 2015, Murdoch et al. 2016), or we were unable
 16 verify the accuracy of the sent data through email correspondence (1)
 17 (Malcolm et al. 2015). MT and single-pulse data were drawn from this larger
 18 sample of 35 studies and 687 healthy participants, which included theta-burst
 19 stimulation and I/O curve datasets in addition to pp data (Table 1). Pp TMS
 20 data were drawn from 16 studies, including 15 SICI and 14 ICF datasets
 21 comprising 295 healthy participants. Figure 1 shows the distribution of single,
 22 pp, and MT data.

23

24 < Table 1 here. Study characteristics >

25

Table 1. Characteristics of included studies.

Study	Author/s	Participants	TMS protocols
1	Barhoun (unp.)	13 healthy (5F, 22.1 ± 3.0 y)	cTBS
2	Beynel et al. (2014)	20 younger (14F, 26.4 ± 7.9 y), 19 older healthy (12F, 63.7 ± 1.7 y)	SICI, ICF
3	Busan et al., (2013)	40 healthy adults (12F, 26.2 ± 6.6 y)	I/O curves
4	Capone et al. (2009)	22 healthy (13F, 27.6 ± 9.0 y)	SICI, ICF
5	Corp et al. (2015)	14 healthy (3F, 29.6 ± 6.7 y)	SICI, ICF
6	Cosentino et al. (2015)	25 cluster headache patients (4F, 37.7 ± 10.5 y), 13 healthy (2F, 35.2 ± 11.2 y)	SICI, ICF
7	Croarkin et al. (2013)	24 MDD (14F, 13.9 ± 2.1 y), 22 healthy (11F, 13.8 ± 2.2 y)	SICI, ICF
8	Di Lazzaro (unp.)	17 healthy (5F, 23.9 ± 5.1 y)	SICI, ICF
9	Di Lazzaro et al. (2008)	12 stroke patients (5F, 69.4 ± 9.5 y), 12 controls (2F, 63.2 ± 5.3 y)	iTBS & cTBS
10	Di Lazzaro et al. (2011)	10 healthy (7F, 26.6 ± 4.1 y)	SICI, ICF, iTBS, cTBS
11	Dickins et al. (2015)	20 younger (10F, 22.9 ± 2.5 y) and 20 older participants (10F, 70.2 ± 3.1 y)	iTBS
12	Dileone et al. (2016)	16 healthy (10F, 23.2 ± 3.8 y)	iTBS
13	Do et al. (2018)	20 healthy (14F, 26.5 ± 3.1 y)	cTBS
14	Fried et al. (2017)	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)	SICI, ICF, iTBS
15	Fuhl et al., (2015)	10 healthy (1F, 24.6 ± 3.9 y)	I/O curves
16	Goldsworthy et al. (2016)	18 healthy (10F, 22.1 ± 4.4 y)	iTBS
17	Gomes-Osman (unp.)	17 healthy (10F, 30.0 ± 12.9 y)	SICI, ICF, iTBS
18	Helm et al. (2015)	11 healthy (2F, 25 ± 4.3 y)	ICF
19	Hoseini et al., (2016)	18-40 y	I/O curves
20	Jannati et al. (2017)	30 healthy (3F, 36.0 ± 14.4 y)	cTBS
21	Koch et al. (2016)	40 AD patients (17F, 71.0 ± 6.4 y) and 24 healthy (12F, 69.3 ± 2.3 y)	iTBS, cTBS
22	Lee et al. (2014)	18 healthy (12F, 73.8 ± 5.1 y)	cTBS
23	Li et al. (2017)	26 GAD patients (13F, 42 ± 9.7 y), 35 controls (20F, 41 ± 10.6 y)	SICI, ICF
24	McDonnell et al. (2013)	25 healthy (9F, 26.8 ± 8.1 y)	cTBS
25	Lücke et al., (2014)	9 healthy (3F, 25 ± 4.2 y)	I/O curves
26	Morris (unp.)	15 healthy (9F, 25 ± 2.7 y)	SICI, ICF, iTBS
27	Munneke et al. (2013)	10 ALS patients (10M, 57.8 ± 1.8 y) and 10 controls (0F, 49.0 ± 3.6 y)	SICI, ICF, cTBS
28	Nettekoven et al. (2014)	16 healthy (9F, 27.0 ± 3.0 y)	iTBS
29	Opie et al. (2013)	13 sleep apnoea patients (2F, 42.6 ± 10.2 y), 11 controls (2F, 43.0 ± 10.3 y)	SICI, cTBS
30	Opie et al. (2015)	13 younger (7F, 22.3 ± 3.8 y) and 15 older healthy (7F, 73.7 ± 4.0 y)	SICI
31	Puri et al. (2016)	33 healthy (21F, 66.0 ± 4.8 y)	iTBS
32	Singh et al. (2016)	10 healthy (6F, 25.4 ± 4.0 y)	SICI, ICF, cTBS
33	Vallence et al. (2015)	18 healthy (10F, 23.1 ± 4.0 y)	cTBS
34	Vernet et al. (2014)	10 healthy (5F, 33.0 ± 18.0 y)	cTBS
35	Young-Bernier et al. (2014)	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. Studies without paired-pulse data were used in single pulse and/or motor threshold analyses. Abbreviations: F = females; y = years old; GAD = generalised anxiety disorder; AD = Alzheimer's disease; ALS = amyotrophic lateral sclerosis; MDD = major depressive disorder; I/O = input/output; FDI = first dorsal interosseous; APB = abductor pollicis brevis.

< Figure 1 here. Histograms for all protocols >

3.1 *Variability analyses*

Table 2 shows measures of reliability for all TMS outcomes. 120% of RMT MEP amplitudes, SICI, and ICF demonstrated higher within, than between, study variance. This is also demonstrated by low ICC values for these outcomes, reflecting little grouping of within study values relative to the overall sample. Consistent with previous reports (Davila-Pérez et al. 2018, Fried et al. 2017a), within and between study reliability was higher for MTs than the aforementioned (120% of RMT) single pulse and pp TMS outcomes.

< Table 2 here – variability analysis >

3.2 *Single pulse TMS regression analysis*

The inclusion of any MT in the model would have substantially reduced the regression sample size. Thus, see post-hoc analyses for these relationships. The final regression model showed that muscle, pulse waveform, the use of neuronavigation, and TMS machine were all significant predictors of 120% of RMT single-pulse MEP amplitude (Table 3). See Figure 2 for single pulse TMS marginal means.

< Table 3 here. Single pulse regression >

Figure 1. Distribution plots. Histograms of single pulse, paired pulse, and motor threshold data. 120% RMT data was used for single-pulse main regression analysis. These data were then compared to single pulse data using the 1 mV method in the 'additional analyses'. In addition to differences in amplitude and variance (see Results), 120% RMT data appear positively skewed, also evidenced by low median value (0.73 mV). 1 mV method data median = 1.03 mV. So that each participant was only represented once within all histograms and scatterplots (multiple data points due to some studies using multiple ISIs, muscles, etc. – see Methods) we take each participant's mean normalised MEP value across their multiple measurements. Note that in regression analyses, multiple measurements were dealt with by including 'participant ID' as a random factor – see Methods.

Table 2. Variability of single and paired-pulse TMS data. ICC = intraclass correlation coefficient; SD = standard deviation; CV = coefficient of variation %.

	<i>ICC within studies</i>	<i>SD within studies</i>	<i>SD between studies</i>	<i>CV within studies (%)</i>	<i>CV between studies (%)</i>
120% RMT MEP	0.14	0.49	0.28	51.80	28.52
SICI	0.10	28.86	14.96	58.34	30.95
ICF	0.10	75.43	38.39	46.15	24.23
Monophasic RMT	0.50	7.78	9.15	19.36	19.67
Biphasic RMT	0.27	8.47	5.82	17.43	11.84
Monophasic AMT	0.56	10.16	7.28	17.62	24.05
Biphasic AMT	0.52	7.45	8.16	17.99	19.25

Table 3. Final single pulse MEP amplitude regression model. B-values for categorical IVs show the differences between the IV levels in mV. e.g. the APB demonstrated 0.27 mV lower MEP amplitudes than the FDI. Bold denotes significance ($p < 0.05$). Participants = 341; studies = 17. *TMS machine had 3 levels (Magstim 200², MagPro, and Nextstim), therefore main effect: $\chi^2 = 11.62$, $df = 2$. See post-hocs for pairwise comparisons between levels.

IV	B	SE	95% CIs			β	p
Muscle	-0.27	0.11	-0.49	-	-0.05	-0.40	0.016
Pulse waveform	0.30	0.05	0.20	-	0.39	0.44	<0.001
Neuronavigation use	0.11	0.04	0.20	-	0.03	0.17	0.011
Machine*							0.003

1 Other IVs not included in final regression model had p-values > 0.10 in both
2 stage 1 and 2 regressions (see Supplementary file 6 for all stage 1 and 2
3 results).

4 < Figure 2 here. Single pulse marginal means >

5

6

7 3.3 Single pulse TMS post-hoc analyses

8 When controlling for all IVs in the final regression model, all four types of MT
9 were significantly negatively associated with single pulse MEP amplitude at
10 120% RMT. Monophasic RMT, $B = -0.015$; $SE = 0.004$; $\beta = 0.31$; $p < 0.001$
11 (studies = 13; $N = 248$). Biphasic RMT, $B = -0.020$; $SE = 0.005$; $\beta = -0.31$; $p <$
12 0.001 (studies = 8; $N = 174$). Monophasic AMT, $B = -0.010$; $SE = 0.004$; $\beta = -$
13 0.20 ; $p = 0.024$ (studies = 3; $N = 62$). Biphasic AMT, $B = -0.017$; $SE = 0.006$;
14 $\beta = -0.29$; $p = 0.005$ (studies = 9; $N = 174$). Figure 3 shows bivariate
15 relationship between single-pulse MEP amplitude and monophasic RMT.

16

17 < Figure 3 here. Single pulse scatterplot >

18

19 In addition, non-linear analyses demonstrated a significant quadratic
20 relationship between single pulse MEP amplitude and biphasic AMT ($p =$
21 0.042), and significant cubic relationships between single pulse MEP
22 amplitude and biphasic RMT, and monophasic AMT ($p = 0.001$ and $p = 0.010$,
23 respectively) (see Supplementary file 7 for scatterplots).

24

25 3.4 SICI regression analysis

Figure2

Figure 2. Marginal means for 120% RMT single pulse MEPs. Marginal means provide an estimate of normalised MEP, adjusted for all variables in the final model. Orange bar shows the overall marginal mean for single pulse MEPs. Grey and white bars show marginal means for each level of the IVs muscle, pulse waveform, neuronavigation (NN), and TMS machine. * denotes a significant difference between levels ($p < 0.05$). Error bars show 95% confidence intervals. Brackets show (studies/ participants). Difference between Magstim 2002 and MagPro was close to significance ($p = 0.078$).

Figure3

Figure 3. Relationships between 120% RMT single pulse MEPs and MTs. All relationships were significant in post-hoc regression analyses. Note that these scatterplots show raw bivariate relationships to give an indication of relationships only, see post-hoc section for results controlled for other IVs in the single pulse TMS model. Green lines fit a smoothed 'lowess' curve through data (smoothing level = 0.8, default).

1 IVs 'TMS machine', 'CS intensity', 'pulse waveform', and 'ISI' were omitted
 2 because they did not include at least three studies within each IV level, while
 3 biphasic AMT and biphasic AMT were $p < 0.10$ in stage 1 regressions but
 4 substantially reduced regression sample size, thus were analysed post-hoc.
 5 The final SICI regression model showed that baseline MEP and M1
 6 hemisphere were both significant predictors of SICI normalised MEP (Table
 7 4). M1 hemisphere was still significant when re-analysed including only data
 8 from only right handers (from the sample in which we had handedness data)
 9 (studies = 9; N = 144; B = -9.04; SE = 2.85; $p = 0.002$).

10

11 Figure 4 shows bivariate relationships for continuous IVs baseline MEP and
 12 age, which were included in the final regression model. See Figure 5 for SICI
 13 marginal means.

14

15 < Insert Table 4 here. SICI regression >

16

17 < Insert Figure 4 here. SICI scatterplots >

18

19 Other IVs not included in final regression model had p-values > 0.10 in both
 20 stage 1 and 2 regressions (see Supplementary file 8 for all stage 1 and 2
 21 results).

22

23 < Figure 5. SICI marginal means >

24

25 3.5 SICI post-hoc analyses

Table 4. Final SICI 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 1mV increase in baseline MEP resulted in a 23.29% reduction in SICI normalised MEP (greater inhibition). Bold denotes significance ($p < 0.05$). Participants = 283; studies = 15. See Figure 5 for IV levels.

IV	B	SE	95% CIs			β	p
Age	0.11	0.11	-0.11	-	0.34	0.04	0.334
Gender	5.67	3.63	-1.45	-	12.78	0.15	0.119
Baseline MEP	-23.29	8.22	-39.41	-	-7.17	-0.33	0.005
Hemisphere	-4.01	1.73	-7.41	-	-0.62	-0.10	0.021

Figure 4. Relationships between continuous IVs and SICI. Baseline MEP amplitude was a significant predictor of SICI. Bivariate scatterplots give an indication of results only; see Table 4 for results controlled for other IVs. Green lines fit a smoothed 'lowess' curve through data. The appearance of a line of datapoints at the top (and to a lesser extent the bottom) of these (and other) scatterplots is due to winsorization; where small and large value outliers are converted to the value of the datapoint at the 2nd and 98th percentile (Field 2009, Tukey 1962) (see Methods).

Figure5

Figure 5. Marginal means for SICI normalised MEP. Orange bar shows the overall marginal mean for SICI. Grey and white bars show marginal means for each level of the IVs gender, M1 hemisphere, interstimulus interval and CS intensity (5% of machine intensity below AMT and 80% of RMT), which were included in the final model or post-hoc tests. * denotes a significant difference between levels ($p < 0.05$). All samples demonstrated significant inhibition ($p < 0.001$). Error bars show 95% confidence intervals. Brackets show (studies/ participants).

1 CS intensity and ISI were omitted from the main analysis, yet we had
2 sufficient data to compare SICl normalised MEP between studies that used an
3 intensity of 80% of RMT to those that used a machine intensity 5% below
4 AMT (5-AMT), and also ISI of 2 ms and 3 ms (> 3 studies for these levels).
5 Neither comparison was significant ($p = 0.900$ and $p = 0.778$, respectively;
6 Figure 5).

7
8 Biphasic AMT was a significant predictor of SICl normalised MEP when
9 controlling for all IVs in the final model: 6 studies, 85 participants; $B = -0.86$;
10 $SE = 0.30$; $\beta = -0.24$; $p = 0.004$. Biphasic RMT was not a significant predictor
11 of normalised MEP: 3 studies, 78 participants; $B = 0.24$; $SE = 0.31$; $\beta = 0.07$;
12 $p = 0.426$.

13
14 There were no significant non-linear relationships between SICl and age,
15 baseline MEP amplitude, or biphasic AMT. Although the quadratic relationship
16 between SICl and baseline MEP amplitude almost reached significance ($p =$
17 0.053).

18
19 **3.6 ICF regression analysis**

20 IVs 'TMS machine', 'CS intensity', 'pulse waveform', and 'ISI' were omitted
21 from ICF regression due to insufficient data. The inclusion of any the MTs as
22 IVs would have led to a substantial reduction in regression sample size,
23 therefore these were analysed post-hoc.

24

25 < Insert Table 5 here. ICF regression

Table 5. Final ICF regression model. Bold denotes significance ($p < 0.05$).
Participants = 242; studies = 13. See Figure 7 for IV levels.

IV	B	SE	95% CIs		β	p
Gender	-4.46	8.24	-20.61	- 11.69	-0.05	0.588
Baseline MEP	-80.82	32.66	-144.83	- -16.81	-0.46	0.013
TS intensity	-33.32	16.43	-65.52	- -1.11	-0.34	0.043

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The final regression model showed that baseline MEP amplitude and TS intensity (i.e. 120% RMT vs 0.5 - 1.5 mV methods) were significant predictors of ICF normalised MEP (Table 5 and Figure 6). See Figure 7 for ICF marginal means. Other IVs not included in final regression model had p-values > 0.10 in both stage 1 and 2 regressions (see Supplementary file 8 for all stage 1 and 2 results).

< Insert Figure 6 here. ICF scatters >

< Figure 7. ICF marginal means >

3.7 ICF post-hoc analyses

While CS intensity and ISI were omitted from the main analysis, we had sufficient data to compare 80% of RMT to 5-AMT CS intensities and to compare 10 ms, 12, ms, and 15 ms ISIs. The CS intensity comparison was not significant ($p = 0.303$), however for ISI, there was significantly higher ICF for 12 ms ISI data compared to both 10 ms ($p = 0.043$) and 15 ms ISI data ($p = 0.042$) (Figure 7).

Of the four types of MT, only biphasic AMT was not significantly positively associated with ICF normalised MEP. Monophasic RMT, $B = 2.09$; $SE = 0.55$; $\beta = 0.29$; $p < 0.001$ (studies = 11; $N = 193$). Biphasic RMT, $B = 1.46$; $SE =$

Figure6

Figure 6. Relationships between continuous IVs and ICF. Baseline MEP and monophasic RMT were significant predictors of ICF MEP change. Bivariate scatterplots give an indication of results only; see Table 5 for results controlled for other IVs. Green lines fit a smoothed 'lowess' curve through data.

Figure7

Figure 7. Marginal means for ICF normalised MEP. Blue bar shows the overall marginal mean for ICF. Grey and white bars show marginal means for each level of the IVs gender, TS intensity, ISI, and CS intensity (5% machine intensity below AMT vs. 80% of RMT) which were included in the final model or post-hoc tests. * denotes a significant difference between levels ($p < 0.05$). All samples demonstrated significant facilitation ($p < 0.001$). Error bars show 95% confidence intervals. Brackets show (studies/participants).

1 0.30; $\beta = 0.16$; $p < 0.001$ (studies = 3; N = 79). Monophasic AMT, B = 1.33;
 2 SE = 0.48; $\beta = 0.19$; $p < 0.005$ (studies = 3; N = 84).
 3
 4 Non-linear analyses demonstrated a significant quadratic and cubic
 5 relationship between ICF and baseline MEP amplitude ($p = 0.025$ and $p =$
 6 0.044, respectively) (Figure 6). There was also a significant quadratic
 7 relationship between ICF and monophasic AMT ($p = 0.001$), and a significant
 8 cubic relationship between ICF and biphasic RMT (scatterplots in
 9 Supplementary file 9).

11 3.8 MT regression analyses

12 Table 6 shows the four final regression models, demonstrating IVs predicting
 13 each type of MT (see captions for IVs omitted due to insufficient data). Age,
 14 M1 hemisphere, and TMS machine were significant predictors of different
 15 types of MT. There was still higher monophasic RMT for the left hemisphere
 16 when including only data from only right handers (from the restricted sample
 17 in which we had handedness data), however this effect was now non-
 18 significant (studies = 18; N = 319; B = -0.69; SE = 0.39; $p = 0.079$). Age
 19 demonstrated a significant positive relationship with monophasic RMT and
 20 biphasic RMT (Figure 8). See Figure 9 for marginal means of each IV level.

22 < Insert Table 6 here. MT regressions >

24 < Insert Figure 8 here. Scatterplots MT and age >

Table 6. Final MT regression models. Separate analyses were conducted to investigate IVs explaining variability in each of the four types of MT. Bold denotes significance ($p < 0.05$). IVs omitted because of insufficient data are listed below. See Figure 9 for all IV levels.

Monophasic RMT

Participants = 518; studies = 26. Omitted IV: TMS machine.

IV	B	SE	95% CIs			β	p
Age	0.08	0.02	0.03	-	0.13	0.12	0.001
Hemisphere	-2.17	0.89	-3.92	-	-0.42	-0.17	0.015

Monophasic AMT

Participants = 123; studies = 6. Omitted IVs: target muscle, TMS machine, neuronavigation.

IV	B	SE	95% CIs			β	p
Age	0.09	0.05	-0.01	-	0.19	0.12	0.079

Biphasic RMT

Participants = 258; studies = 12. Omitted IV: target muscle, M1 hemisphere. *TMS machine had 3 levels (Magstim 200², MagPro, and Nextstim), therefore main effect: $\chi^2 = 24.97$, $df = 2$. See Figure 9 for pairwise comparisons between levels.

IV	B	SE	95% CIs			β	p
Age	0.14	0.06	0.02	-	0.27	0.25	0.026
Gender	2.62	1.49	-0.31	-	5.55	0.25	0.080
Neuronavigation use	-2.27	2.16	-1.97	-	6.50	0.21	0.295
Machine*							<0.001

Biphasic AMT

Participants = 277; studies = 14. Omitted IVs: M1 hemisphere, target muscle.

IV	B	SE	95% CIs			β	p
Machine	9.91	2.41	5.18	-	14.63	0.88	<0.001
Neuronavigation use	-3.60	3.32	-2.90	-	10.11	0.32	0.277

Figure8

Figure 8. Relationship between age and motor threshold. Monophasic RMT and biphasic RMT showed a significant positive linear relationship with age (Table 6), indicating reduced corticospinal excitability in older adults. There were also significant non-linear relationships between age and monophasic AMT and biphasic AMT (see Results). Green lines fit a smoothed 'lowess' curve through data. Bivariate scatterplots give an indication of results only.

1

2 Other IVs not included in the final regression models had p-values > 0.10 in
3 both stage 1 and 2 regressions (see Supplementary file 10 for all stage 1 and
4 2 results).

5

6 < Insert Figure 9 here. MT marginal means >

7

8 3.9 MT post-hoc analyses

9 There was a significant quadratic and cubic relationship between monophasic
10 AMT and age ($p < 0.001$ and $p = 0.031$, respectively). A cubic relationship
11 between biphasic RMT and age did not reach significance ($p = 0.070$) (Figure
12 8).

13

14 3.10 Additional analyses

15 Two stage regression analysis demonstrated a significant difference between
16 single pulse TMS MEP amplitudes collected using 120% of RMT, compared
17 with those collected using the 1 mV method: 120% RMT marginal mean
18 (studies = 17; $N = 341$) = 0.87 mV; 95% CIs = 0.78 – 0.96; 1 mV method
19 marginal mean (studies = 9; $N = 189$) = 1.09 mV; 95% CIs = 0.97 – 1.21; $B =$
20 0.22; $SE = 0.09$; $p = 0.015$. This effect of TS intensity method was still
21 significant when not controlling for any covariates ($p = 0.013$) (see Figure 1 for
22 histograms of both methods).

23

24 Studies that employed the 120% RMT method also displayed higher average
25 variance between participants' MEP amplitudes: 120% RMT method studies

Figure9

Figure 9. Marginal means for motor threshold. Coloured bars show overall marginal means for monophasic RMT, monophasic AMT, biphasic RMT, and biphasic AMT. Grey and white bars show marginal means of levels of the IVs M1 hemisphere, gender, TMS machine, and neuronavigation (NN), which were included in final regression models. * denotes a significant difference between levels ($p < 0.05$) Error bars show 95% confidence intervals. Brackets show (studies/participants).

1 average SD = 0.55 mV; average CV = 62.8%. 1 mV method studies average
2 SD = 0.39 mV; average CV = 33.8%. Levene's robust test demonstrated that
3 the higher MEP amplitude variance for the 120% RMT method was significant
4 ($F = 23.35$; $df = 1, 573$, $p < 0.001$). This lower variance for the 1mV method
5 was expected, given that operators set the machine intensity to evoke this
6 predefined 1mV amplitude output.

7

8 There were strong significant positive correlations between the four types of
9 MT (all $p < 0.001$): monophasic RMT x biphasic RMT, $N = 153$, $R = 0.856$;
10 monophasic RMT x monophasic AMT, $N = 123$, $R = 0.933$; monophasic RMT
11 x biphasic AMT, $N = 223$, $R = 0.659$; biphasic RMT x biphasic AMT, $N = 83$, R
12 $= 0.749$, monophasic AMT x biphasic AMT, $N = 21$, $R = 0.916$ (no
13 observations for biphasic RMT x monophasic AMT).

14

15 **4. Discussion**

16 This study pooled data from 35 studies to demonstrate factors explaining
17 interindividual variability in response to single and pp TMS. We suggest
18 reasons for these observed sources of variability and propose specific
19 methodological adjustments to reduce for their potential influence. We hope
20 that these findings will lead to greater standardisation of single and pp TMS
21 methods in the brain stimulation community, thereby increasing their utility as
22 a clinical and experimental tool.

23

24 **4.1 Baseline MEP amplitude**

1 As in Corp et al. (2020), who applied the present method to TBS data, this
2 study has demonstrated significant negative relationships between baseline
3 MEP amplitude and (SICI and ICF) normalised MEP. That is, lower baseline
4 responses resulted in higher amplitude conditioned MEPs, regardless of the
5 pp TMS or TBS protocol. We suggest three main reasons as to why these
6 relationships may occur in both pp TMS and TBS data (Corp et al. 2020):
7 regression to the mean; floor and ceiling effects; and different cortical
8 networks being probed between individuals. Regression to the mean is the
9 statistical phenomenon by which an initial extreme measurement is more
10 likely to be closer to the mean if measured for a second time (Bland and
11 Altman 1994, Stigler 1997). By this logic, conditioned MEP responses are
12 more likely to show facilitation (or ameliorated inhibition) if a person records
13 extremely low baseline MEP amplitudes, and vice versa (Corp et al. 2020).
14 Floor and ceiling effects occur when TMS intensities are too close to a floor
15 (minimal activation) or ceiling (maximal activation of neurons), and thus
16 further inputs fail to produce discernible changes in MEP amplitude (Devanne
17 et al. 1997). While TS intensities are individualised, usually to 120% RMT or a
18 1 mV value, there can be substantial variability in relation to where these
19 stimulus intensities occur in relation to each individual's input/output curve
20 (Goldsworthy et al. 2016b, Houdayer et al. 2008, Pitcher et al. 2015). In other
21 words, these individualised TS intensities can be a relatively low or high
22 between individuals. This can bias the effects of the CS, with 'inhibition' less
23 likely for individuals with low relative TS intensities, and 'facilitation' less likely
24 for those with high relative TS intensities (Amandusson et al. 2017,
25 Goldsworthy et al. 2016b). If we assume that those with low baseline MEP

1 amplitudes received TMS pulses at relatively low intensities, this would agree
 2 with the negative relationship in the present study, where low baseline MEP
 3 amplitudes resulted in greater ICF effects yet ameliorated SICI effects
 4 (Figures 4 & 6). However, this is speculative given that we could not directly
 5 assess the relative stimulus intensities at which the pulses were applied.
 6 Lastly, it has been shown that TS intensity influences the cortical circuits
 7 activated by the TMS pulse (Di Lazzaro et al. 1998). Thus, if the TS intensity
 8 used for an individual does not probe the circuits activated by the initial CS,
 9 SICI and ICF may not be revealed (Di Lazzaro et al. 1998, Garry and
 10 Thomson 2009). Based on this, the negative relationship for baseline MEP
 11 amplitude in the present study may suggest that SICI is best probed by high
 12 relative TS intensities and ICF best probed by low relative TS intensities.
 13 However, this does not agree with previous research showing that SICI and
 14 ICF are maximal at moderate TS intensities (Cosentino et al. 2018, Garry and
 15 Thomson 2009). This suggests that regression to the mean and floor and
 16 ceiling effects may have been stronger influences on SICI and ICF response,
 17 however again this is speculative, given that we could not directly test the
 18 relative intensities at which the pulses were applied within individuals.

19

20 4.2 Motor threshold predicts single and paired-pulse TMS response

21 Our data demonstrated that MT predicted single pulse MEP amplitude, SICI,
 22 and ICF response. For single pulse TMS, this is in agreement with Peterchev
 23 et al. (2013), who showed that individuals with lower MTs have steeper I/O
 24 slopes (Peterchev et al. 2013). We demonstrate a similar result here by
 25 showing that individuals with lower MTs have higher MEP amplitudes at one

1 stimulus intensity along the I/O curve (120% RMT). For SICI and ICF, this
 2 phenomenon may be in part caused by the fact that the conditioning stimulus
 3 intensity (as a percentage of the machine output) is adjusted to an individual's
 4 MT. This is designed to ensure the activation of a similar proportion of
 5 corticospinal neurons between individuals. However, SICI and ICF
 6 mechanisms are dependent on *intracortical*, rather than *corticospinal* neurons,
 7 and the threshold for activation of these two networks does not necessarily
 8 correlate (Chen et al. 1998). Thus, those with higher MTs receive a higher
 9 intensity CS (as a percentage of machine output), and this could cause
 10 stronger activation of intracortical mechanisms (Amandusson et al. 2017) (and
 11 thus an increased SICI and ICF effect, as demonstrated here). However,
 12 these relationships could also be caused by inherent differences in SICI and
 13 ICF for individuals with low or high MTs, with the differential effects of stimulus
 14 intensity and MT unable to be disentangled here due to machine output being
 15 adjusted to MT in all studies.

16

17 4.3 Effect of age on corticospinal excitability

18 Linear regression showed that, on average, monophasic RMT and biphasic
 19 AMT significantly increased with age. However, this reduction in corticospinal
 20 excitability does not appear to be linear across the lifespan, demonstrated by
 21 significant quadratic relationships for monophasic AMT, and biphasic AMT,
 22 and fitted 'lowess' lines through MT data indicating curved patterns at
 23 particular age points (Figure 8). These fitted lines suggest an initial stage of
 24 hypoexcitability for people under ~20 years of age, with MT then reaching its
 25 lowest point at about the age of 25. After this age, there seemed to be

1 different patterns in monophasic and biphasic data, with monophasic MTs
 2 increasing through middle age, then reducing again in older age, as opposed
 3 to biphasic MTs - which continued to increase with age. The divergent
 4 patterns observed in monophasic and biphasic data could be due to different
 5 cortical mechanisms activated by these pulse waveforms; biphasic pulses
 6 may activate later I-waves compared to monophasic posterior-anterior
 7 stimulation (Di Lazzaro et al. 2001). However, the pattern of activation may
 8 also depend on stimulus intensity, and the initial current direction of the
 9 biphasic pulse (Di Lazzaro et al. 2001), for which we had incomplete
 10 information. The curved pattern of response for monophasic MTs is similar to
 11 that of Shibuya et al. (2016), who demonstrated the lowest monophasic RMTs
 12 for 20-25 year olds and older adults (study age range: 20-83), and maximal
 13 RMT at approximately 50 years of age, and a significant quadratic effect.

14
 15 Interestingly, the higher monophasic RMT for < 20 year olds (Figure 8) did not
 16 translate to a significant quadratic or cubic effect. This may be because the
 17 majority of these observations came from one study (Croarkin et al. 2013),
 18 and these values would have been adjusted given that we included 'study ID'
 19 as a random variable to account for the fact that data came from different
 20 studies. However, the relationships between corticospinal excitability and age
 21 observed in the present study should be interpreted with caution given the
 22 relative dearth of data for adolescents and middle-aged adults (Figure 7).

23

24 4.4 Effect of hemisphere on cortical excitability

1 Our results demonstrated reduced SICl and increased monophasic RMT in
2 the left hemisphere. These effects were similar when including only data from
3 right handers from our restricted sample for which we had handedness data
4 (although the effect became non-significant for monophasic RMT, $p = 0.079$).
5 Thus, while we do observe these effects in right handers, we cannot say
6 whether they are driven by the fact that the left hemisphere is the dominant
7 M1, or whether it is simply an effect of the left hemisphere across both right
8 and left handers. The collection of additional data from left handers will be
9 required to answer this question. In regards to previous literature, Ilic et al.
10 (2004), also showed reduced SICl in the left M1 in right handed participants.
11 These authors suggested that less SICl in the dominant hemisphere for right
12 handers may provide an advantage for the readiness and ease to carry out
13 movements with the dominant hand (Ilic et al. 2004). In contrast, our
14 monophasic RMT findings differ to Ilic et al. (2004), who showed *reduced*
15 monophasic RMT in the left hemisphere for right handers. It is not clear as to
16 why we obtained conflicting MT results. However, given our non-significant
17 results when only including right handers, and the small sample size of Ilic et
18 al. (2004) (9 right handers), these effects are not conclusive, and additional
19 hemisphere and handedness data needs to be gathered.

20

21 4.5 *Effect of machine on corticospinal excitability*

22 We found that Nexstim machines were more powerful than MagPro machines
23 for single pulse MEP amplitude, yet observed higher biphasic RMT and
24 biphasic AMT for the Magstim Rapid machine than MagPro and Nexstim
25 machines. Much of this effect is likely due to the use of Magstim Rapid

1 machines for biphasic MT assessment prior to repetitive TMS protocols
 2 (delivered with biphasic pulses), which have a reduced power output in
 3 comparison to Magstim 200² (Kammer et al. 2001), and MagPro X100
 4 machines (Koponen et al. 2020). These differential effects highlight the
 5 importance of the inclusion of TMS machine (and study location if applicable)
 6 as a covariate in statistical analyses on data that are pooled collaboratively
 7 using different machines. Researchers should also be aware that the various
 8 configurations of the Magstim BiStim machine (i.e. two connected Magstim
 9 200² machines) produce different power outputs, which may confound
 10 electrophysiological results if configured incorrectly (Do et al. 2019). We did
 11 not collect information on these configurations in the present study, which
 12 may have affected results.

13

14 4.6 Limitations

15 A number of limitations should be acknowledged. First, we were limited to
 16 analysing the variables that were available to us, and so could not measure
 17 the impact of IVs such as menstrual cycle (Hattemer et al. 2007), or
 18 neuroimaging markers (Silbert et al. 2006) on corticospinal excitability.
 19 Second, our approach pooled data from separate studies, and thus does not
 20 have the precision of a repeated-measures design. Pooling different studies'
 21 results increases the risk of between-study variability being caused by factors
 22 such as sampling error, study setting, and experimenter behaviour (Higgins
 23 and Green 2011). Next, of the nine studies using neuronavigation, none
 24 reported coordinates of the motor hotspot, nor coil shift data from the motor
 25 hotspot. Thus, unaccounted for differences in coil position may have

1 explained some unobserved intraindividual variability in TMS outcomes. Next,
2 we were limited by the incomplete dataset that we could gather for
3 handedness, and also the small number of left-handers within that dataset.
4 Thus, we do not know whether our ‘hemisphere’ effects were driven by
5 hemispheric differences between left and right handers, or by handedness.
6 Next, we did not measure the potential impact of TMS machine coil size or
7 type, or initial waveform direction (i.e. AP or PA), on cortical excitability.
8 Finally, it should be acknowledged that a portion of interindividual variability in
9 MEP amplitudes occurs due to differences in the excitability of spinal circuits
10 (Kiers et al. 1993, Lackmy and Marchand-Pauvert 2010), and we could not
11 account for this given that the included studies did not measure sub-cortical
12 responses such as the M-max or H-reflex.

13

14 4.7 Recommendations

15 We first propose some steps to counter the significant relationships observed
16 between baseline MEP amplitude and SIC/ICF. To avoid regression to the
17 mean caused by chance occurrences of high or low MEP amplitudes, we
18 recommend that investigators: 1) collect a sufficient number (20-30) of MEPs
19 in their TMS blocks (Chang et al. 2016, Goldsworthy et al. 2016a); 2) avoid
20 possible initial states of hyperexcitability within TMS sessions (Brasil-Neto et
21 al. 1994, Schmidt et al. 2009); and 3) include baseline MEP amplitude as a
22 covariate in statistical analyses. To avoid floor and ceiling effects, the CS
23 could be normalised to 50% of maximal inhibition/facilitation (McAllister et al.
24 2009), while the TS could be normalised to 50% of maximal MEP amplitude
25 (Goldsworthy et al. 2016b, Houdayer et al. 2008). This would also circumvent

1 the aforementioned issues with normalising the CS to MT (Chen et al. 1998).
2 However, it has previously been suggested that the use of this TS intensity
3 may still result in substantial between-subject differences in the in the neural
4 circuits probed by the TMS pulse (i.e. relative D- and I-wave contributions to
5 the MEP) (Goldsworthy et al. 2016b). Until this can be empirically investigated
6 (most likely through recordings from the cervical epidural space, e.g. Di
7 Lazzaro et al. (2001)), we recommend that researchers minimise the
8 aforementioned biases by collecting data across a range of stimulus
9 intensities (i.e. pp input/output curves) (Ilić et al. 2002, Orth et al. 2003).
10 However, in addition to the increased complexity in analysing pp input/output
11 curve data, their collection is time consuming, especially if varying both CS
12 and TS intensities. Thus, further effort should be directed towards the
13 formulation of time effective methods of collection of (single and) pp TMS
14 curve data, and increased standardisation in their analysis. Next, in order to
15 reduce possible variability due to coil position, we suggest that where
16 neuronavigation can be used, researchers should report the coordinates of
17 the motor hotspot, and report or analyse the impact of shifts from the motor
18 hotspot for individual participants. Lastly, when making age comparisons,
19 investigators should be aware that the relationship between age and
20 corticospinal excitability may not be linear across the lifespan.

21

22 4.8 Conclusions

23 The present study pooled individual participant data across 35 studies to
24 demonstrate sources of interindividual variability in single and pp TMS
25 measurements, including baseline MEP amplitude, age, TS intensity, M1

1 hemisphere, ISI, TMS machine, and MT. We have highlighted possible
2 reasons for these sources of variability and made specific methodological
3 recommendations to reduce their influence. These findings highlight the need
4 for increased standardisation of single and pp TMS methods across the brain
5 stimulation community, which we hope will be facilitated through this
6 collaborative approach. We are currently expanding the 'Big TMS Data
7 Collaboration' through the construction of an individual participant TMS data
8 repository at www.bigtmsdata.com, and welcome additional brain stimulation
9 researchers to contribute to this database.

10

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14

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16

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10

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- 20
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Supplementary file 2. Search syntax.

Search ((intermittent theta-burst stimulation OR intermittent theta burst stimulation OR iTBS)) AND (Transcranial magnetic stimulation OR TMS) Filters: Publication date from 2013/01/01 to 2016/12/31. Results = 126

((continuous theta-burst stimulation OR continuous theta burst stimulation OR cTBS)) AND (Transcranial magnetic stimulation OR TMS) Filters: Publication date from 2012/01/01 to 2016/12/31 Results = 239

((short-interval intracortical inhibition OR short interval intracortical inhibition OR SICI)) AND (Transcranial magnetic stimulation OR TMS) Filters: Publication date from 2014/01/01 to 2016/12/31. Results = 218

((intracortical facilitation OR ICF)) AND (Transcranial magnetic stimulation OR TMS) Filters: Publication date from 2014/01/01 to 2016/12/31. Results = 152

((input-output curve* OR stimulus-response curve* OR I-O curve* OR IO curve* OR S-R curve* OR SR curve*)) AND (Transcranial magnetic stimulation OR TMS) Filters: Publication date from 2013/01/01 to 2016/12/31. Results = 69

Supplementary file 3. Distribution plots. Histograms show distribution of MEP data for single pulse, SICI and ICF protocols, prior to outlier winsorization.

Supplementary file 4: Reproducibility data from Beynel et al. (2014)

Methods

Test-retest data were taken from 35 healthy participants (19 females; mean age: 44.67 ± 20.12) at a month interval. Single pulse MEP data were assessed at 120% of RMT, while SICl and ICF were assessed at 80% and 120% of RMT, for conditioning and test stimuli, respectively, with interstimulus intervals of 2 ms (SICl) and 15 ms (ICF). Ten MEPs were collected per condition, per session. Please see the published study (Beynel et al., 2014) for further methodological details. As in the main manuscript (Corp et al.), for SICl and ICF, each individual's mean conditioned MEP amplitude was normalised to their mean baseline MEP amplitude.

Results

The intraclass correlation coefficients (McGraw et al., 1996) for each TMS protocol were as follows: biphasic RMT = 0.845; single pulse MEP amplitude = 0.375; ICF = 0.376; and SICl = 0.367.

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Supplementary file 5. The use of z-scores grouped by study to run correlation analyses. Table shows an example of this method, using the correlations between monophasic RMT and biphasic RMT.

Study	R-value
Dickins et al. (2015)	0.913
Do et al. (2018)	0.880
Fried et al. (2016)	0.902
Goldsworthy et al. (2016)	0.904
Gomes-Osman (unpublished)	0.826
Nettekoven et al. (2014)	0.607
Vallence et al. (2015)	0.838
Average R-value across studies	0.839
R-value of correlated z-scores across sample, first grouped by study (used in manuscript)	0.856
*R-value of correlated MTs across sample (without obtaining z-scores grouped by study)	0.127

*We include this analysis to demonstrates the importance of using z-scores to calculate these correlations. If not, variance is caused by the different methods used for obtaining MTs between studies.

*Step 1 regressions for 120% RMT single pulse MEP amplitude. Examining the variance in MEP amplitudes explained by each IV separately, while controlling for the age and gender of participants.

Abbreviations:

MEP change = Normalised MEP (DV)
 Age
 Gender
 BaseMEP_wins = 120% RMT single pulse MEP amplitude
 Machine_spulse = TMS machine
 Muscle = Target muscle
 Hemisphere = M1 hemisphere
 ppCSint = paired pulse conditioning stimulus intensity
 ppTSint = paired pulse test stimulus intensity
 PulseType/PulseType2 = Pulse waveform
 ISI = interstimulus interval
 MonoRMT = Monophasic RMT
 MonoAMT = Monophasic AMT
 BiRMT = Biphasic RMT
 BiAMT = Biphasic AMT
 TSint_comparison = denotes the analysis of 120% RMT data
 Studyno = Study ID
 newPartID = Participant ID

*IVs omitted because of insufficient data (did not include at least three studies within each IV level):

Machine Muscle PulseType2 MonoRMT MonoAMT BiRMT BiAMT

```
.
. for var Hemisphere Muscle Machine_spulse PulseType2 Neuronavigation
MonoRMT BiRM
> T MonoAMT BiAMT : mixed BaseMEP_wins Age Gender c.X if
TSint_comparison ==0 ///
> || Studyno: || newPartID:,robust noretable
```

```
-> mixed BaseMEP_wins Age Gender c.Hemisphere if TSint_comparison ==0 ||
Studyno: |
> | newPartID:,robust noretable
```

Performing EM optimization:

Performing gradient-based optimization:

```

Iteration 0:    log pseudolikelihood = -429.45103
Iteration 1:    log pseudolikelihood = -429.43954
Iteration 2:    log pseudolikelihood = -429.43954

```

Computing standard errors:

```

Mixed-effects regression                                Number of obs    =
462

```

Group Variable		No. of Groups	Observations per Group		
			Minimum	Average	Maximum
Studyno		17	10	27.2	70
newPartID		347	1	1.3	2

```

                                                                Wald chi2(3)    =
1.78
Log pseudolikelihood = -429.43954                            Prob > chi2      =
0.6190

```

(Std. Err. adjusted for 17 clusters in Studyno)

BaseMEP_wins Interval]		Coef.	Robust Std. Err.	z	P> z	[95% Conf.
Age		-.0027805	.0033584	-0.83	0.408	-.0093628
.0038019						
Gender		-.0087345	.0740265	-0.12	0.906	-.1538238
.1363548						
Hemisphere		.0273188	.0333839	0.82	0.413	-.0381124
.09275						
_cons		.9897414	.1289038	7.68	0.000	.7370946
1.242388						

```

-> mixed BaseMEP_wins Age Gender c.Muscle if TSint_comparison ==0 ||
Studyno: || ne
> wPartID:,robust noretable

```

Performing EM optimization:

Performing gradient-based optimization:

```

Iteration 0:    log pseudolikelihood = -434.6118
Iteration 1:    log pseudolikelihood = -434.59578
Iteration 2:    log pseudolikelihood = -434.59578

```

```
Mixed-effects regression      Number of obs      =
474
```

Group Variable	No. of Groups	Observations per Group		
		Minimum	Average	Maximum
StudyNo	18	10	26.3	70
newPartID	359	1	1.3	2

22.47	Wald chi2(3)	=
Log pseudolikelihood = -434.59578	Prob > chi2	=
0.0001		

(Std. Err. adjusted for 18 clusters in Studyno)

BaseMEP_wins Interval]	Coef.	Robust Std. Err.	z	P> z	[95% Conf.	
Age	-.0025503	.0030264	-0.84	0.399	-.008482	
Gender	-.0002533	.0699914	-0.00	0.997	-.137434	
Muscle	-.3206196	.0721294	-4.45	0.000	-.4619907	-
_cons	1.07201	.1289905	8.31	0.000	.8191928	

```
-> mixed BaseMEP_wins Age Gender c.Machine_spulse if TSint_comparison
==0 || Studyn
> o: || newPartID:,robust noretale
```

Performing EM optimization:

Performing gradient-based optimization:

```
Iteration 0:    log pseudolikelihood = -414.96007
Iteration 1:    log pseudolikelihood = -414.93493
Iteration 2:    log pseudolikelihood = -414.93492
```

Computing standard errors:

```
Mixed-effects regression                                Number of obs    =
456
```


Group Variable		No. of Groups	Observations per Group		
			Minimum	Average	Maximum
Studyno		17	10	26.8	70
newPartID		341	1	1.3	2

38.91
Log pseudolikelihood = -414.93492
0.0000

Wald chi2(3) =
Prob > chi2 =

(Std. Err. adjusted for 17 clusters in Studyno)

BaseMEP_wins Interval]		Coef.	Robust Std. Err.	z	P> z	[95% Conf.
Age		-.0038426	.0028052	-1.37	0.171	-.0093407
Gender		-.0293734	.0699193	-0.42	0.674	-.1664127
Machine_spulse		.2408224	.0420787	5.72	0.000	.1583496
_cons		.9272276	.1144897	8.10	0.000	.702832

```
-> mixed BaseMEP_wins Age Gender c.PulseType2 if TSint_comparison ==0 ||
Studyno: |
> | newPartID:,robust noretale
```

Performing EM optimization:

Performing gradient-based optimization:

Iteration 0: log pseudolikelihood = -424.34173
Iteration 1: log pseudolikelihood = -424.33683
Iteration 2: log pseudolikelihood = -424.33683

Computing standard errors:

Mixed-effects regression
474

Number of obs =

Group Variable		No. of Groups	Observations per Group		
			Minimum	Average	Maximum

Study	18	10	26.3	70
newPartID	359	1	1.3	2

Wald chi2(3) = 177.91
 Log pseudolikelihood = -424.33683 Prob > chi2 = 0.0000

(Std. Err. adjusted for 18 clusters in Study)

	Coef.	Robust Std. Err.	z	P> z	[95% Conf. Interval]
Age	-.0031481	.0029437	-1.07	0.285	-.0089176 .0026214
Gender	.0034524	.0689223	0.05	0.960	-.1316327 .1385376
PulseType2	.3376344	.0334713	10.09	0.000	.2720318 .403237
_cons	.926825	.1191044	7.78	0.000	.6933845 1.160265

```
-> mixed BaseMEP_wins Age Gender c.Neuronavigation if TSint_comparison
==0 || Study
> no: || newPartID:,robust noretale
```

Performing EM optimization:

Performing gradient-based optimization:

Iteration 0: log pseudolikelihood = -434.25844
 Iteration 1: log pseudolikelihood = -434.24201
 Iteration 2: log pseudolikelihood = -434.24201

Computing standard errors:

Mixed-effects regression Number of obs = 474

Group Variable	No. of Groups	Observations per Group	Minimum	Average	Maximum
Study	18	10	26.3	70	
newPartID	359	1	1.3	2	

13.74 Wald chi2(3) =
 Log pseudolikelihood = -434.24201 Prob > chi2 =
 0.0033

(Std. Err. adjusted for 18 clusters in Studyno)

		Coef.	Robust Std. Err.	z	P> z	[95% Conf. Interval]
BaseMEP_wins						
Age		-.0028702	.0028519	-1.01	0.314	-.0084598
Gender		-.0052331	.0692731	-0.08	0.940	-.141006
Neuronavigation		-.29488	.0954175	-3.09	0.002	-.4818949
_cons		1.180095	.112362	10.50	0.000	.959869

```
-> mixed BaseMEP_wins Age Gender c.MonoRMT if TSint_comparison ==0 ||
Studyno: || n
> ewPartID:,robust noretale
```

Performing EM optimization:

Performing gradient-based optimization:

Iteration 0: log pseudolikelihood = -278.81131
 Iteration 1: log pseudolikelihood = -278.80319
 Iteration 2: log pseudolikelihood = -278.80319

Computing standard errors:

Mixed-effects regression Number of obs =
 363

Group Variable	No. of Groups	Minimum	Average	Maximum
Studyno	13	11	27.9	70
newPartID	248	1	1.5	2

44.03 Wald chi2(3) =

Log pseudolikelihood = -278.80319 Prob > chi2 =
0.0000

(Std. Err. adjusted for 13 clusters in Studyno)

		Coef.	Robust Std. Err.	z	P> z	[95% Conf. Interval]
BaseMEP_wins						
Age		.0030643	.0029831	1.03	0.304	-.0027824
Gender		-.0092131	.0532958	-0.17	0.863	-.113671
MonoRMT		-.0146129	.0028081	-5.20	0.000	-.0201167
_cons		1.490094	.1688795	8.82	0.000	1.159097

-> mixed BaseMEP_wins Age Gender c.BiRMT if TSint_comparison ==0 ||
Studyno: || new
> PartID:,robust noretale

Performing EM optimization:

Performing gradient-based optimization:

Iteration 0: log pseudolikelihood = -235.75133
Iteration 1: log pseudolikelihood = -235.56781
Iteration 2: log pseudolikelihood = -235.56733
Iteration 3: log pseudolikelihood = -235.56733

Computing standard errors:

Mixed-effects regression Number of obs =
214

Group Variable	No. of Groups	Observations per Group Minimum Average Maximum
Studyno	8	10 26.8 51
newPartID	174	1 1.2 2

Wald chi2(3) =
14.59
Log pseudolikelihood = -235.56733 Prob > chi2 =
0.0022

(Std. Err. adjusted for 8 clusters in Studyno)

	Coef.	Robust Std. Err.	z	P> z	[95% Conf. Interval]
Age	-.0014456	.0035162	-0.41	0.681	-.0083372
Gender	.0284975	.1527012	0.19	0.852	-.2707914
BiRMT	-.0193975	.0052949	-3.66	0.000	-.0297753
_cons	2.029973	.2791479	7.27	0.000	1.482853

```
-> mixed BaseMEP_wins Age Gender c.MonoAMT if TSint_comparison ==0 ||
Studyno: || n
> ewPartID:,robust noretale
```

Performing EM optimization:

Performing gradient-based optimization:

```
Iteration 0:    log pseudolikelihood = -67.441544
Iteration 1:    log pseudolikelihood = -67.389585
Iteration 2:    log pseudolikelihood = -67.371305
Iteration 3:    log pseudolikelihood =  -67.37035
Iteration 4:    log pseudolikelihood =  -67.37035
```

Computing standard errors:

```
Mixed-effects regression      Number of obs      =
124
```

Group Variable	No. of Groups	Observations per Group		
		Minimum	Average	Maximum
Studyno	3	20	41.3	70
newPartID	62	2	2.0	2

```

.                                     Wald chi2(2)      =
Log pseudolikelihood = -67.37035      Prob > chi2      =
.
```

(Std. Err. adjusted for 3 clusters in Studyno)

		Robust			
BaseMEP_wins	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]
Age	-.0032472	.0024551	-1.32	0.186	-.0080591
Gender	.0360827	.0363064	0.99	0.320	-.0350766
MonoAMT	-.0079267	.0029001	-2.73	0.006	-.0136109
_cons	1.295731	.2591768	5.00	0.000	.7877538

```

-> mixed BaseMEP_wins Age Gender c.BiAMT if TSint_comparison ==0 ||
Studyno: || new
> PartID:,robust norettable

```

Performing EM optimization:

Performing gradient-based optimization:

```

Iteration 0: log pseudolikelihood = -204.47578
Iteration 1: log pseudolikelihood = -204.45425
Iteration 2: log pseudolikelihood = -204.45425

```

Computing standard errors:

```

Mixed-effects regression                               Number of obs   =
214

```

Group Variable	No. of Groups	Observations per Group	Minimum	Average	Maximum
Studyno	9	10	23.8	51	
newPartID	174	1	1.2	2	

```

Wald chi2(3) =
34.74
Log pseudolikelihood = -204.45425      Prob > chi2 =
0.0000

```

(Std. Err. adjusted for 9 clusters in Studyno)

```

Robust

```


newPartID		341	1	1.3	2	
-----------	--	-----	---	-----	---	--

864.57
Log pseudolikelihood = -404.3133
0.0000

Wald chi2(5) =
Prob > chi2 =

(Std. Err. adjusted for 17 clusters in Studyno)

BaseMEP_wins Interval]		Coef.	Robust Std. Err.	z	P> z	[95% Conf.
---------------------------	--	-------	---------------------	---	------	------------

Muscle						
APB		-0.2685	0.1112	-2.41	0.016	-0.4865

-0.0504

Machine_spulse						
MagPro		-0.2358	0.1340	-1.76	0.078	-0.4984

0.0269

Nexstim		0.0045	0.1347	0.03	0.973	-0.2594
---------	--	--------	--------	------	-------	---------

0.2684

PulseType2						
Biphasic		0.2955	0.0488	6.05	0.000	0.1998

0.3912

Neuronavigation						
No		-0.1146	0.0448	-2.56	0.011	-0.2025

-0.0267

_cons		1.0168	0.1112	9.14	0.000	0.7987
-------	--	--------	--------	------	-------	--------

1.2348

Random-effects Parameters		Estimate	Robust Std. Err.	[95% Conf.
---------------------------	--	----------	---------------------	------------

Studyno: Identity				
var(_cons)		0.0004	0.0121	0.0000

5.1e

newPartID: Identity				
var(_cons)		0.3334	0.0853	0.2020

0.5505


```

-----+-----
-----
                                var(Residual) |      0.0992      0.0105      0.0805
0.1221
-----
-----

```

```

.
. *Iterating

. mixed BaseMEP_wins i.Muscle i.Machine_spulse i.PulseType2
i.Neuronavigation Age i
> f TSint_comparison ==0 || Studyno: || newPartID:, robust
cformat(%5.4f)

```

Performing EM optimization:

Performing gradient-based optimization:

```

Iteration 0:   log pseudolikelihood = -403.41713
Iteration 1:   log pseudolikelihood = -403.16827
Iteration 2:   log pseudolikelihood = -403.16497
Iteration 3:   log pseudolikelihood = -403.16497

```

Computing standard errors:

```

Mixed-effects regression                                Number of obs      =
456

```

```

-----+-----
Group Variable |      No. of      Observations per Group
               |      Groups      Minimum      Average      Maximum
-----+-----
      Studyno |           17           10           26.8           70
    newPartID |          341            1            1.3            2
-----+-----

```

```

                                                                Wald chi2(6)      =
4381.19
Log pseudolikelihood = -403.16497                      Prob > chi2      =
0.0000

```

```

                                                                (Std. Err. adjusted for 17 clusters in
Studyno)

```

```

-----+-----
               |      Coef.      Robust      z      P>|z|      [95% Conf.
BaseMEP_wins |      Coef.      Std. Err.      z      P>|z|      Interval]
-----+-----

```

	Muscle					
0.0080	APB		-0.2258	0.1193	-1.89	0.058 -0.4596
	Machine_spulse					
0.1045	MagPro		-0.1602	0.1351	-1.19	0.236 -0.4250
0.4305	Nexstim		0.1092	0.1639	0.67	0.505 -0.2120
	PulseType2					
0.3845	Biphasic		0.2980	0.0441	6.75	0.000 0.2115
	Neuronavigation					
0.0645	No		-0.0672	0.0672	-1.00	0.317 -0.1990
0.0028	Age		-0.0032	0.0031	-1.04	0.299 -0.0092
1.2887	_cons		1.0603	0.1165	9.10	0.000 0.8319

Random-effects Parameters		Estimate	Robust Std. Err.	[95% Conf. Interval]
---------------------------	--	----------	------------------	----------------------

-----+-----

Studyno: Identity				
var(_cons)		0.0000	.	.

-----+-----

newPartID: Identity				
var(_cons)		0.3307	0.0800	0.2059

-----+-----

var(Residual)		0.0993	0.0105	0.0807
---------------	--	--------	--------	--------


```
.
. mixed BaseMEP_wins i.Muscle i.Machine_spulse i.PulseType2
i.Neuronavigation i. Gen
> der if TSint_comparison ==0 || ///
> Studyno: || newPartID:,robust cformat(%5.4f)
```

Performing EM optimization:

```
Iteration 0:    log pseudolikelihood = -404.44629
Iteration 1:    log pseudolikelihood = -404.31143
Iteration 2:    log pseudolikelihood = -404.30786
Iteration 3:    log pseudolikelihood = -404.30774
Iteration 4:    log pseudolikelihood = -404.30774
```

```
Mixed-effects regression      Number of obs      =
456
```

Group Variable	No. of Groups	Observations per Group		
		Minimum	Average	Maximum
StudyNo	17	10	26.8	70
newPartID	341	1	1.3	2

```

1660.75                                Wald chi2(6)      =
Log pseudolikelihood = -404.30774      Prob > chi2       =
0.0000

```

(Std. Err. adjusted for 17 clusters in Studyno)

	BaseMEP_wins Interval]	Coef.	Robust Std. Err.	z	P> z	[95% Conf.
	Muscle APB	-0.2680	0.1104	-2.43	0.015	-0.4844
-0.0516						
	Machine_spulse MagPro	-0.2364	0.1346	-1.76	0.079	-0.5002
0.0274						
	Nexstim	0.0048	0.1340	0.04	0.971	-0.2577
0.2673						
	PulseType2 Biphasic	0.2952	0.0483	6.11	0.000	0.2005
0.3900						
	Neuronavigation No	-0.1149	0.0454	-2.53	0.011	-0.2038
-0.0260						
	Gender					


```

newPartID |          329          1          1.3          2
-----
Wald chi2(6) =
998.22
Log pseudolikelihood = -396.35867 Prob > chi2 =
0.0000

(Std. Err. adjusted for 16 clusters in
Studyno)
-----
BaseMEP_wins |          Coef.      Robust      z      P>|z|      [95% Conf.
Interval]
-----+-----
Muscle |
  APB |      -0.2591      0.1245      -2.08      0.037      -0.5030
-0.0151
Machine_spulse |
  MagPro |      -0.2296      0.1467      -1.57      0.117      -0.5171
0.0579
  Nexstim |       0.0141      0.1458       0.10      0.923      -0.2717
0.2999
  PulseType2 |
    Biphasic |       0.2966      0.0485       6.12      0.000       0.2017
0.3916
Neuronavigation |
  No |      -0.1213      0.0419      -2.89      0.004      -0.2034
-0.0392
  Hemisphere |
    R |       0.0210      0.0329       0.64      0.524      -0.0435
0.0854
  _cons |       1.0074      0.1245       8.09      0.000       0.7634
1.2513
-----
-----

```

```

. *Final model

```

```

. mixed BaseMEP_wins i.Muscle i.Machine_spulse i.PulseType2
i.Neuronavigation if TSint_comparison ==0 || ///

```

Studyno: || newPartID:,robust cformat(%5.4f)

Performing EM optimization:

Performing gradient-based optimization:

Iteration 0: log pseudolikelihood = -404.44997
Iteration 1: log pseudolikelihood = -404.31675
Iteration 2: log pseudolikelihood = -404.31339
Iteration 3: log pseudolikelihood = -404.3133
Iteration 4: log pseudolikelihood = -404.3133

Computing standard errors:

Mixed-effects regression Number of obs =
456

		Observations per Group		
Group Variable	No. of Groups	Minimum	Average	Maximum
Studyno	17	10	26.8	70
newPartID	341	1	1.3	2

Wald chi2(5) =
864.57
Log pseudolikelihood = -404.3133 Prob > chi2 =
0.0000

(Std. Err. adjusted for 17 clusters in
Studyno)

BaseMEP_wins Interval]	Coef.	Robust Std. Err.	z	P> z	[95% Conf.
Muscle APB	-0.2685	0.1112	-2.41	0.016	-0.4865
-0.0504					
Machine_spulse MagPro	-0.2358	0.1340	-1.76	0.078	-0.4984
0.0269					
Nexstim	0.0045	0.1347	0.03	0.973	-0.2594
0.2684					
PulseType2 Biphasic	0.2955	0.0488	6.05	0.000	0.1998
0.3912					
Neuronavigation

Supplementary file 7. Non-linear relationships for 120% RMT single pulse MEP amplitude. Post-hoc analyses demonstrated significant non-linear relationships between single pulse MEP amplitude and monophasic AMT, biphasic RMT, and biphasic AMT.

*Step 1 regressions for SICI. Examining the variance in SICI explained by each IV separately, while controlling for the age and gender of participants.

Abbreviations:

MEP change = Normalised MEP (DV)
 Age
 Gender
 BaseMEP = Baseline MEP amplitude
 Machine_ppulse = TMS machine
 Muscle = Target muscle
 Hemisphere = M1 hemisphere
 ppCSint = paired pulse conditioning stimulus intensity
 ppTSint = paired pulse test stimulus intensity
 PulseType/PulseType2/ppPulseType = Pulse waveform
 ISI = interstimulus interval
 MonoRMT = Monophasic RMT
 MonoAMT = Monophasic AMT
 BiRMT = Biphasic RMT
 BiAMT = Biphasic AMT
 Mono_cmb = Monophasic MT combined
 Bi_cmb = Biphasic MT combined
 RMTcmb = RMT combined
 AMTcmb = AMT combined
 MTcmb = MT combined
 TSint_comparison = denotes the analysis of 120% RMT data
 Studyno = Study ID
 newPartID = Participant ID

*IVs omitted because of insufficient data (did not include at least three studies within each IV level):
 Machine ppCSint PulseType ISI

```
. for var      BaseMEP Muscle Hemisphere ppTSint Neuronavigation
MonoRMT BiRMT MonoAMT BiAMT: mixed
>             MEPchange c.X Age Gender  if      Protocol ==      0 &
Dx==0 || Studyno: || newPartID:,robust
```

```
-> mixed MEPchange c.BaseMEP Age Gender if Protocol == 0 & Dx==0 ||
Studyno: || new
> PartID:,robust
```

Performing EM optimization:

```
Iteration 0:    log pseudolikelihood = -2244.3611
Iteration 1:    log pseudolikelihood = -2244.3202
Iteration 2:    log pseudolikelihood = -2244.3202
```

```
Mixed-effects regression          Number of obs    =
456
```

Group Variable	No. of Groups	Observations per Group		
		Minimum	Average	Maximum
Studyno	15	10	30.4	70
newPartID	283	1	1.6	4

19.77	Wald chi2(3)	=
Log pseudolikelihood = -2244.3202	Prob > chi2	=
0.0002		

(Std. Err. adjusted for 15 clusters in Studyno)

	MEPchange Interval]	Coef.	Robust Std. Err.	z	P> z	[95% Conf.
BaseMEP	-23.50364	8.243706	-2.85	0.004	-39.661	-
Age	.1166655	.1139816	1.02	0.306	-.1067342	
Gender	5.69354	3.657288	1.56	0.120	-1.474614	
_cons	64.0576	13.5553	4.73	0.000	37.4897	

Random-effects Parameters	Estimate	Robust Std. Err.	[95% Conf. Interval]
Study: Identity			

```

var(_cons) | 211.1977 79.42076 101.0638
441.3499
-----+-----
newPartID: Identity |
var(_cons) | 449.2635 100.4846 289.8124
696.4426
-----+-----
var(Residual) | 679.1771 155.2948 433.865
1063.191
-----
-----

```

```

-> mixed MEPchange c.Muscle Age Gender if Protocol == 0 & Dx==0 ||
Studyno: || newP
> artID:,robust

```

Performing EM optimization:

Performing gradient-based optimization:

```

Iteration 0: log pseudolikelihood = -2268.3673
Iteration 1: log pseudolikelihood = -2268.3479
Iteration 2: log pseudolikelihood = -2268.3479

```

Computing standard errors:

```

Mixed-effects regression Number of obs =
456

```

```

-----
Group Variable | No. of Observations per Group
                | Groups Minimum Average Maximum
-----+-----
Studyno        | 15 10 30.4 70
newPartID      | 283 1 1.6 4
-----

```

```

Wald chi2(3) =
4.10
Log pseudolikelihood = -2268.3479 Prob > chi2 =
0.2505

```

(Std. Err. adjusted for 15 clusters in Studyno)

```

-----
MEPchange | Robust
          | Coef. Std. Err. z P>|z| [95% Conf.
Interval]
-----+-----
-----

```

Muscle	2.545915	7.464516	0.34	0.733	-12.08427
17.1761					
Age	.2345451	.1188491	1.97	0.048	.0016051
.4674851					
Gender	3.53026	3.33707	1.06	0.290	-3.010278
10.0708					
_cons	38.16864	7.953772	4.80	0.000	22.57954
53.75775					

Random-effects Parameters	Estimate	Robust Std. Err.	[95% Conf. Interval]
Studyno: Identity			
var(_cons)	151.0635	63.43315	66.33324
344.0234			
newPartID: Identity			
var(_cons)	529.4172	146.5689	307.7112
910.8626			
var(Residual)	747.3456	197.9418	444.7055
1255.945			

```
-> mixed MEPchange c.Hemisphere Age Gender if Protocol == 0 & Dx==0 ||
Studyno: ||
> newPartID:,robust
```

Performing EM optimization:

Performing gradient-based optimization:

```
Iteration 0: log pseudolikelihood = -2267.3607
Iteration 1: log pseudolikelihood = -2267.3419
Iteration 2: log pseudolikelihood = -2267.3419
```

Computing standard errors:

Mixed-effects regression Number of obs =
456

Group Variable	No. of Groups	Observations per Group
		Minimum Average Maximum

Studyno		15	10	30.4	70
newPartID		283	1	1.6	4

Wald chi2(3) = 16.12

Log pseudolikelihood = -2267.3419 Prob > chi2 = 0.0011

(Std. Err. adjusted for 15 clusters in Studyno)

MEPchange Interval]	Coef.	Robust Std. Err.	z	P> z	[95% Conf.
Hemisphere	-5.273922	1.748358	-3.02	0.003	-8.700641 -
Age	.220899	.1200631	1.84	0.066	-.0144204
Gender	3.494108	3.30978	1.06	0.291	-2.992941
_cons	40.70547	7.366821	5.53	0.000	26.26676

Random-effects Parameters Interval]	Estimate	Robust Std. Err.	[95% Conf.
Studyno: Identity			
var(_cons)	139.5504	69.44456	52.61957
newPartID: Identity			
var(_cons)	532.0593	147.2917	309.2568
var(Residual)	742.8034	195.1739	443.8315

```

-> mixed MEPchange c.ppTSint Age Gender if Protocol == 0 & Dx==0 ||
Studyno: || new
> PartID:,robust

```


Random-effects Parameters		Robust	
		Std. Err.	[95% Conf.
Interval]			
-----+-----			

```

Studyno: Identity |
                var(_cons) | 123.4359 45.64036 59.80123
254.7844
-----+-----
----
newPartID: Identity |
                var(_cons) | 554.4496 152.2201 323.721
949.6276
-----+-----
----
                var(Residual) | 757.9096 202.9583 448.4115
1281.026
-----+-----
-----

```

```

-> mixed MEPchange c.Neuronavigation Age Gender if Protocol == 0 & Dx==0
|| Studyno
> : || newPartID:,robust

```

Performing EM optimization:

Performing gradient-based optimization:

```

Iteration 0: log pseudolikelihood = -2268.3452
Iteration 1: log pseudolikelihood = -2268.3259
Iteration 2: log pseudolikelihood = -2268.3259

```

Computing standard errors:

```

Mixed-effects regression                                Number of obs    =
456

```

```

-----+-----
Group Variable |      No. of      Observations per Group
              |      Groups      Minimum    Average    Maximum
-----+-----
      Studyno |           15           10      30.4       70
    newPartID |          283            1       1.6         4
-----+-----

```

```

Wald chi2(3) =
3.78
Log pseudolikelihood = -2268.3259    Prob > chi2 =
0.2866

```

```

                                (Std. Err. adjusted for 15 clusters in
Studyno)
-----+-----
-----
      MEPchange |      Coef.      Robust      z      P>|z|      [95% Conf.
Interval]
-----+-----
-----

```

Neuronavigation	-2.980393	7.835779	-0.38	0.704	-18.33824
12.37745					
Age	.2272705	.1231058	1.85	0.065	-.0140124
.4685535					
Gender	3.33641	3.282533	1.02	0.309	-3.097236
9.770055					
_cons	41.2268	9.153757	4.50	0.000	23.28577
59.16783					

Random-effects Parameters	Estimate	Robust Std. Err.	[95% Conf. Interval]
Studyno: Identity			
var(_cons)	150.0159	66.1064	63.24769
355.8197			
newPartID: Identity			
var(_cons)	529.4786	146.6327	307.6936
911.126			
var(Residual)	747.3772	197.8844	444.8009
1255.781			

```
-> mixed MEPchange c.MonoRMT Age Gender if Protocol == 0 & Dx==0 ||
Studyno: || new
> PartID:,robust
```

Performing EM optimization:

Performing gradient-based optimization:

```
Iteration 0: log pseudolikelihood = -2027.8725
Iteration 1: log pseudolikelihood = -2027.8662
Iteration 2: log pseudolikelihood = -2027.8662
```

Computing standard errors:

Mixed-effects regression Number of obs =
407

Group Variable	No. of Groups	Observations per Group
		Minimum Average Maximum

Studyno		13	10	31.3	70
newPartID		234	1	1.7	4

		Wald chi2(3)	=
1.17			
Log pseudolikelihood = -2027.8662		Prob > chi2	=
0.7608			

(Std. Err. adjusted for 13 clusters in Studyno)

MEPchange Interval]	Coef.	Robust Std. Err.	z	P> z	[95% Conf.
-----+-----					

MonoRMT	.1084704	.236866	0.46	0.647	-.3557785
.5727192					
Age	.1210917	.1127784	1.07	0.283	-.0999499
.3421332					
Gender	2.468356	3.36346	0.73	0.463	-4.123904
9.060616					
_cons	38.00508	16.24395	2.34	0.019	6.167529
69.84264					

Random-effects Parameters Interval]		Estimate	Robust Std. Err.	[95% Conf.
-----+-----				

Studyno: Identity				
var(_cons)		157.0305	65.08373	69.6932
353.8162				
-----+-----				

newPartID: Identity				
var(_cons)		558.6721	178.3212	298.8574
1044.359				
-----+-----				

var(Residual)		758.9709	212.5291	438.3987
1313.956				

```
-> mixed MEPchange c.BiRMT Age Gender if Protocol == 0 & Dx==0 ||
Studyno: || newPa
> rtID:,robust
```

Random-effects Parameters	Estimate	Robust Std. Err.	[95% Conf. Interval]
Study: Identity			

```

            var(_cons) |    100.9924    111.1754        11.67511
873.608
-----+-----
----
newPartID: Identity    |
            var(_cons) |    1467.58    426.827        829.9287
2595.153
-----+-----
----
            var(Residual) |    206.6208    79.56925        97.13552
439.5113
-----+-----
-----

```

```

-> mixed MEPchange c.MonoAMT Age Gender if Protocol == 0 & Dx==0 ||
Studyno: || new
> PartID:,robust

```

Performing EM optimization:

Performing gradient-based optimization:

```

Iteration 0:    log pseudolikelihood = -1294.0376
Iteration 1:    log pseudolikelihood = -1294.0375

```

Computing standard errors:

```

Mixed-effects regression                                Number of obs    =
263

```

```

-----+-----
Group Variable |      No. of      Observations per Group
               |      Groups      Minimum    Average    Maximum
-----+-----
      Studyno |           6          20      43.8      70
newPartID |          123           1       2.1       4
-----+-----

```

```

                                           Wald chi2(3)    =
2.46
Log pseudolikelihood = -1294.0375          Prob > chi2    =
0.4820

```

```

                                           (Std. Err. adjusted for 6 clusters in
Studyno)

```

```

-----+-----
MEPchange |      Coef.      Robust      z      P>|z|      [95% Conf.
Interval]
-----+-----
MonoAMT |   -.490092   .4207196   -1.16   0.244   -1.314687
.3345032

```


Studyno		6	10	17.8	33
newPartID		85	1	1.3	3

Wald chi2(3) = 5.17

Log pseudolikelihood = -541.85928 Prob > chi2 = 0.1599

(Std. Err. adjusted for 6 clusters in Studyno)

MEPchange Interval]		Coef.	Robust Std. Err.	z	P> z	[95% Conf.
BiAMT		-.6226971	.3247755	-1.92	0.055	-1.259245
Age		.4843482	.2664709	1.82	0.069	-.0379252
Gender		9.836636	7.351436	1.34	0.181	-4.571914
_cons		55.12375	12.62634	4.37	0.000	30.37658

Random-effects Parameters Interval]		Estimate	Robust Std. Err.	[95% Conf.
Studyno: Identity				
var(_cons)		1.52e-18	6.41e-15	0
newPartID: Identity				
var(_cons)		269.623	10006.22	6.94e-30
var(Residual)		1210.3	50865.76	2.04e-33

*Step 2 regressions for SICI.

*This is the starting step 2 model for SICI - all variables that obtained a p-value < 0.10 in stage 1 regressions.

```
. mixed MEPchange                Age Gender BaseMEP Hemisphere if
  (Protocol == 0)
> & Dx==0 || Studyno: || newPartID:,robust
```

Performing EM optimization:

Performing gradient-based optimization:

```
Iteration 0:    log pseudolikelihood = -2243.7127
Iteration 1:    log pseudolikelihood = -2243.6731
Iteration 2:    log pseudolikelihood = -2243.6731
```

Computing standard errors:

```
Mixed-effects regression                Number of obs    =
456
```

Group Variable		No. of	Observations per Group		
		Groups	Minimum	Average	Maximum

Studyno		15	10	30.4	70
newPartID		283	1	1.6	4

```

                                Wald chi2(4)    =
20.22
Log pseudolikelihood = -2243.6731          Prob > chi2    =
0.0005
```

(Std. Err. adjusted for 15 clusters in Studyno)

MEPchange		Coef.	Robust Std. Err.	z	P> z	[95% Conf. Interval]

Age		.1107418	.1146213	0.97	0.334	-.1139117
.3353954						
Gender		5.665736	3.632083	1.56	0.119	-1.453015
12.78449						
BaseMEP		-23.28733	8.223553	-2.83	0.005	-39.4052
7.169461						-

Hemisphere		-4.013009	1.732368	-2.32	0.021	-7.408388	-
.6176303							
_cons		65.08157	13.67916	4.76	0.000	38.27091	
91.89222							

Random-effects Parameters		Estimate	Robust Std. Err.	[95% Conf. Interval]
Study: Identity				
var(_cons)		195.8329	85.9892	82.81851
463.0669				
newPartID: Identity				
var(_cons)		452.7606	101.2762	292.0564
701.8924				
var(Residual)		676.0384	154.0466	432.5247
1056.652				

```

*Iterating

for var      Muscle ppTSint MonoRMT BiRMT MonoAMT BiAMT: mixed
MEPchange
>            c.X Age Gender BaseMEP Hemisphere if Protocol == 0 ///
>            & Dx==0 || Study: || newPartID:,robust

-> mixed MEPchange c.Muscle Age Gender BaseMEP Hemisphere if Protocol ==
0 & Dx==0
> || Study: || newPartID:,robust

Performing EM optimization:

Performing gradient-based optimization:

Iteration 0:  log pseudolikelihood = -2243.6699
Iteration 1:  log pseudolikelihood = -2243.6302
Iteration 2:  log pseudolikelihood = -2243.6301

Computing standard errors:

```

Number of obs =

Group Variable	No. of Groups	Observations per Group		
		Minimum	Average	Maximum
Studyno	15	10	30.4	70
newPartID	283	1	1.6	4

23.28	Wald chi2(5)	=
Log pseudolikelihood = -2243.6301	Prob > chi2	=
0.0003		

(Std. Err. adjusted for 15 clusters in Studyno)

	MEPchange Interval]	Coef.	Robust Std. Err.	z	P> z	[95% Conf.	
14.46703	Muscle	-2.724574	8.771385	-0.31	0.756	-19.91617	
.3386741	Age	.1088982	.1172347	0.93	0.353	-.1208777	
12.66541	Gender	5.613454	3.598004	1.56	0.119	-1.438504	
7.014239	BaseMEP	-23.35856	8.339092	-2.80	0.005	-39.70288	-
.5828523	Hemisphere	-4.010334	1.748747	-2.29	0.022	-7.437816	-
95.79614	_cons	65.97491	15.2152	4.34	0.000	36.15367	

Random-effects Parameters	Estimate	Robust Std. Err.	[95% Conf. Interval]
Studyno: Identity			
var(_cons)	193.7342	84.36848	82.51254
newPartID: Identity			


```

              var(_cons) |    452.8735    101.1909        292.269
701.7317
-----+-----
-----
              var(Residual) |    676.0504    153.9417        432.6674
1056.341
-----+-----
-----

```

```

-> mixed MEPchange c.ppTSint Age Gender BaseMEP Hemisphere if Protocol
== 0 & Dx==0
> || Studyno: || newPartID:,robust

```

Performing EM optimization:

Performing gradient-based optimization:

```

Iteration 0:    log pseudolikelihood = -2176.7583
Iteration 1:    log pseudolikelihood = -2176.7255
Iteration 2:    log pseudolikelihood = -2176.7254

```

Computing standard errors:

```

Mixed-effects regression                                Number of obs    =
442

```

```

-----+-----
Group Variable |      No. of      Observations per Group
               |      Groups      Minimum   Average   Maximum
-----+-----
      Studyno |           14           10       31.6       70
    newPartID |          269           1        1.6         4
-----+-----

```

```

                                           Wald chi2(5)    =
17.30
Log pseudolikelihood = -2176.7254        Prob > chi2    =
0.0040

```

(Std. Err. adjusted for 14 clusters in Studyno)

```

-----+-----
MEPchange |      Coef.      Robust      z      P>|z|      [95% Conf.
Interval]
-----+-----
      ppTSint | -8.031322    8.808018    -0.91    0.362    -25.29472
9.232076
      Age |   .0921402   .1233165     0.75    0.455    -.1495558
.3338361
      Gender |   5.559368   3.72985     1.49    0.136    -1.751004
12.86974

```

BaseMEP		-25.74774	9.044947	-2.85	0.004	-43.47551	-
8.019972							
Hemisphere		-4.110605	1.684179	-2.44	0.015	-7.411535	-
.8096746							
_cons		71.8413	15.80493	4.55	0.000	40.8642	
102.8184							

Random-effects Parameters		Estimate	Robust Std. Err.	[95% Conf. Interval]
StudyID: Identity				
var(_cons)		204.9906	72.52314	102.4682
410.0894				
newPartID: Identity				
var(_cons)		466.0944	103.4138	301.7277
720.0003				
var(Residual)		678.809	153.7985	435.4015
1058.291				

```
-> mixed MEPchange c.MonoRMT Age Gender BaseMEP Hemisphere if Protocol
== 0 & Dx==0
> || Studyno: || newPartID:,robust
```

Performing EM optimization:

Performing gradient-based optimization:

```
Iteration 0: log pseudolikelihood = -2000.6636
Iteration 1: log pseudolikelihood = -2000.6426
Iteration 2: log pseudolikelihood = -2000.6426
```

Computing standard errors:

Mixed-effects regression Number of obs =
407

Group Variable		No. of Groups	Observations per Group	Minimum	Average	Maximum
StudyID		13	10	31.3	70	
newPartID		234	1	1.7	4	

```

-----
Wald chi2(5) =
28.84
Log pseudolikelihood = -2000.6426 Prob > chi2 =
0.0000

```

(Std. Err. adjusted for 13 clusters in Studyno)

MEPchange Interval]	Coef.	Robust Std. Err.	z	P> z	[95% Conf.
MonoRMT	-.349762	.3247811	-1.08	0.282	-.9863212
Age	.1424259	.1185159	1.20	0.229	-.089861
Gender	4.353436	4.096342	1.06	0.288	-3.675246
BaseMEP	-29.64184	10.55421	-2.81	0.005	-50.32772
Hemisphere	-5.605659	1.897601	-2.95	0.003	-9.324888
_cons	89.87277	28.39005	3.17	0.002	34.2293

Random-effects Parameters Interval]	Estimate	Robust Std. Err.	[95% Conf.
Studyno: Identity			
var(_cons)	282.1264	104.4826	136.5243
newPartID: Identity			
var(_cons)	443.2318	111.2133	271.0516
var(Residual)	673.8053	156.6797	427.1741

```
-> mixed MEPchange c.BiRMT Age Gender BaseMEP Hemisphere if Protocol ==
0 & Dx==0 |
> | Studyno: || newPartID:,robust
```

Performing EM optimization:

Performing gradient-based optimization:

```
Iteration 0: log pseudolikelihood = -397.78284
Iteration 1: log pseudolikelihood = -397.78282 (not concave)
Iteration 2: log pseudolikelihood = -397.78282 (backed up)
```

Computing standard errors:

```
Mixed-effects regression                               Number of obs      =
78
```

		Observations per Group		
Group Variable	No. of Groups	Minimum	Average	Maximum
Studyno	3	15	26.0	39
newPartID	78	1	1.0	1

```

Wald chi2(2) =
.
Log pseudolikelihood = -397.78282      Prob > chi2 =
.
```

(Std. Err. adjusted for 3 clusters in Studyno)

	MEPchange	Coef.	Robust Std. Err.	z	P> z	[95% Conf. Interval]
BiRMT		.2470882	.3100845	0.80	0.426	-.3606662
Age		.1444077	.1741899	0.83	0.407	-.1969982
Gender		15.61687	4.818079	3.24	0.001	6.173611
BaseMEP		-18.17106	9.119013	-1.99	0.046	-36.044
Hemisphere		-2.415782	2.125187	-1.14	0.256	-6.581073
_cons		47.3614	36.95123	1.28	0.200	-25.06168

Random-effects Parameters		Estimate	Robust Std. Err.	[95% Conf. Interval]
-----+-----				

Studyno: Identity				
var(_cons)		91.40858	148.2462	3.806362
2195.148				
-----+-----				

newPartID: Identity				
var(_cons)		1315.182	315.9672	821.274
2106.122				
-----+-----				

var(Residual)		204.8791	117.1965	66.77083
628.6495				


```
-> mixed MEPchange c.MonoAMT Age Gender BaseMEP Hemisphere if Protocol
== 0 & Dx==0
> || Studyno: || newPartID:,robust
```

Performing EM optimization:

Performing gradient-based optimization:

```
Iteration 0: log pseudolikelihood = -1270.5645
Iteration 1: log pseudolikelihood = -1270.5636
Iteration 2: log pseudolikelihood = -1270.5636
```

Computing standard errors:

```
Mixed-effects regression                                Number of obs    =
263
```


Group Variable		No. of Groups	Observations per Group		
			Minimum	Average	Maximum
-----+-----					
Studyno		6	20	43.8	70
newPartID		123	1	2.1	4

```
Wald chi2(5) =
429.73
Log pseudolikelihood = -1270.5636    Prob > chi2 =
0.0000
```

(Std. Err. adjusted for 6 clusters in Studyno)

MEPchange Interval]	Coef.	Robust Std. Err.	z	P> z	[95% Conf.
MonoAMT	-.9197529	.7011269	-1.31	0.190	-2.293936
Age	.192005	.1362812	1.41	0.159	-.0751012
Gender	7.086305	7.54868	0.94	0.348	-7.708835
BaseMEP	-37.90118	18.88504	-2.01	0.045	-74.91517
Hemisphere	-5.014506	1.640793	-3.06	0.002	-8.230402
_cons	113.7038	45.2527	2.51	0.012	25.01012

Random-effects Parameters Interval]	Estimate	Robust Std. Err.	[95% Conf.
Studyno: Identity			
var(_cons)	294.2187	150.6621	107.8428
newPartID: Identity			
var(_cons)	333.4856	126.739	158.3374
var(Residual)	617.1795	188.3234	339.3748

```
-> mixed MEPchange c.BiAMT Age Gender BaseMEP Hemisphere if Protocol ==
0 & Dx==0 |
> | Studyno: || newPartID:,robust
```

Performing EM optimization:

Performing gradient-based optimization:

```
Iteration 0: log pseudolikelihood = -537.39432
Iteration 1: log pseudolikelihood = -536.72862
```

```
Iteration 2: log pseudolikelihood = -536.72642
Iteration 3: log pseudolikelihood = -536.72642
```

Computing standard errors:

```
Mixed-effects regression      Number of obs      =
107
```

Group Variable	No. of Groups	Observations per Group		
		Minimum	Average	Maximum
Studyno	6	10	17.8	33
newPartID	85	1	1.3	3

1445.07	Wald chi2(5)	=
Log pseudolikelihood = -536.72642	Prob > chi2	=
0.0000		

(Std. Err. adjusted for 6 clusters in Studyno)

	MEPchange Interval]	Coef.	Robust Std. Err.	z	P> z	[95% Conf.	
BiAMT		-.8642859	.2980498	-2.90	0.004	-1.448453	-
Age		.3718181	.3588239	1.04	0.300	-.3314639	
Gender		8.742461	7.38026	1.18	0.236	-5.722582	
BaseMEP		-26.34473	6.81125	-3.87	0.000	-39.69453	-
Hemisphere		-23.37366	12.19491	-1.92	0.055	-47.27525	
_cons		95.81923	22.85276	4.19	0.000	51.02865	

Random-effects Parameters	Estimate	Robust Std. Err.	[95% Conf. Interval]
-----+-----			

Study: Identity			

```

                var(_cons) |    108.7552    283.307    .6592848
17940.2
-----+-----
----
newPartID: Identity      |
                var(_cons) |    144.245    103.915    35.14713
591.9862
-----+-----
----
                var(Residual) |    1129.344    163.3617    850.5473
1499.527
-----
-----

```

. *This is the final model

```

. mixed MEPchange Age i.Gender BaseMEP i.Hemisphere if (Protocol == 0) &
Dx==0 || Studyno: || newPartID:,robust

```

Performing EM optimization:

Performing gradient-based optimization:

```

Iteration 0:    log pseudolikelihood = -2243.7127
Iteration 1:    log pseudolikelihood = -2243.6731
Iteration 2:    log pseudolikelihood = -2243.6731

```

Computing standard errors:

```

Mixed-effects regression                                Number of obs    =
456

```

```

-----
Group Variable |      No. of      Observations per Group
               |      Groups      Minimum    Average    Maximum
-----+-----
      Studyno |           15           10      30.4       70
    newPartID |          283            1       1.6        4
-----

```

```

                                                Wald chi2(4)    =
20.22
Log pseudolikelihood = -2243.6731          Prob > chi2    =
0.0005

```

(Std. Err. adjusted for 15 clusters in Studyno)

MEPchange Interval]	Coef.	Robust Std. Err.	z	P> z	[95% Conf.	

Age	.1107418	.1146213	0.97	0.334	-.1139117	
.3353954						
Gender						
Female	5.665736	3.632083	1.56	0.119	-1.453015	
12.78449						
BaseMEP	-23.28733	8.223553	-2.83	0.005	-39.4052	-
7.169461						
Hemisphere						
R	-4.013009	1.732368	-2.32	0.021	-7.408388	-
.6176303						
_cons	65.08157	13.67916	4.76	0.000	38.27091	
91.89222						

*Step 1 regressions for ICF. Examining the variance in ICF explained by each IV separately, while controlling for the age and gender of participants.

*IVs omitted because not enough studies: Machine_ppulse ppCSint ppPulseType ISI

```
.
.
. for var      BaseMEP Muscle Hemisphere  ppTSint Neuronavigation
MonoRMT  MonoAMT : mixed MEPchange      ///
>          c.X Age Gender  if      Protocol ==      1 &      Dx==0
|| Studyno: || newPartID:,robust noretale
```

```
-> mixed MEPchange c.BaseMEP Age Gender if Protocol == 1 & Dx==0 ||
Studyno: || new
> PartID:,robust noretale
```

Performing EM optimization:

Performing gradient-based optimization:

```
Iteration 0: log pseudolikelihood = -2294.6159
Iteration 1: log pseudolikelihood = -2294.5463
Iteration 2: log pseudolikelihood = -2294.5463
```

Computing standard errors:

```
Mixed-effects regression                               Number of obs    =
393
```

		Observations per Group		
Group Variable	No. of Groups	Minimum	Average	Maximum
Studyno	14	10	28.1	70
newPartID	256	1	1.5	3

```
Wald chi2(3) =
6.41
Log pseudolikelihood = -2294.5463      Prob > chi2 =
0.0931
```

(Std. Err. adjusted for 14 clusters in Studyno)

	MEPchange	Coef.	Robust Std. Err.	z	P> z	[95% Conf. Interval]
BaseMEP		-71.83875	28.90853	-2.49	0.013	-128.4984 - 15.17908
Age		-.0014924	.4610102	-0.00	0.997	-.9050559 .9020711
Gender		-4.805832	8.276008	-0.58	0.561	-21.02651 11.41485
_cons		227.2174	38.17283	5.95	0.000	152.4 302.0347

```
-> mixed MEPchange c.Muscle Age Gender if Protocol == 1 & Dx==0 ||
Studyno: || newP
```

```
> artID:,robust noretale
```

```
Performing EM optimization:
```

```
Performing gradient-based optimization:
```

```
Iteration 0:    log pseudolikelihood = -2327.4999
```

```
Iteration 1:    log pseudolikelihood = -2327.4307
```

```
Iteration 2:    log pseudolikelihood = -2327.4307
```

```
Computing standard errors:
```

```
Mixed-effects regression                                Number of obs    =  
393
```

```
-----  
Group Variable |      No. of      Observations per Group  
               |      Groups      Minimum    Average    Maximum  
-----+-----  
      Studyno |          14          10      28.1      70  
    newPartID |         256           1       1.5       3  
-----
```

```
Wald chi2(3) =  
10.30  
Log pseudolikelihood = -2327.4307      Prob > chi2 =  
0.0162
```

```
(Std. Err. adjusted for 14 clusters in  
Studyno)
```

```
-----  
-----  
      MEPchange |      Coef.      Robust      z      P>|z|      [95% Conf.  
Interval]-----  
-----  
      Muscle |    1.376667    28.52563     0.05    0.962    -54.53254  
57.28588  
      Age |     .5851793     .3642238     1.61    0.108     -.1286862  
1.299045  
      Gender |   -12.14622     8.690536    -1.40    0.162    -29.17936  
4.886914  
      _cons |    146.1589    17.15735     8.52    0.000     112.5312  
179.7867  
-----  
-----
```

```
-> mixed MEPchange c.Hemisphere Age Gender if Protocol == 1 & Dx==0 ||  
Studyno: ||  
> newPartID:,robust noretale
```

```
Performing EM optimization:
```

```
Iteration 0: log pseudolikelihood = -2327.5024
Iteration 1: log pseudolikelihood = -2327.4321
Iteration 2: log pseudolikelihood = -2327.4321
```

Mixed-effects regression
393

5.98	Wald chi2(3)	=
Log pseudolikelihood = -2327.4321	Prob > chi2	=
0.1127		

MEPchange Interval]	Coef.	Robust Std. Err.	z	P> z	[95% Conf.
-----+-----					
Hemisphere 23.77765	-.3405924	12.30545	-0.03	0.978	-24.45883
Age 1.317194	.5841057	.3740313	1.56	0.118	-.1489822
Gender 5.383583	-12.20163	8.972212	-1.36	0.174	-29.78684
_cons 183.0417	146.7153	18.53423	7.92	0.000	110.3889

```
Iteration 0: log pseudolikelihood = -2245.4248
Iteration 1: log pseudolikelihood = -2245.3709
```

Computing standard errors:

```
Mixed-effects regression      Number of obs      =
393
```

Group Variable	No. of Groups	Observations per Group		
		Minimum	Average	Maximum
StudyID	14	10	28.1	70
newPartID	256	1	1.5	3

15.27	Wald chi2(3)	=
Log pseudolikelihood = -2326.6911	Prob > chi2	=
0.0016		

(Std. Err. adjusted for 14 clusters in Studyno)

	MEPchange Interval]	Coef.	Robust Std. Err.	z	P> z	[95% Conf.
Neuronavigation	12.24266	-25.58969	19.30257	-1.33	0.185	-63.42203
Age	1.277491	.4761308	.4088646	1.16	0.244	-.3252292
Gender	3.33353	-13.51574	8.596723	-1.57	0.116	-30.36501
_cons	208.0742	167.4227	20.74099	8.07	0.000	126.7711

```
-> mixed MEPchange c.MonoRMT Age Gender if Protocol == 1 & Dx==0 ||
Studyno: || new
> PartID:, robust noretale
```

Performing EM optimization:

Performing gradient-based optimization:

```
Iteration 0:    log pseudolikelihood = -2014.7811
Iteration 1:    log pseudolikelihood = -2014.7426
Iteration 2:    log pseudolikelihood = -2014.7426
```

Computing standard errors:

```
Mixed-effects regression      Number of obs      =
344
```

Group Variable		No. of Groups	Observations per Group		
			Minimum	Average	Maximum
Studyno		12	10	28.7	70
newPartID		207	1	1.7	3

Wald chi2(3) = 57.35
 Log pseudolikelihood = -2014.7426 Prob > chi2 = 0.0000

(Std. Err. adjusted for 12 clusters in Studyno)

MEPchange Interval]		Coef.	Robust Std. Err.	z	P> z	[95% Conf.	
MonoRMT		2.963653	.6799572	4.36	0.000	1.630962	
4.296345							
Age		.5288319	.5960899	0.89	0.375	-.6394829	
1.697147							
Gender		-16.31275	7.716366	-2.11	0.035	-31.43655	-
1.188948							
_cons		-1.168291	22.69199	-0.05	0.959	-45.64378	
43.3072							

```
-> mixed MEPchange c.MonoAMT Age Gender if Protocol == 1 & Dx==0 ||
Studyno: || new
> PartID:,robust noretale
```

Performing EM optimization:

Performing gradient-based optimization:

```
Iteration 0: log pseudolikelihood = -1008.8916
Iteration 1: log pseudolikelihood = -1008.7753
Iteration 2: log pseudolikelihood = -1008.7717
Iteration 3: log pseudolikelihood = -1008.7717
```

Computing standard errors:

Mixed-effects regression Number of obs = 168

Group Variable		No. of Groups	Observations per Group		
			Minimum	Average	Maximum

```

Studyno | 4 20 42.0 70
newPartID | 84 2 2.0 2
-----

Wald chi2(3) =
241480.47
Log pseudolikelihood = -1008.7717 Prob > chi2 =
0.0000

(Std. Err. adjusted for 4 clusters in
Studyno)
-----
-----
MEPchange | Coef. Robust z P>|z| [95% Conf.
Interval]
-----+-----
MonoAMT | 2.951797 .5354576 5.51 0.000 1.90232
4.001275
Age | .6873275 .61033 1.13 0.260 -.5088973
1.883552
Gender | -26.80652 6.322692 -4.24 0.000 -39.19877 -
14.41427
_cons | 42.1005 11.17352 3.77 0.000 20.20081
64.00019
-----
-----

. .
. * Doing this separately here bc have to take out the newPartID
. mixed MEPchange c.BiAMT c.Age i.Gender if (Protocol ==
1) & Dx==0
> || Studyno: ,robust

Performing EM optimization:

Performing gradient-based optimization:

Iteration 0: log pseudolikelihood = -442.40142
Iteration 1: log pseudolikelihood = -442.3021
Iteration 2: log pseudolikelihood = -442.3021

Computing standard errors:

Mixed-effects regression Number of obs =
75
Group variable: Studyno Number of groups =
5

Obs per group:
min =
10

```



```

15.0
25
8.07
Log pseudolikelihood = -442.3021
0.0446
Wald chi2(3) =
Prob > chi2 =

```

(Std. Err. adjusted for 5 clusters in Studyno)

		Coef.	Robust Std. Err.	z	P> z	[95% Conf. Interval]
MEPchange						
BiAMT		3.663754	2.684226	1.36	0.172	-1.597232
Age		-.0134243	1.033459	-0.01	0.990	-2.038967
Gender						
Female		-18.24444	35.65254	-0.51	0.609	-88.12214
_cons		44.28037	74.17977	0.60	0.551	-101.1093

Random-effects Parameters		Estimate	Robust Std. Err.	[95% Conf. Interval]
Studyno: Identity				
var(_cons)		8.70e-15	2.29e-12	3.6e-239
var(Residual)		7760.838	2052.043	4622.133

```

. mixed MEPchange c.BiRMT c.Age i.Gender if (Protocol ==
1) & Dx==0
> || Studyno: ,robust

```

Performing EM optimization:

```
Iteration 0:    log pseudolikelihood = -470.62869
Iteration 1:    log pseudolikelihood = -470.62852
Iteration 2:    log pseudolikelihood = -470.62852
```

```
Mixed-effects regression      Number of obs    =
79                             Number of groups   =
Group variable: Studyno
3
```

```
Obs per group:
      min =
      avg =
      max =
```

```
Wald chi2(2)      =
Prob > chi2       =
```

	MEPchange Interval]	Coef.	Robust Std. Err.	z	P> z	[95% Conf.
BiRMT	3.357921	2.52194	.4265283	5.91	0.000	1.68596
Age	1.124852	-.0098836	.5789575	-0.02	0.986	-1.144619
Gender Female	43.99739	-5.543591	25.27648	-0.22	0.826	-55.08457
_cons	126.1698	57.58981	34.99041	1.65	0.100	-10.99014

Random-effects Parameters	Estimate	Robust Std. Err.	[95% Conf. Interval]
---------------------------	----------	------------------	----------------------

```

-----+-----
----
Studyno: Identity |
                var(_cons) | 247.7845 234.8425 38.66621
1587.876
-----+-----
----
                var(Residual) | 8567.765 1500.114 6079.001
12075.44
-----
-----

```

*Step 2 regressions for ICF.

*This is the starting step 2 model for ICF - all variables that obtained a p-value < 0.10 in stage 1 regressions.

```

.
. mixed MEPchange c.BaseMEP i.Gender if (Protocol == 1) &
Dx==0 || St
> udynd: || newPartID:,robust

```

Performing EM optimization:

Performing gradient-based optimization:

```

Iteration 0: log pseudolikelihood = -2294.6156
Iteration 1: log pseudolikelihood = -2294.5463
Iteration 2: log pseudolikelihood = -2294.5463

```

Computing standard errors:

```

Mixed-effects regression                               Number of obs    =
393

```

```

-----+-----
Group Variable |      No. of      Observations per Group
              |      Groups      Minimum    Average    Maximum
-----+-----
      Studyno |           14          10      28.1       70
    newPartID |          256           1       1.5        3
-----

```

```

6.39
Log pseudolikelihood = -2294.5463
0.0410

Wald chi2(2) =
Prob > chi2 =

```

(Std. Err. adjusted for 14 clusters in Studyno)

MEPchange Interval]	Coef.	Robust Std. Err.	z	P> z	[95% Conf.	
-----+-----						
BaseMEP 15.11728	-71.8332	28.93723	-2.48	0.013	-128.5491	-
Gender Female 11.24729	-4.802347	8.188739	-0.59	0.558	-20.85198	
_cons 294.3182	227.1622	34.26389	6.63	0.000	160.0062	

Random-effects Parameters					Robust	
Interval]					Std. Err.	[95% Conf.
-----+-----					-----	
Studyno: Identity						
var(_cons)					859.9823	387.4785
2079.753					355.6045	
-----+-----					-----	
newPartID: Identity						
var(_cons)					3415.069	947.5544
5882.693					1982.544	
-----+-----					-----	
var(Residual)					3837.627	1319.951
7530.665					1955.655	
-----					-----	
-----					-----	

*Iterating

```
.
. for var      Age  ppTSint Muscle Hemisphere: mixed MEPchange  ///
>              c.X  BaseMEP Gender if Protocol ==      1 &      Dx==0
|| Studyno: || newPartID:,robust noretale
```

```
-> mixed MEPchange c.Age BaseMEP Gender if Protocol == 1 & Dx==0 ||
Studyno: || new
> PartID:,robust norettable
```

Performing EM optimization:

Performing gradient-based optimization:

```
Iteration 0: log pseudolikelihood = -2294.6159
Iteration 1: log pseudolikelihood = -2294.5463
Iteration 2: log pseudolikelihood = -2294.5463
```

Computing standard errors:

```
Mixed-effects regression                               Number of obs      =
393
```

		Observations per Group		
Group Variable	No. of Groups	Minimum	Average	Maximum
Studyno	14	10	28.1	70
newPartID	256	1	1.5	3

```
Wald chi2(3) =
6.41
Log pseudolikelihood = -2294.5463      Prob > chi2 =
0.0931
```

(Std. Err. adjusted for 14 clusters in Studyno)

	MEPchange	Coef.	Robust Std. Err.	z	P> z	[95% Conf. Interval]
	Age	-.0014924	.4610102	-0.00	0.997	-.9050559
	BaseMEP	-71.83875	28.90852	-2.49	0.013	-128.4984
	Gender	-4.805832	8.276008	-0.58	0.561	-21.02651
	_cons	227.2174	38.17283	5.95	0.000	152.4

```
-> mixed MEPchange c.ppTSint BaseMEP Gender if Protocol == 1 & Dx==0 ||
Studyno: ||
> newPartID:,robust norettable
```

Performing gradient-based optimization:

```

Iteration 0:    log pseudolikelihood = -2294.5445
Iteration 1:    log pseudolikelihood = -2294.4752
Iteration 2:    log pseudolikelihood = -2294.4752

```

Computing standard errors:

```

Mixed-effects regression              Number of obs      =
393

```

Group Variable		No. of Groups	Observations per Group		
			Minimum	Average	Maximum
Studyno		14	10	28.1	70
newPartID		256	1	1.5	3

```

                                Wald chi2(3)      =
11.74
Log pseudolikelihood = -2294.4752              Prob > chi2      =
0.0083

```

(Std. Err. adjusted for 14 clusters in Studyno)

MEPchange Interval]		Coef.	Robust Std. Err.	z	P> z	[95% Conf.	
Muscle		-7.852723	23.7672	-0.33	0.741	-54.43558	
38.73013							
BaseMEP		-71.99152	28.69792	-2.51	0.012	-128.2384	-
15.74464							
Gender		-5.000234	8.025518	-0.62	0.533	-20.72996	
10.72949							
_cons		229.7268	30.53341	7.52	0.000	169.8824	
289.5712							

```

-> mixed MEPchange c.Hemisphere BaseMEP Gender if Protocol == 1 & Dx==0
|| Studyno:
> || newPartID:,robust norettable

```

Performing EM optimization:

Performing gradient-based optimization:

```

Iteration 0:    log pseudolikelihood = -2294.5567
Iteration 1:    log pseudolikelihood = -2294.4875
Iteration 2:    log pseudolikelihood = -2294.4875

```

```
Mixed-effects regression      Number of obs      =
393
```

Group	Variable	No. of Groups	Observations per Group		
			Minimum	Average	Maximum
	StudyNo	14	10	28.1	70
	newPartID	256	1	1.5	3

6.40	Wald	chi2(3)	=
Log pseudolikelihood = -2294.4875	Prob	> chi2	=
0.0938			

(Std. Err. adjusted for 14 clusters in Studyno)

	MEPchange Interval]	Coef.	Robust Std. Err.	z	P> z	[95% Conf.
Hemisphere	25.6566	3.108259	11.50447	0.27	0.787	-19.44008
BaseMEP	15.17237	-72.00222	28.99535	-2.48	0.013	-128.8321
Gender	11.19566	-4.817496	8.170127	-0.59	0.555	-20.83065
_cons	293.4671	226.4826	34.17639	6.63	0.000	159.4981

```

. *ppTSint becomes p <0.10. Iterate again.
.
. for var      Age      Muscle Hemisphere: mixed      MEPchange
. ///
. >
. >      c.X  BaseMEP Gender ppTSint if  Protocol ==
1 &      Dx
> ==0 || Studyno: || newPartID:,robust noretale

-> mixed MEPchange c.Age BaseMEP Gender ppTSint if Protocol == 1 & Dx==0
|| Studyno

```



```
> : || newPartID:,robust noretale
```

```
Performing EM optimization:
```

```
Performing gradient-based optimization:
```

```
Iteration 0: log pseudolikelihood = -2209.5674
```

```
Iteration 1: log pseudolikelihood = -2209.5174
```

```
Iteration 2: log pseudolikelihood = -2209.5174
```

```
Computing standard errors:
```

```
Mixed-effects regression Number of obs = 379
```

		Observations per Group		
Group Variable	No. of Groups	Minimum	Average	Maximum
Studyno	13	10	29.2	70
newPartID	242	1	1.6	3

```
Wald chi2(4) = 8.01
Log pseudolikelihood = -2209.5174 Prob > chi2 = 0.0914
```

```
(Std. Err. adjusted for 13 clusters in Studyno)
```

	MEPchange	Coef.	Robust Std. Err.	z	P> z	[95% Conf. Interval]
	Age	-.1797049	.4539419	-0.40	0.692	-1.069415
	BaseMEP	-81.56248	32.36383	-2.52	0.012	-144.9944
	Gender	-4.877201	8.339107	-0.58	0.559	-21.22155
	ppTSint	-34.70664	16.96814	-2.05	0.041	-67.96358
	_cons	252.5945	41.95015	6.02	0.000	170.3737

```
-> mixed MEPchange c.Muscle BaseMEP Gender ppTSint if Protocol == 1 & Dx==0 || Stud
> yno: || newPartID:,robust noretale
```

Performing EM optimization:

```
.
. *None more become sig. Thus:
.
.
. *This is the final model.
```

```
. mixed MEPchange                c.BaseMEP i.ppTSint i.Gender if
(Protocol == 1) &
> Dx==0 || Studyno: || newPartID:,robust
```

Performing EM optimization:

Performing gradient-based optimization:

```
Iteration 0:    log pseudolikelihood = -2209.6579
Iteration 1:    log pseudolikelihood = -2209.607
Iteration 2:    log pseudolikelihood = -2209.607
```

Computing standard errors:

```
Mixed-effects regression                Number of obs    =
379
```

		Observations per Group		
Group Variable	No. of Groups	Minimum	Average	Maximum
Studyno	13	10	29.2	70
newPartID	242	1	1.6	3

```
Wald chi2(3) =
7.46
Log pseudolikelihood = -2209.607    Prob > chi2 =
0.0586
```

(Std. Err. adjusted for 13 clusters in Studyno)

	MEPchange	Coef.	Robust Std. Err.	z	P> z	[95% Conf. Interval]
BaseMEP		-80.82001	32.65889	-2.47	0.013	-144.8303 - 16.80976
ppTSint						
0.5-1.5MV		-33.31513	16.43076	-2.03	0.043	-65.51884 - 1.111425
Gender						
Female		-4.461701	8.240202	-0.54	0.588	-20.6122 11.6888
_cons		245.4519	38.38918	6.39	0.000	170.2105 320.6933

Supplementary file 9. Non-linear relationships for ICF. Post-hoc analyses demonstrated significant non-linear relationships between ICF normalised MEP and monophasic AMT and biphasic RMT.

*Step 1 regressions for Monophasic RMT. Examining the variance in Monophasic RMT explained by each IV separately, while controlling for the age and gender of participants.

Abbreviations:

MEP change = Normalised MEP (DV)
 Age
 Gender
 BaseMEP = Baseline MEP amplitude
 Machine_MonoRMT = TMS machine
 Muscle = Target muscle
 Hemisphere = M1 hemisphere
 ppCSint = paired pulse conditioning stimulus intensity
 ppTSint = paired pulse test stimulus intensity
 PulseType/PulseType2 = Pulse waveform
 ISI = interstimulus interval
 MonoRMT = Monophasic RMT
 MonoAMT = Monophasic AMT
 BiRMT = Biphasic RMT
 BiAMT = Biphasic AMT
 Mono_cmb = Monophasic MT combined
 Bi_cmb = Biphasic MT combined
 RMTcmb = RMT combined
 AMTcmb = AMT combined
 MTcmb = MT combined
 TSint_comparison = denotes the analysis of 120% RMT data
 Studyno = Study ID
 newPartID = Participant ID

*IVs omitted because of insufficient data (did not include at least three studies within each IV level):
 Machine_MonoRMT

```
. for var Muscle Hemisphere Neuronavigation: mixed MonoRMT c.X Age
Gender || Stud
> yno: || newPartID:,robust noretable

-> mixed MonoRMT c.Muscle Age Gender || Studyno: || newPartID:,robust
noretable
```

Performing EM optimization:

Performing gradient-based optimization:

```
Iteration 0: log pseudolikelihood = -2158.0198
Iteration 1: log pseudolikelihood = -2157.8946
Iteration 2: log pseudolikelihood = -2157.8946
```

Mixed-effects regression
603

Number of obs =

Group Variable	No. of Groups	Observations per Group		
		Minimum	Average	Maximum
StudyNo	26	9	23.2	70
newPartID	516	1	1.2	2

12.91	Wald chi2(3)	=
Log pseudolikelihood = -2157.8946	Prob > chi2	=
0.0048		

(Std. Err. adjusted for 26 clusters in Studyno)

		Robust			
	Coef.	Std. Err.	z	P> z	[95% Conf.
Interval]					
-----+-----					

Muscle	-.6826993	4.429782	-0.15	0.878	-9.364912
7.999513					
Age	.0884303	.0252986	3.50	0.000	.0388461
.1380146					
Gender	.8208809	.8529145	0.96	0.336	-.8508007
2.492563					
_cons	43.6129	2.011456	21.68	0.000	39.67052
47.55528					
-----+-----					

```
-> mixed MonoRMT c.Hemisphere Age Gender || Studyno: ||
newPartID:, robust noretale
```

Performing EM optimization:

Performing gradient-based optimization:

```
Iteration 0:    log pseudolikelihood = -2152.894
Iteration 1:    log pseudolikelihood = -2152.824
Iteration 2:    log pseudolikelihood = -2152.824
```

Computing standard errors:

```
Mixed-effects regression                                Number of obs    =
603
```

Group Variable		No. of Groups	Observations per Group		
			Minimum	Average	Maximum
Studyno		26	9	23.2	70
newPartID		516	1	1.2	2

15.87
 Log pseudolikelihood = -2152.824
 0.0012

Wald chi2(3) =
 Prob > chi2 =

(Std. Err. adjusted for 26 clusters in Studyno)

MonoRMT Interval]		Coef.	Robust Std. Err.	z	P> z	[95% Conf.	
Hemisphere		-2.167551	.8941427	-2.42	0.015	-3.920038	-
.4150636							
Age		.0877955	.0250402	3.51	0.000	.0387177	
.1368733							
Gender		.8295988	.8551474	0.97	0.332	-.8464594	
2.505657							
_cons		43.8205	2.032247	21.56	0.000	39.83737	
47.80363							

```

-> mixed MonoRMT c.Neuronavigation Age Gender || Studyno: ||
newPartID:,robust nore
> table

```

Performing EM optimization:

Performing gradient-based optimization:

Iteration 0: log pseudolikelihood = -2157.1211
 Iteration 1: log pseudolikelihood = -2156.9948
 Iteration 2: log pseudolikelihood = -2156.9948

Computing standard errors:

Mixed-effects regression
 603

Number of obs =

Group Variable		No. of Groups	Observations per Group		
			Minimum	Average	Maximum

Studyno		26	9	23.2	70	
newPartID		516	1	1.2	2	

				Wald chi2(3)	=	
13.06						
Log pseudolikelihood = -2156.9948					Prob > chi2	=
0.0045						
(Std. Err. adjusted for 26 clusters in Studyno)						

		Robust				
MonoRMT		Coef.	Std. Err.	z	P> z	[95% Conf.
Interval]						

Neuronavigation		-5.554583	5.132827	-1.08	0.279	-15.61474
4.505573						
Age		.0876297	.0243342	3.60	0.000	.0399355
.1353238						
Gender		.8071669	.851408	0.95	0.343	-.8615621
2.475896						
_cons		47.73867	4.603463	10.37	0.000	38.71605
56.7613						

*Step 2 regressions for Monophasic RMT.

*This is the starting step 2 model for Monophasic RMT - all variables that obtained a p-value < 0.10 in stage 1 regressions.

```
. for var Gender Neuronavigation Muscle : mixed MonoRMT c.X Age
Hemisphere || Stu
> dyno: || newPartID:,robust
```

```
-> mixed MonoRMT c.Gender Age Hemisphere || Studyno: ||
newPartID:,robust
```

Performing EM optimization:

Performing gradient-based optimization:

```
Iteration 0: log pseudolikelihood = -2152.894
Iteration 1: log pseudolikelihood = -2152.824
Iteration 2: log pseudolikelihood = -2152.824
```

```
Mixed-effects regression          Number of obs    =
603
```

15.87	Wald	chi2(3)	=
Log pseudolikelihood = -2152.824	Prob	> chi2	=
0.0012			

		Coef.	Robust Std. Err.	z	P> z	[95% Conf. Interval]
Gender		.8295988	.8551474	0.97	0.332	-.8464594
Age		.0877955	.0250402	3.51	0.000	.0387177
Hemisphere		-2.167551	.8941426	-2.42	0.015	-3.920038
_cons		43.8205	2.032247	21.56	0.000	39.83737

Random-effects Parameters		Estimate	Robust Std. Err.	[95% Conf. Interval]
-----+-----				

Studyno: Identity				
var(_cons)		77.38606	17.71462	49.4097
121.203				
-----+-----				

newPartID: Identity				
var(_cons)		53.48898	11.72573	34.80695
82.19827				

```

-----+-----
-----
var(Residual) | 19.07504 7.344056 8.969026
40.56817
-----
-----

```

```

-> mixed MonoRMT c.Neuronavigation Age Hemisphere || Studyno: ||
newPartID:, robust

```

Performing EM optimization:

Performing gradient-based optimization:

```

Iteration 0: log pseudolikelihood = -2175.4234
Iteration 1: log pseudolikelihood = -2175.3661
Iteration 2: log pseudolikelihood = -2175.3661

```

Computing standard errors:

```

Mixed-effects regression                               Number of obs    =
605

```

```

-----+-----
Group Variable | No. of      Observations per Group
                | Groups      Minimum   Average   Maximum
-----+-----
Studyno        | 26          9        23.3     70
newPartID      | 518         1        1.2      2
-----+-----

```

```

Wald chi2(3) =
13.89
Log pseudolikelihood = -2175.3661      Prob > chi2 =
0.0031

```

(Std. Err. adjusted for 26 clusters in Studyno)

```

-----+-----
MonoRMT | Coef.      Robust      z      P>|z|      [95% Conf.
Interval]
-----+-----
Neuronavigation | -4.980313  5.229877   -0.95   0.341    -15.23068
5.270059
Age             | .082273    .023767    3.46    0.001     .0356905
.1288556
Hemisphere     | -2.141702  .9041601   -2.37    0.018    -3.913823 -
.3695807
_cons          | 48.37788   4.655561   10.39    0.000     39.25315
57.50261

```


Random-effects Parameters		Estimate	Robust Std. Err.	[95% Conf. Interval]
-----+-----				
Studyno: Identity				
var(_cons)		75.8943	19.76945	45.54938
126.4549				
-----+-----				
newPartID: Identity				
var(_cons)		57.86444	14.15748	35.82213
93.46996				
-----+-----				
var(Residual)		19.23085	7.543812	8.914396
41.48632				


```
-> mixed MonoRMT c.Muscle Age Hemisphere || Studyno: ||
newPartID:,robust
```

Performing EM optimization:

Performing gradient-based optimization:

```
Iteration 0: log pseudolikelihood = -2176.1127
Iteration 1: log pseudolikelihood = -2176.056
Iteration 2: log pseudolikelihood = -2176.056
```

Computing standard errors:

```
Mixed-effects regression          Number of obs    =
605
```

Group Variable		No. of Groups	Observations per Group		
			Minimum	Average	Maximum
-----+-----					
Studyno		26	9	23.3	70
newPartID		518	1	1.2	2

```
15.48                                Wald chi2(3)      =
Log pseudolikelihood = -2176.056      Prob > chi2      =
0.0015
```

(Std. Err. adjusted for 26 clusters in Studyno)

		Coef.	Robust Std. Err.	z	P> z	[95% Conf. Interval]
Muscle		-.3326077	4.704501	-0.07	0.944	-9.553259
Age		.083011	.0246176	3.37	0.001	.0347614
Hemisphere		-2.172428	.8909239	-2.44	0.015	-3.918607
_cons		44.61384	2.055979	21.70	0.000	40.5842

Random-effects Parameters		Estimate	Robust Std. Err.	[95% Conf. Interval]
-----+-----				

Studyno: Identity				
var(_cons)		80.05252	17.88173	51.66993
124.0258				
-----+-----				

newPartID: Identity				
var(_cons)		57.87658	14.14898	35.84357
93.45327				
-----+-----				

var(Residual)		19.22974	7.514983	8.93972
41.36405				


```
.
. *Final model
. mixed MonoRMT Age i.Hemisphere || Studyno: || newPartID:,robust
```

Performing EM optimization:

Performing gradient-based optimization:

Random-effects Parameters		Estimate	Robust Std. Err.	[95% Conf. Interval]
-----+-----				

Studyno: Identity				
var(_cons)		80.05865	17.80914	51.76754
123.8109				
-----+-----				

```

newPartID: Identity |
                var(_cons) | 57.87702 14.14931 35.84357
93.4547
-----+-----
-----
                var(Residual) | 19.22993 7.515469 8.93943
41.36619
-----
-----

```

*Step 1 regressions for Monophasic AMT. Examining the variance in Monophasic AMT explained by each IV separately, while controlling for the age and gender of participants.

*IVs omitted because of insufficient data (did not include at least three studies within each IV level):

Machine_MonoAMT Neuronavigation Muscle

```

. for var Hemisphere: mixed MonoAMT c.X Age Gender || Studyno: ||
newPartID:,robus
> t

```

```

-> mixed MonoAMT c.Hemisphere Age Gender || Studyno: ||
newPartID:,robust

```

Performing EM optimization:

Performing gradient-based optimization:

```

Iteration 0:   log pseudolikelihood = -643.86716
Iteration 1:   log pseudolikelihood = -643.86501
Iteration 2:   log pseudolikelihood = -643.86501

```

Computing standard errors:

```

Mixed-effects regression                                Number of obs    =
185

```

```

-----
Group Variable |      No. of      Observations per Group
               |      Groups      Minimum      Average      Maximum
-----+-----
      Studyno |           6          11          30.8          70
    newPartID |          123           1           1.5           2
-----

```

16.56	Wald	chi2(3)	=
Log pseudolikelihood = -643.86501	Prob	> chi2	=
0.0009			

(Std. Err. adjusted for 6 clusters in Studyno)

	MonoAMT	Coef.	Robust Std. Err.	z	P> z	[95% Conf. Interval]
Hemisphere	-2.044264	1.406067	-1.45	0.146	-4.800104	.7115761
Age	.0881807	.0461307	1.91	0.056	-.0022337	.1785952
Gender	.1843289	1.909437	0.10	0.923	-3.558099	3.926756
_cons	40.02314	4.788737	8.36	0.000	30.63739	49.40889

*Step 2 regressions for Monophasic AMT.

```
. for var Hemisphere Gender: mixed MonoAMT c.X Age || Studyno: ||
newPartID:, robust
```

```
-> mixed MonoAMT c.Hemisphere Age || Studyno: || newPartID:, robust
```

Performing EM optimization:

Performing gradient-based optimization:

```
Iteration 0:    log pseudolikelihood = -643.87551
Iteration 1:    log pseudolikelihood = -643.87335
Iteration 2:    log pseudolikelihood = -643.87335
```

Computing standard errors:

```
Mixed-effects regression                                Number of obs    =
185
```

Group Variable	No. of Groups	Observations per Group		
		Minimum	Average	Maximum

Studyno		6	11	30.8	70
newPartID		123	1	1.5	2

Wald chi2(2) = 3.75

Log pseudolikelihood = -643.87335 Prob > chi2 = 0.1536

(Std. Err. adjusted for 6 clusters in Studyno)

		Coef.	Robust Std. Err.	z	P> z	[95% Conf. Interval]
Hemisphere		-2.043988	1.408105	-1.45	0.147	-4.803822
Age		.0876773	.0500413	1.75	0.080	-.0104019
_cons		40.12775	4.312104	9.31	0.000	31.67618

Random-effects Parameters		Estimate	Robust Std. Err.	[95% Conf. Interval]
Studyno: Identity				
var(_cons)		76.12289	49.24335	21.42294
newPartID: Identity				
var(_cons)		38.35551	4.93975	29.79908
var(Residual)		26.01736	11.17431	11.21185

```
-> mixed MonoAMT c.Gender Age || Studyno: || newPartID:,robust
```

Performing EM optimization:

Performing gradient-based optimization:

```
newPartID: Identity
```

```

                    var(_cons) |    36.97731    6.037561    26.85056
50.9234
-----+-----
-----
                    var(Residual) |    28.04595    13.90795    10.6111
74.12759
-----+-----
-----

```

```

.
. *None became p<0.10

```

```

. *Final model

```

```

. mixed MonoAMT Age || Studyno: || newPartID:,robust

```

```

Performing EM optimization:

```

```

Performing gradient-based optimization:

```

```

Iteration 0:    log pseudolikelihood = -646.29055
Iteration 1:    log pseudolikelihood = -646.28708
Iteration 2:    log pseudolikelihood = -646.28708

```

```

Computing standard errors:

```

```

Mixed-effects regression                                Number of obs    =
185

```

Group Variable		No. of Groups	Observations per Group		
			Minimum	Average	Maximum
Studyno		6	11	30.8	70
newPartID		123	1	1.5	2

```

                                                    Wald chi2(1)    =
3.08
Log pseudolikelihood = -646.28708                Prob > chi2      =
0.0792

```

```

                                                    (Std. Err. adjusted for 6 clusters in
Studyno)

```

```

-----+-----
-----

```

MonoAMT		Coef.	Robust Std. Err.	z	P> z	[95% Conf. Interval]

```

-----+-----
-----

```

Age		.0890822	.0507524	1.76	0.079	-.0103907
.1885551						
_cons		39.22307	3.944292	9.94	0.000	31.4924
46.95374						

Random-effects Parameters		Estimate	Robust Std. Err.	[95% Conf. Interval]
-----+-----				
Studyno: Identity				
var(_cons)		76.27532	47.52051	22.4944
258.6388				
-----+-----				
newPartID: Identity				
var(_cons)		36.94212	6.136794	26.67601
51.15907				
-----+-----				
var(Residual)		28.06474	13.90492	10.62737
74.11332				

*Step 1 regressions for Biphasic RMT. Examining the variance in Monophasic RMT explained by each IV separately, while controlling for the age and gender of participants.

*IVs omitted because of insufficient data (did not include at least three studies within each IV level):
Hemisphere Muscle

```
. mixed BiRMT i. Machine_BiRMT c.Age i.Gender || Studyno: ||
newPartID:, robust
```

Performing EM optimization:

Performing gradient-based optimization:

```
Iteration 0: log pseudolikelihood = -969.62614
Iteration 1: log pseudolikelihood = -968.34263
Iteration 2: log pseudolikelihood = -968.33654
```

Random-effects Parameters	Estimate	Robust Std. Err.	[95% Conf. Interval]
Study: Identity			

```

var(_cons) | 12.53973 6.461749 4.567327
34.42818
-----+-----
newPartID: Identity |
var(_cons) | 33.78715 4.451385 26.09802
43.74169
-----+-----
var(Residual) | 40.24614 1.19274 37.97501
42.65309
-----

```

. contrast Machine

Contrasts of marginal linear predictions

Margins : asbalanced

```

-----+-----
| df chi2 P>chi2
-----+-----
BiRMT |
Machine_BiRMT | 2 26.97 0.0000
-----+-----

```

```

. mixed BiRMT c.Age i.Gender i.Neuronavigation || Studyno: ||
newPartID:,robust

```

Performing EM optimization:

Performing gradient-based optimization:

```

Iteration 0: log pseudolikelihood = -972.37348
Iteration 1: log pseudolikelihood = -971.11579
Iteration 2: log pseudolikelihood = -971.10897
Iteration 3: log pseudolikelihood = -971.10895

```

Computing standard errors:

```

Mixed-effects regression Number of obs =
269

```

```

-----+-----
| No. of Observations per Group
Group Variable | Groups Minimum Average Maximum
-----+-----
Studyno | 12 10 22.4 40
newPartID | 258 1 1.0 2
-----+-----

```

```

Wald chi2(3) =
8.58

```

Log pseudolikelihood = -971.10895 Prob > chi2 =
0.0355

(Std. Err. adjusted for 12 clusters in
Studyno)

	BiRMT	Coef.	Robust Std. Err.	z	P> z	[95% Conf. Interval]
	Age	.1398177	.0658581	2.12	0.034	.0107382
.2688973						
	Gender Female	2.668809	1.40876	1.89	0.058	-.0923103
5.429929						
	Neuronavigation No	6.090487	2.782046	2.19	0.029	.6377772
11.5432						
	_cons	40.70272	3.260771	12.48	0.000	34.31172
47.09371						

	Random-effects Parameters	Estimate	Robust Std. Err.	[95% Conf. Interval]
	Studyno: Identity			
	var(_cons)	21.995	8.800499	10.0403
48.18383				
	newPartID: Identity			
	var(_cons)	33.69647	4.428642	26.04432
43.5969				
	var(Residual)	40.35693	1.177169	38.11444
42.73137				

*Machine age gender Neuronav are p<0.10, so are all in the final model
and no need for Step 2.

```
*Final model
mixed BiRMT c.Age i.Gender i.Neuronavigation i.Machine_BiRMT ||
Studyno: || newPartID:,robust
```

Performing EM optimization:

Performing gradient-based optimization:

```
Iteration 0: log pseudolikelihood = -969.32567
Iteration 1: log pseudolikelihood = -968.0294
Iteration 2: log pseudolikelihood = -968.02312
Iteration 3: log pseudolikelihood = -968.02311
```

Computing standard errors:

```
Mixed-effects regression                               Number of obs      =
269
```

		Observations per Group		
Group Variable	No. of Groups	Minimum	Average	Maximum
Studyno	12	10	22.4	40
newPartID	258	1	1.0	2

```

Wald chi2(5) =
49.48
Log pseudolikelihood = -968.02311      Prob > chi2 =
0.0000
```

```
(Std. Err. adjusted for 12 clusters in Studyno)
```

	BiRMT	Coef.	Robust Std. Err.	z	P> z	[95% Conf. Interval]
Age		.1436453	.0645893	2.22	0.026	.0170525 .2702381
Gender						
Female		2.619628	1.494448	1.75	0.080	-.3094365 5.548692
Neuronavigation						
No		2.266546	2.162414	1.05	0.295	-1.971707 6.5048
Machine_BiRMT						

Nexstim		-.1489169	4.535256	-0.03	0.974	-9.037856
8.740022						
MagstimRapid		7.517018	3.305649	2.27	0.023	1.038064
13.99597						
_cons		38.43295	2.867652	13.40	0.000	32.81245
44.05344						

*Step 1 regressions for Biphasic AMT. Examining the variance in Biphasic AMT explained by each IV separately, while controlling for the age and gender of participants.

*IVs omitted because of insufficient data (did not include at least three studies within each IV level):
Hemisphere Muscle

```
.
. *Step 1
. mixed BiAMT i.Machine_BiAMT c.Age i.Gender || Studyno:,robust
```

Performing EM optimization:

Performing gradient-based optimization:

```
Iteration 0: log pseudolikelihood = -964.26939
Iteration 1: log pseudolikelihood = -964.26939
```

Computing standard errors:

Mixed-effects regression	Number of obs	=
277		
Group variable: Studyno	Number of groups	=
14		
	Obs per group:	
	min	=
10		
	avg	=
19.8		
	max	=
38		
	Wald chi2(3)	=
25.58		

Log pseudolikelihood = -964.26939 Prob > chi2 =
0.0000

(Std. Err. adjusted for 14 clusters in Studyno)

		Coef.	Robust Std. Err.	z	P> z	[95% Conf. Interval]
Machine_BiAMT						
MagstimRapid		11.47653	2.860075	4.01	0.000	5.870888
17.08218						
Age		.0102896	.0291013	0.35	0.724	-.0467479
.067327						
Gender						
Female		1.212589	.8673283	1.40	0.162	-.4873428
2.912522						
_cons		36.43792	2.406274	15.14	0.000	31.7217
41.15413						

Random-effects Parameters		Estimate	Robust Std. Err.	[95% Conf. Interval]
Studyno: Identity				
var(_cons)		25.89262	9.841236	12.29284
54.53806				
var(Residual)		55.19693	7.153314	42.81564
71.15861				

. mixed BiAMT i.Neuronavigation c.Age i.Gender || Studyno:,robust

Performing EM optimization:

Performing gradient-based optimization:

Iteration 0: log pseudolikelihood = -967.26622
Iteration 1: log pseudolikelihood = -967.26622

Computing standard errors:

Mixed-effects regression
 277
 Group variable: Studyno
 14

Number of obs =

Number of groups =

Obs per group:

min =

10

avg =

19.8

max =

38

Wald chi2(3) =

11.74

Log pseudolikelihood = -967.26622

Prob > chi2 =

0.0083

(Std. Err. adjusted for 14 clusters in

Studyno)

	BiAMT	Coef.	Robust Std. Err.	z	P> z	[95% Conf. Interval]
-----+-----						

Neuronavigation	No	8.215334	3.889127	2.11	0.035	.592785
15.83788						
	Age	.0058006	.0295783	0.20	0.845	-.0521718
.063773						
	Gender					
	Female	1.207429	.8690058	1.39	0.165	-.4957914
2.910649						
	_cons	36.88192	3.047584	12.10	0.000	30.90877
42.85508						

Random-effects Parameters		Estimate	Robust Std. Err.	[95% Conf. Interval]
-----+-----				
Studyno: Identity				
	var(_cons)	41.76348	11.79172	24.01397
72.63222				
-----+-----				

```

var(Residual) | 55.18199 7.155373 42.79797
71.14944
-----
-----

```

*Step 2 regressions for Biphasic AMT.

*This is the starting step 2 model for Biphasic AMT - all variables that obtained a p-value < 0.10 in stage 1 regressions.

```

. *iterating
. mixed BiAMT i.Machine_BiAMT i.Neuronavigation c.Age || Studyno:, robust

```

Performing EM optimization:

Performing gradient-based optimization:

```

Iteration 0: log pseudolikelihood = -964.48931
Iteration 1: log pseudolikelihood = -964.48931

```

Computing standard errors:

```

Mixed-effects regression                               Number of obs      =
277                                                    Number of groups   =
Group variable: Studyno                               Number of groups   =
14                                                    Obs per group:
                                                    min =
10                                                    avg =
19.8                                                    max =
38
                                                    Wald chi2(3)       =
20.17                                                    Prob > chi2        =
Log pseudolikelihood = -964.48931
0.0002

```

(Std. Err. adjusted for 14 clusters in Studyno)

```

-----
-----
          |
          |          Robust
          |          Coef.   Std. Err.      z    P>|z|    [95% Conf.
Interval]
-----+-----
Machine_BiAMT |

```

MagstimRapid		9.884012	2.375768	4.16	0.000	5.227592
14.54043						
Neuronavigation						
No		3.56965	3.31251	1.08	0.281	-2.922751
10.06205						
Age		.004566	.0277584	0.16	0.869	-.0498394
.0589714						
_cons		35.91625	3.373647	10.65	0.000	29.30402
42.52848						

Random-effects Parameters		Estimate	Robust Std. Err.	[95% Conf. Interval]
Study: Identity				
var(_cons)		24.44731	9.193287	11.69879
51.08826				
var(Residual)		55.43709	7.315971	42.80242
71.80134				

```
. mixed BiAMT i.Machine_BiAMT i.Neuronavigation i.Gender ||
Study: , robust
```

Performing EM optimization:

Performing gradient-based optimization:

```
Iteration 0: log pseudolikelihood = -963.7224
Iteration 1: log pseudolikelihood = -963.7224
```

Computing standard errors:

Mixed-effects regression	Number of obs	=
277		
Group variable: Study	Number of groups	=
14		
	Obs per group:	
	min	=
10		
	avg	=
19.8		
	max	=
38		

30.30 Wald chi2(3) =
 Log pseudolikelihood = -963.7224 Prob > chi2 =
 0.0000

(Std. Err. adjusted for 14 clusters in Studyno)

	BiAMT	Coef.	Robust Std. Err.	z	P> z	[95% Conf. Interval]
Machine_BiAMT						
MagstimRapid		9.841807	2.475184	3.98	0.000	4.990535
14.69308						
Neuronavigation						
No		3.597779	3.33627	1.08	0.281	-2.941191
10.13675						
Gender						
Female		1.189822	.8518392	1.40	0.162	-.4797519
2.859396						
_cons		35.51965	3.12057	11.38	0.000	29.40344
41.63585						

Random-effects Parameters		Estimate	Robust Std. Err.	[95% Conf. Interval]
Studyno: Identity				
var(_cons)		24.31386	8.664651	12.09244
48.88705				
var(Residual)		55.13081	7.159201	42.74238
71.1099				

*Final model

Study						
Study	Model	Coef.	Robust Std. Err.	z	P> z	[95% Conf. Interval]
Machine_BiAMT						
MagstimRapid		9.907476	2.41017	4.11	0.000	5.183629
14.63132						
Neuronavigation						
No		3.604187	3.317984	1.09	0.277	-2.898942
10.10732						
_cons		36.07587	3.342481	10.79	0.000	29.52472
42.62701						