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Large-scale analysis of interindividual variability in single and paired-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.

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Abbreviations and nomenclature

TMS: Transcranial magnetic stimulation

MEP: motor evoked potential

pp: paired-pulse

SICI: short-interval intracortical inhibition

ICF: intracortical facilitation

IV: independent variable

DV: dependent variable

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

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

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

ISI: interstimulus interval

RMT: resting motor threshold

AMT: active motor threshold

Pulse waveform: monophasic or biphasic pulse waveforms

Highlights

- 687 healthy participant's TMS data was pooled across 35 studies
- Significant relationships between age and resting motor threshold
- Significant relationships between baseline MEP amplitude and 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 (Iscan 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 (Iscan 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

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

2. Methods

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

2.1 Article identification strategy

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

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2.2 Variables of interest and data used for present analyses

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

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

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predicting single pulse MEP amplitude, and pp normalised MEP. Other IVs investigated were: age, gender, target muscle, M1 hemisphere, conditioning stimulus (CS) intensity, test stimulus (TS) intensity, pulse waveform (i.e. monophasic or biphasic), inter-stimulus interval (ISI), baseline MEP amplitude, the use/absence of neuronavigation, and TMS machine (Corp et al. 2020). Studies used either a Magstim 200^2 TMS machine, a Magstim Rapid TMS machine, a Nexstim NBS TMS, or a MagPro TMS machine. We could not determine the specific MagPro model used in all studies, therefore these machines were grouped based on the brand. We controlled for pulse waveform in regression analyses to ensure that the effect of TMS machine was not due the differential use of monophasic or biphasic pulses. For TS intensity, studies used either 120% of RMT or a machine stimulus output evoking an MEP amplitude of 0.5 mV, 0.5 - 1 mV, 1 mV MEP, or 0.5 - 1.5 mV. To increase statistical power, we grouped these intensities into machine stimulus output evoking an MEP amplitude of 0.5 - 1.5 mV. Three studies did not use a TS intensity evoking 0.5 - 1.5 mV or 120% of RMT (Corp et al. 2015, Puri et al. 2016, Singh et al. 2016), and were therefore excluded from this comparison. We were not able to obtain baseline MEP amplitude data from one study (Munneke et al. 2013), thus these values were imputed as per the method of Corp et al. (2020). For studies that tested the effect of external interventions on TMS outcomes (e.g. exercise Singh et al. (2016)), only control/baseline data were analysed. We collected handedness data for 21 studies, yet there were only nine left handers represented across five studies, therefore this IV could not be analysed statistically.

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

All statistical analyses were conducted using Stata 13.0 (StataCorp, USA). First, data were checked for outliers using histograms and descriptive statistics. A number of outliers were detected in single and pp MEP data, therefore values falling outside of the 2nd and 98th percentiles were winsorized (Field 2009, Tukey 1962). Histograms prior to outlier winsorization are provided in Supplementary file 3.

2.3 Variability analyses

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

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

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

2.4 Main regression analysis

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

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

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

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

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

2.5 Post-hoc analyses

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

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2.6 Additional analyses

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

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

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machine intensity to evoke a 1mV amplitude, we still thought it valuable to quantify these (possible) differences.

Lastly, we analysed correlations between the four types of MT. Because different studies use different methods for obtaining MTs and therefore vary in their average MT values, we normalised MTs to z-values within study, then performed Pearson's correlation analyses on these z-values across the sample. This gives similar results to correlating MT values within studies, then taking the average of these correlations (Supplementary file 5).

3. Results

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

< Table 1 here. Study characteristics >

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.

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< 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 >

Figure1

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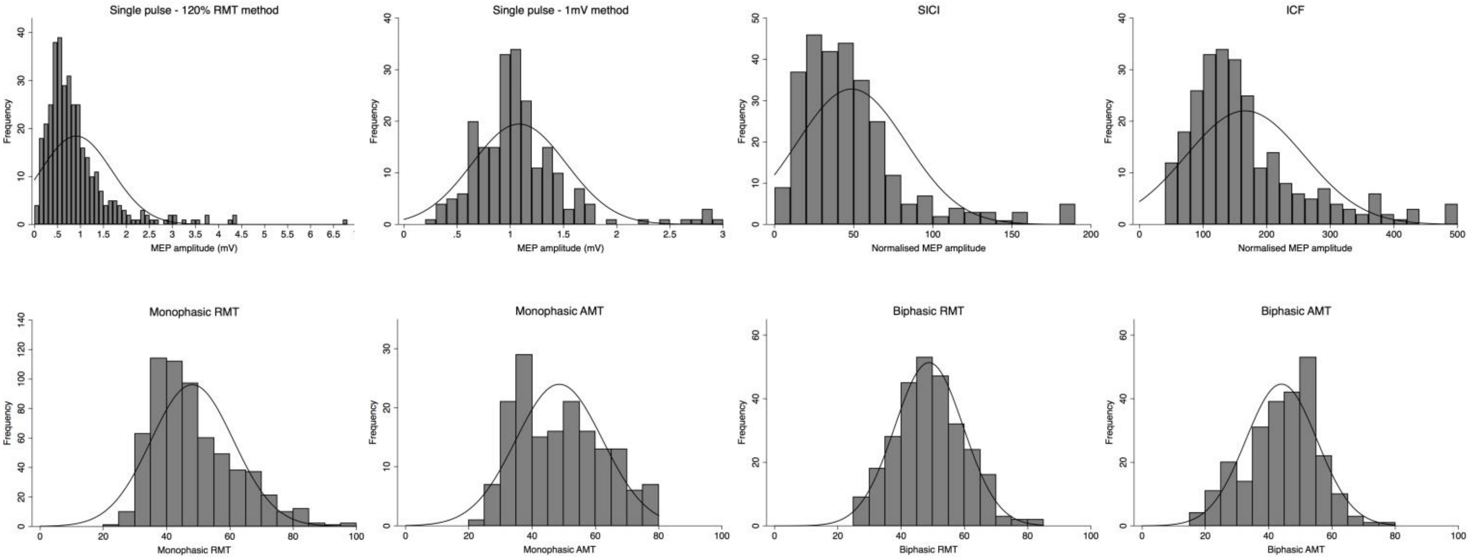

Figure 1. Distribution plots. Histograms of single pulse, paired pulse, and motor threshold data. 120% RMT data was used for single-pulse main regression analysis. These data were then compared to single pulse data using the 1 mV method in the 'additional analyses'. In addition to differences in amplitude 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.

Table2

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

	ICC within studies	*SD within studies*	*SD between studies*	*CV within studies (%)*	*CV between studies (%)*
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

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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 200[2], 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**			**ß**	**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**

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

< Figure 2 here. Single pulse marginal means >

3.3 Single pulse TMS post-hoc analyses

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

< Figure 3 here. Single pulse scatterplot >

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

3.4 SICI regression analysis

Figure2

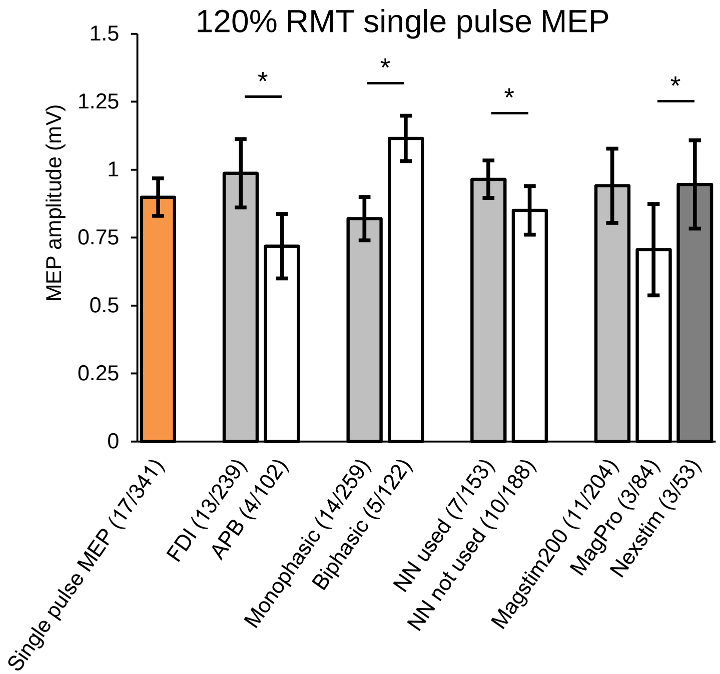

Figure 2. Marginal means for 120% RMT single pulse MEPs. Marginal means provide an estimate of normalised MEP, adjusted for all variables in the final model. Orange bar shows the overall marginal mean for single pulse MEPs. Grey and white bars show marginal means for each level of the IVs muscle, pulse 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

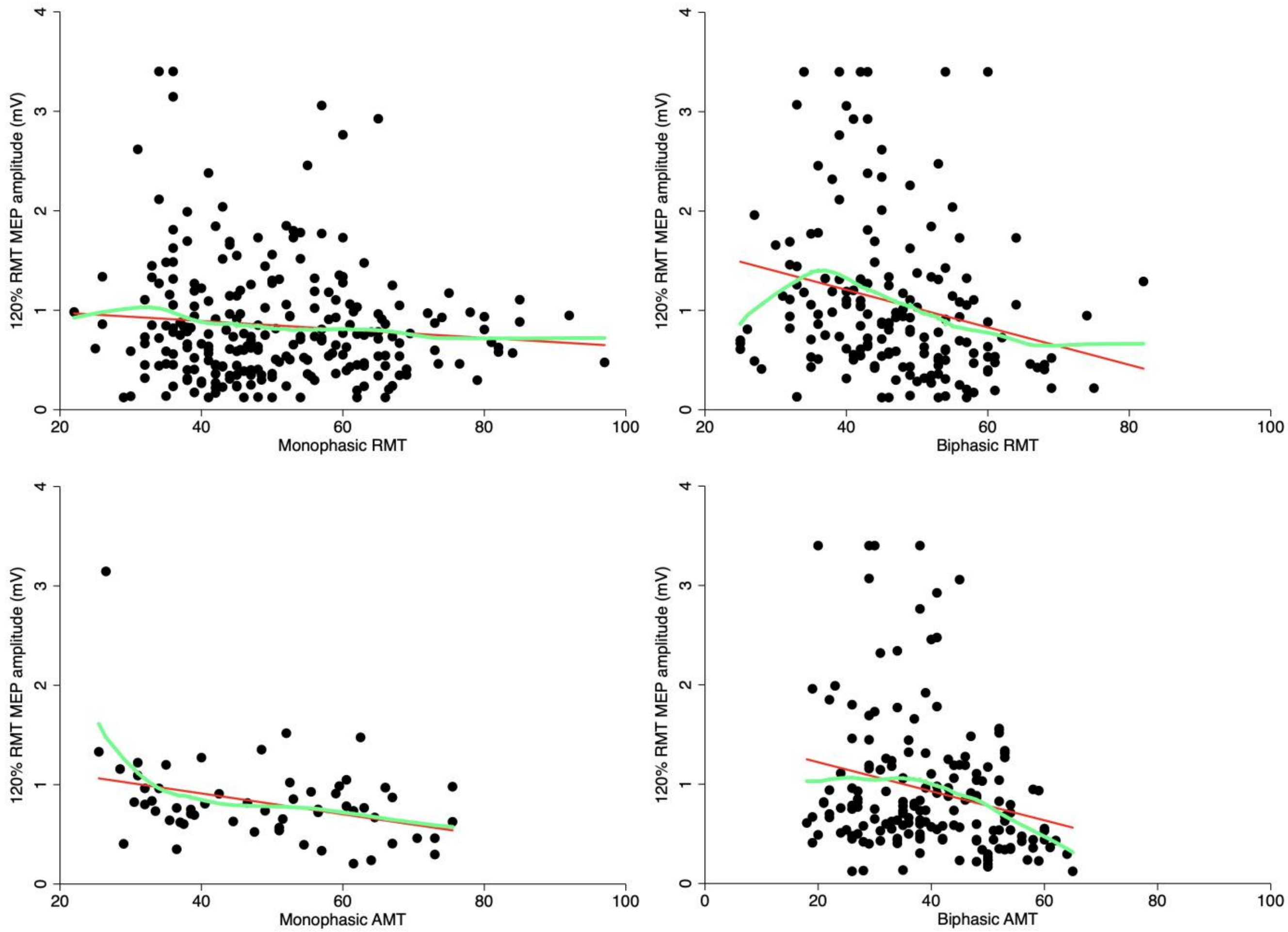

Figure 3. Relationships between 120% RMT single pulse MEPs and MTs. All relationships were significant in post-hoc regression analyses. Note that these scatterplots show raw bivariate relationships to give an indication of relationships only, see post-hoc section for results controlled for other IVs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

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

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

< Insert Table 4 here. SICI regression >

< Insert Figure 4 here. SICI scatterplots >

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).

< Figure 5. SICI marginal means >

3.5 SICI post-hoc analyses

Table4

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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**			**ß**	**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**

Figure4

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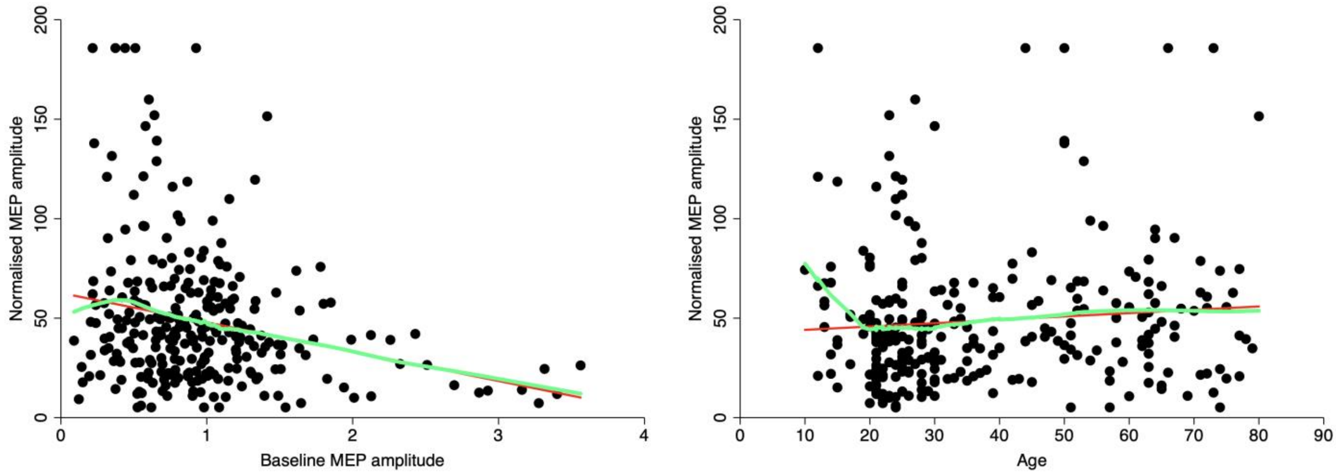

Figure 4. Relationships between continuous IVs and SICI. Baseline MEP amplitude was a significant predictor of SICI. Bivariate scatterplots give an indication of results only; see Table 4 for results controlled for other IVs. Green lines fit a smoothed 'lowess' curve through data. The appearance of a 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

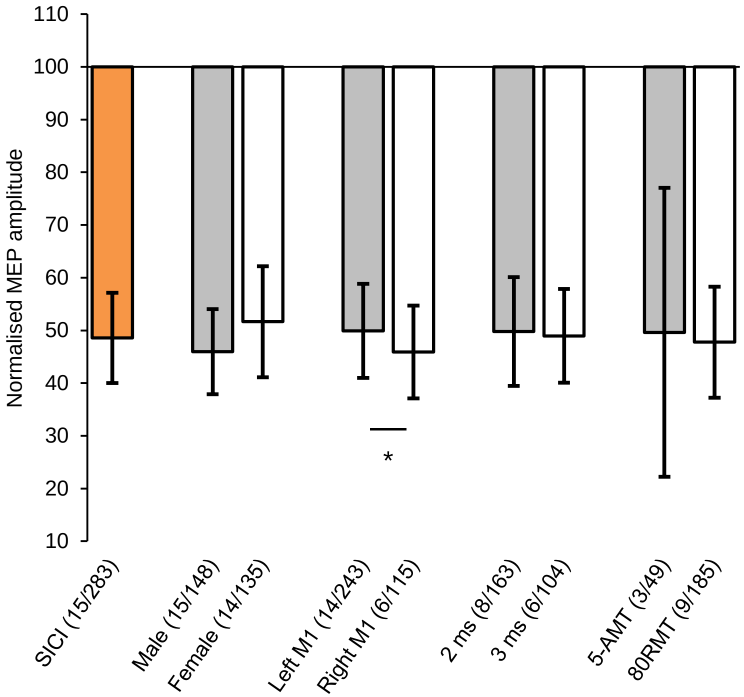

Figure 5. Marginal means for SICI normalised MEP. Orange bar shows the overall marginal mean for SICI. Grey and white bars show marginal means for each level of the IVs gender, M1 hemisphere, interstimulus interval and CS intensity (5% of machine intensity below AMT and 80% of RMT), which were included 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).

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

Biphasic AMT was a significant predictor of SICI normalised MEP when controlling for all IVs in the final model: 6 studies, 85 participants; B = -0.86; SE = 0.30; ß = -0.24; $p = 0.004$. Biphasic RMT was not a significant predictor of normalised MEP: 3 studies, 78 participants; B = 0.24; SE = 0.31; ß = 0.07; $p = 0.426$.

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

3.6 ICF regression analysis

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

< Insert Table 5 here. ICF regression

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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			ß	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; ß = 0.29; $p < 0.001$ (studies = 11; N = 193). Biphasic RMT, B = 1.46; SE =

Figure6

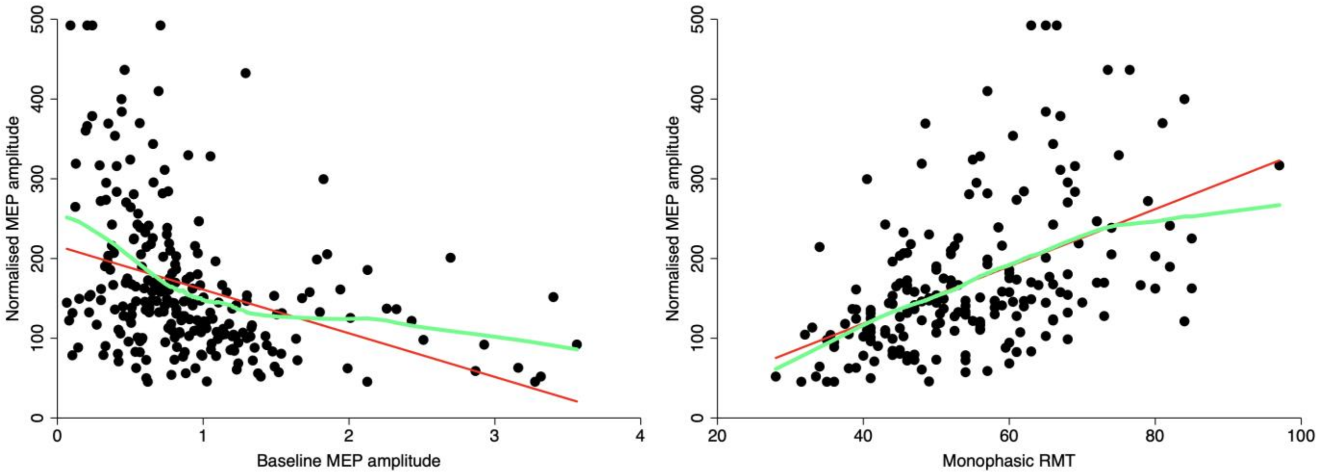

Figure 6. Relationships between continuous IVs and ICF. Baseline MEP and monophasic RMT were significant predictors of ICF MEP change. Bivariate scatterplots give an indication of results only; see Table 5 for results controlled for other IVs. Green lines fit a smoothed ‘lowess’ curve through data.

Figure7

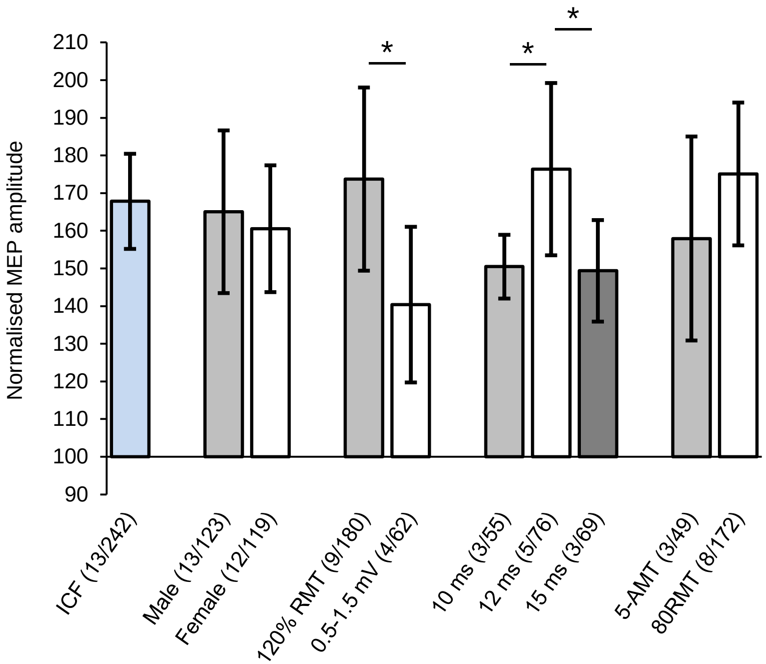

Figure 7. Marginal means for ICF normalised MEP. Blue bar shows the overall marginal mean for ICF. Grey and white bars show marginal means for each level of the IVs gender, TS intensity, ISI, and CS intensity (5% machine intensity below AMT vs. 80% of RMT) which were included in the final model or post-hoc 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).

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0.30; ß = 0.16; $p < 0.001$ (studies = 3; N = 79). Monophasic AMT, B = 1.33; SE = 0.48; ß = 0.19; $p < 0.005$ (studies = 3; N = 84).

Non-linear analyses demonstrated a significant quadratic and cubic relationship between ICF and baseline MEP amplitude (p = 0.025 and p = 0.044, respectively) (Figure 6). There was also a significant quadratic relationship between ICF and monophasic AMT (p = 0.001), and a significant cubic relationship between ICF and biphasic RMT (scatterplots in Supplementary file 9).

3.8 MT regression analyses

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

< Insert Table 6 here. MT regressions >

< Insert Figure 8 here. Scatterplots MT and age >

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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			ß	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			ß	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 200[2], 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			ß	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			ß	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

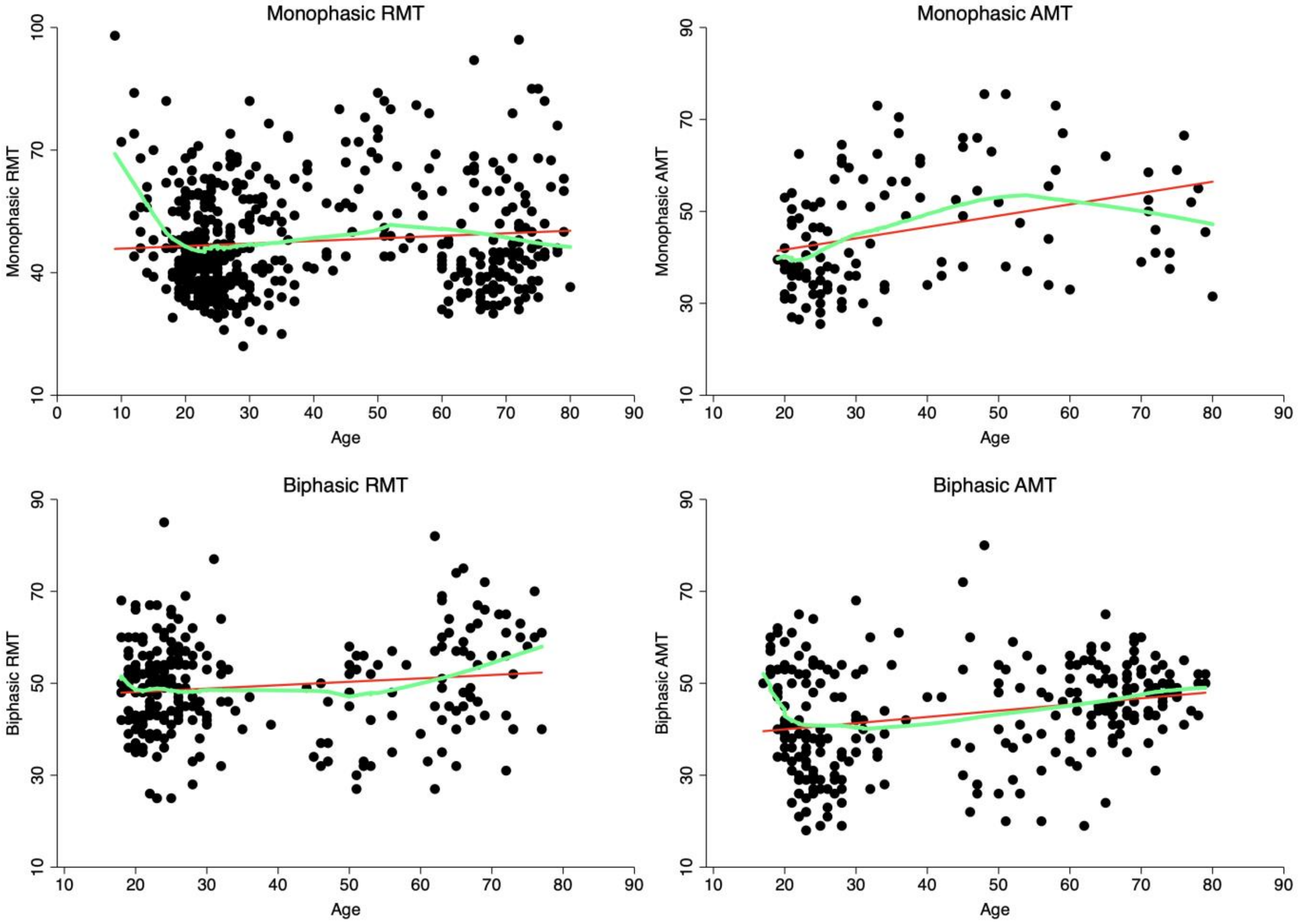

Figure 8. Relationship between age and motor threshold. Monophasic RMT and biphasic RMT showed a significant positive linear relationship with age (Table 6), indicating reduced corticospinal excitability in older adults. There were also significant non-linear relationships between age and monophasic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

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

< Insert Figure 9 here. MT marginal means >

3.9 MT post-hoc analyses

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

3.10 Additional analyses

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

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

Figure9

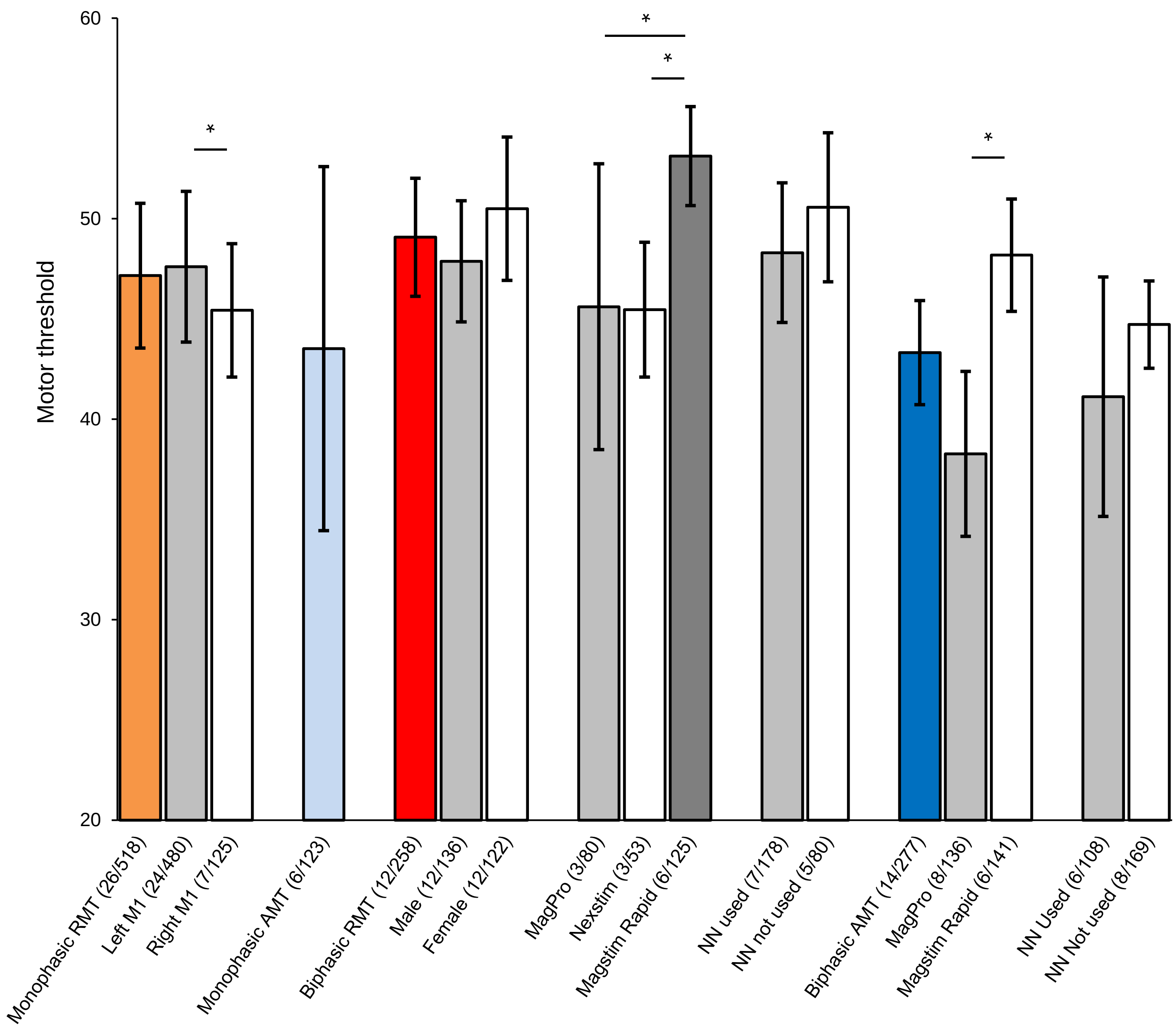

Figure 9. Marginal means for motor threshold. Coloured bars show overall marginal means for monophasic RMT, monophasic AMT, biphasic RMT, and biphasic AMT. Grey and white bars show marginal means of levels of the IVs M1 hemisphere, gender, TMS machine, and neuronavigation (NN), which were included in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

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

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

4. Discussion

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

4.1 Baseline MEP amplitude

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

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

4.2 Motor threshold predicts single and paired-pulse TMS response

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

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

4.3 Effect of age on corticospinal excitability

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

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

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

4.4 Effect of hemisphere on cortical excitability

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

4.5 Effect of machine on corticospinal excitability

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

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machines for biphasic MT assessment prior to repetitive TMS protocols (delivered with biphasic pulses), which have a reduced power output in comparison to Magstim 200^2 (Kammer et al. 2001), and MagPro X100 machines (Koponen et al. 2020). These differential effects highlight the importance of the inclusion of TMS machine (and study location if applicable) as a covariate in statistical analyses on data that are pooled collaboratively using different machines. Researchers should also be aware that the various configurations of the Magstim BiStim machine (i.e. two connected Magstim 200^2 machines) produce different power outputs, which may confound electrophysiological results if configured incorrectly (Do et al. 2019). We did not collect information on these configurations in the present study, which may have affected results.

4.6 Limitations

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

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

4.7 Recommendations

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

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

4.8 Conclusions

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

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

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Declarations of interest: none

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stimulation with electroencephalography and magnetic resonance imaging. J.G.O. was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number KL2TR002737. P.B.F. is supported by a NHMRC Practitioner Fellowship (1078567). P.B.F. has received equipment for research from MagVenture A/S, Medtronic Ltd, Neuronetics and Brainsway Ltd. and funding for research from Neuronetics. He is on scientific advisory boards for Bionomics Ltd and LivaNova and is a founder of TMS Clinics Australia. P. G. E. is supported by a Future Fellowship from the Australian Research Council (FT160100077).

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Supplementary file 1
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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

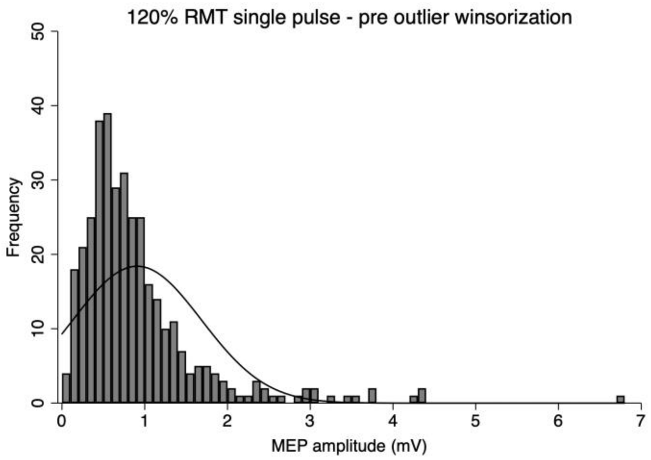
((continuous theta-burst stimulation OR continuous theta burst stimulation OR cTBS)) AND (Transcranial magnetic stimulation OR TMS) Filters: Publication date from 2012/01/01 to 2016/12/31 Results = 239

((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

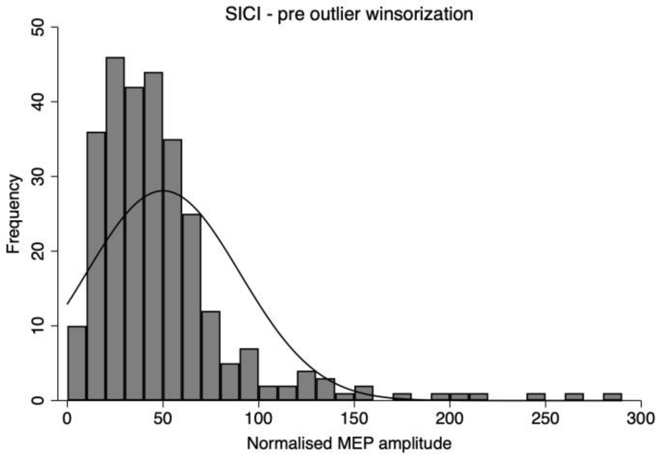
((intracortical facilitation OR ICF)) AND (Transcranial magnetic stimulation OR TMS) Filters: Publication date from 2014/01/01 to 2016/12/31. Results = 152

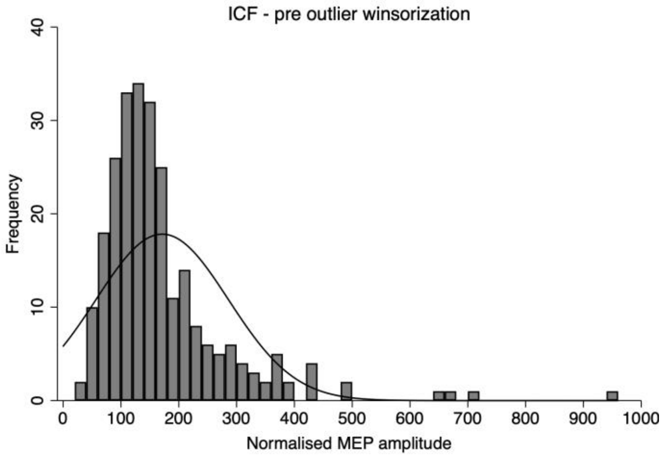
((input-output curve* OR stimulus-response curve* OR I-O curve* OR IO curve* OR S-R curve* OR SR curve*)) AND (Transcranial magnetic stimulation OR TMS) Filters: Publication date from 2013/01/01 to 2016/12/31. Results = 69

Supplementary file 3



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





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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 SICI and ICF were assessed at 80% and 120% of RMT, for conditioning and test stimuli, respectively, with interstimulus intervals of 2 ms (SICI) 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 SICI 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 SICI = 0.367.

References

Beynel L, Chauvin A, Guyader N, Harquel S, Marendaz C. Age-related changes in intracortical inhibition are mental-cognitive state-dependent. Biol Psychol 2014; 101: 9-12.

McGraw KO, Wong S. Forming inferences about some intraclass correlation coefficients. Psychological methods 1996; 1: 30.

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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

-------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     Groups    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)
--------------------------------------------------------------------------
-----
             |               Robust
BaseMEP_wins |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+------------------------------------------------------------
----
         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
```

```
Computing standard errors:

Mixed-effects regression                        Number of obs     =
474

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

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

                               (Std. Err. adjusted for 18 clusters in
Studyno)
----------------------------------------------------------------------------
-----
             |               Robust
BaseMEP_wins |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+--------------------------------------------------------------
----
         Age |  -.0025503   .0030264    -0.84   0.399     -.008482
.0033813
      Gender |  -.0002533   .0699914    -0.00   0.997     -.137434
.1369274
      Muscle |  -.3206196   .0721294    -4.45   0.000    -.4619907   -
.1792485
       _cons |    1.07201   .1289905     8.31   0.000     .8191928
1.324826
----------------------------------------------------------------------------
-----

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

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
```

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

                                                Wald chi2(3)      =
38.91
Log pseudolikelihood = -414.93492               Prob > chi2       =
0.0000

                                 (Std. Err. adjusted for 17 clusters in
Studyno)
-----------------------------------------------------------------------
-------
               |               Robust
  BaseMEP_wins |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
---------------+-------------------------------------------------------
------
           Age |  -.0038426   .0028052    -1.37   0.171    -.0093407
.0016555
        Gender |  -.0293734   .0699193    -0.42   0.674    -.1664127
.1076658
Machine_spulse |   .2408224   .0420787     5.72   0.000     .1583496
.3232951
         _cons |   .9272276   .1144897     8.10   0.000      .702832
1.151623
-----------------------------------------------------------------------
-------

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

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                        Number of obs     =
474

-------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     Groups    Minimum    Average    Maximum
```

```
----------------+--------------------------------------------
        Studyno |         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
Studyno)
-----------------------------------------------------------------------------
-----
             |               Robust
BaseMEP_wins |      Coef.   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 noretable

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

-------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     Groups    Minimum    Average    Maximum
----------------+--------------------------------------------
        Studyno |         18         10       26.3         70
      newPartID |        359          1        1.3          2
-------------------------------------------------------------
```

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

                                  (Std. Err. adjusted for 18 clusters in
Studyno)
--------------------------------------------------------------------------
--------
                |               Robust
   BaseMEP_wins |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
----------------+---------------------------------------------------------
-------
            Age |  -.0028702   .0028519    -1.01   0.314    -.0084598
.0027194
         Gender |  -.0052331   .0692731    -0.08   0.940     -.141006
.1305398
Neuronavigation |    -.29488   .0954175    -3.09   0.002    -.4818949   -
.1078651
          _cons |   1.180095    .112362    10.50   0.000      .959869
1.40032
--------------------------------------------------------------------------
--------

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

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

-------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     Groups    Minimum    Average    Maximum
----------------+--------------------------------------------
        Studyno |         13         11       27.9         70
      newPartID |        248          1        1.5          2
-------------------------------------------------------------

                                                Wald chi2(3)      =
44.03
```

```
Log pseudolikelihood = -278.80319               Prob > chi2       =
0.0000

                               (Std. Err. adjusted for 13 clusters in
Studyno)
--------------------------------------------------------------------------
-----
             |               Robust
BaseMEP_wins |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+------------------------------------------------------------
----
         Age |   .0030643   .0029831     1.03   0.304    -.0027824
.008911
      Gender |  -.0092131   .0532958    -0.17   0.863     -.113671
.0952448
     MonoRMT |  -.0146129   .0028081    -5.20   0.000    -.0201167   -
.0091092
       _cons |   1.490094   .1688795     8.82   0.000     1.159097
1.821092
--------------------------------------------------------------------------
-----

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

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

-------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     Groups    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)
--------------------------------------------------------------------------
-----
             |               Robust
BaseMEP_wins |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+------------------------------------------------------------
----
         Age |  -.0014456   .0035162    -0.41   0.681    -.0083372
.005446
      Gender |   .0284975   .1527012     0.19   0.852    -.2707914
.3277864
       BiRMT |  -.0193975   .0052949    -3.66   0.000    -.0297753   -
.0090197
       _cons |   2.029973   .2791479     7.27   0.000     1.482853
2.577093
--------------------------------------------------------------------------
-----

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

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

-------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     Groups    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
.0015647
      Gender |   .0360827   .0363064     0.99   0.320    -.0350766
.107242
     MonoAMT |  -.0079267   .0029001    -2.73   0.006    -.0136109   -
.0022425
       _cons |   1.295731   .2591768     5.00   0.000     .7877538
1.803708
------------------------------------------------------------------------------
-----

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

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

-------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     Groups    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
```

```
BaseMEP_wins |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+----------------------------------------------------------------
----
         Age |    .002146   .0024305     0.88   0.377    -.0026177
.0069097
      Gender |  -.0775646     .08062    -0.96   0.336    -.2355768
.0804476
       BiAMT |  -.0154547   .0026378    -5.86   0.000    -.0206247   -
.0102846
       _cons |   1.515444   .2121489     7.14   0.000     1.099639
1.931248
------------------------------------------------------------------------------
-----
```

*Step 2 regressions for single pulse.

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

```
. 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

-------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     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)
--------------------------------------------------------------------------
--------
                |                 Robust
   BaseMEP_wins |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
----------------+---------------------------------------------------------
-------
         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
--------------------------------------------------------------------------
--------

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

-------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     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)
--------------------------------------------------------------------------
--------
                |               Robust
   BaseMEP_wins |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
----------------+---------------------------------------------------------
-------
```

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

--------------------------------------------------------------------------
-----
                              |                Robust
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf.
Interval]
------------------------------+-------------------------------------------
----
Studyno: Identity             |
                  var(_cons) |     0.0000          .             .
.
------------------------------+-------------------------------------------
----
newPartID: Identity           |
                  var(_cons) |     0.3307     0.0800        0.2059
0.5313
------------------------------+-------------------------------------------
----
               var(Residual) |     0.0993     0.0105        0.0807
0.1222
--------------------------------------------------------------------------
-----

.
. 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:
```

```
Performing gradient-based 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

Computing standard errors:

Mixed-effects regression                        Number of obs     =
456

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

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

                                  (Std. Err. adjusted for 17 clusters in
Studyno)
-------------------------------------------------------------------------
--------
                |               Robust
   BaseMEP_wins |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
----------------+--------------------------------------------------------
-------
         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 |
```

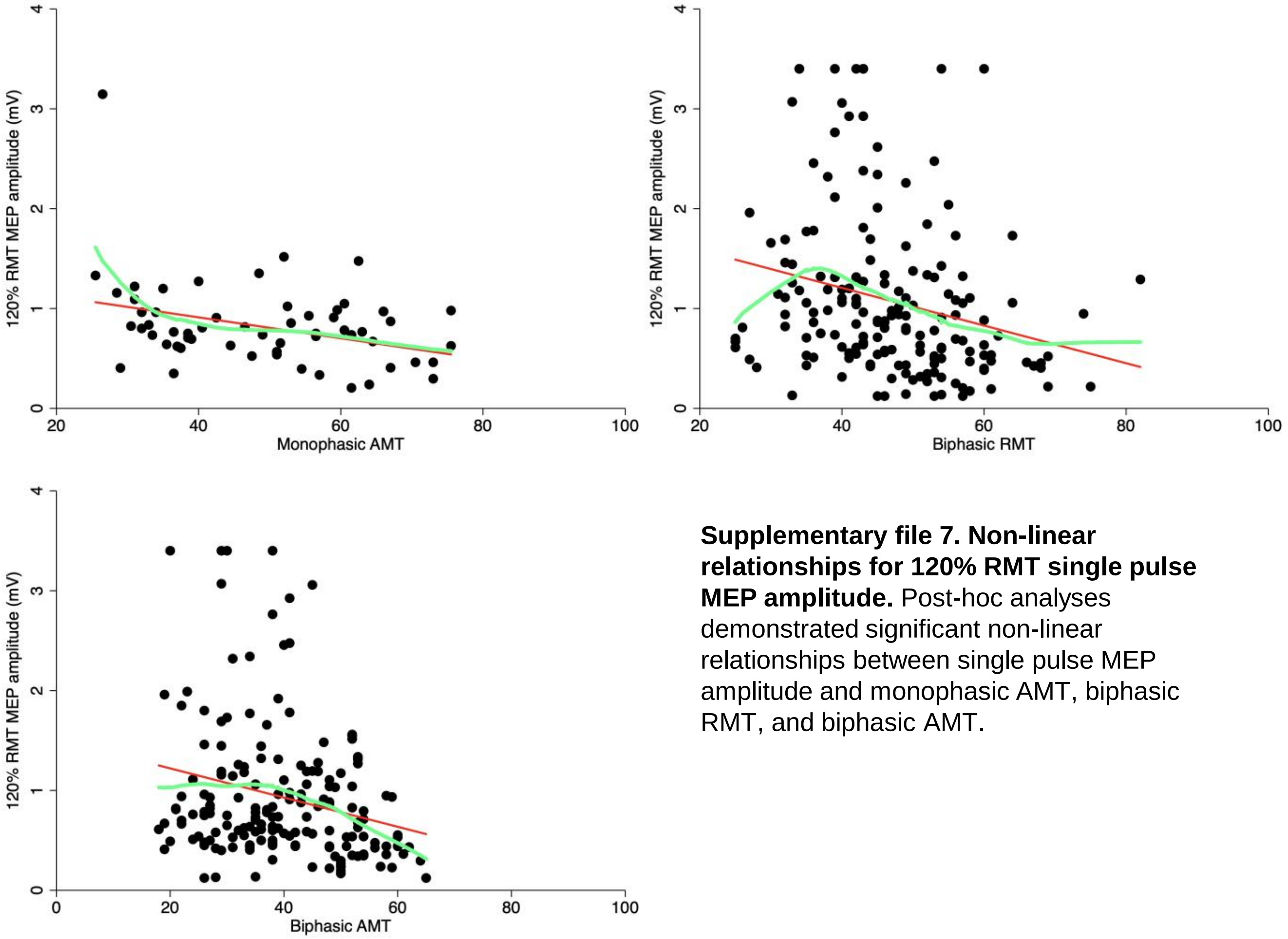
```
       Female  |    -0.0074     0.0713    -0.10   0.917      -0.1472
0.1323
        _cons |     1.0205     0.1234     8.27   0.000       0.7786
1.2624
--------------------------------------------------------------------------
--------

--------------------------------------------------------------------------
-----
                             |                 Robust
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf.
Interval]
-----------------------------+--------------------------------------------
----
Studyno: Identity            |
                  var(_cons) |     0.0004     0.0120        0.0000
5.1e
-----------------------------+--------------------------------------------
----
newPartID: Identity          |
                  var(_cons) |     0.3335     0.0853        0.2019
0.5507
-----------------------------+--------------------------------------------
----
               var(Residual) |     0.0992     0.0105        0.0805
0.1221
--------------------------------------------------------------------------
-----

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

Performing EM optimization:

Performing gradient-based optimization:

Iteration 0:   log pseudolikelihood = -396.44941
Iteration 1:   log pseudolikelihood = -396.35985
Iteration 2:   log pseudolikelihood = -396.35867
Iteration 3:   log pseudolikelihood = -396.35867

Computing standard errors:

Mixed-effects regression                        Number of obs     =
444

-------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     Groups    Minimum    Average    Maximum
----------------+--------------------------------------------
        Studyno |         16         10       27.8         70
```

```
      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)
--------------------------------------------------------------------------
--------
                |               Robust
   BaseMEP_wins |      Coef.   Std. Err.      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

-------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     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)
--------------------------------------------------------------------------
--------
                |               Robust
   BaseMEP_wins |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
----------------+---------------------------------------------------------
-------
         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
------------------------------------------------------------------------------------------
```

Supplementary file 7



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:
```

```
Performing gradient-based optimization:

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

Computing standard errors:

Mixed-effects regression                        Number of obs      =
456

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

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

                               (Std. Err. adjusted for 15 clusters in
Studyno)
-------------------------------------------------------------------------
-----
             |               Robust
   MEPchange |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+-----------------------------------------------------------
----
     BaseMEP |  -23.50364   8.243706    -2.85   0.004      -39.661   -
7.346269
         Age |   .1166655   .1139816     1.02   0.306    -.1067342
.3400653
      Gender |    5.69354   3.657288     1.56   0.120    -1.474614
12.86169
       _cons |    64.0576    13.5553     4.73   0.000      37.4897
90.6255
-------------------------------------------------------------------------
-----

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

-------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     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)
------------------------------------------------------------------------------
-----
             |               Robust
   MEPchange |      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
-------------------------------------------------------------------------
-----

-------------------------------------------------------------------------
-----
                              |               Robust
  Random-effects Parameters  |   Estimate   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

-------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     Groups    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)
-------------------------------------------------------------------------
-----
             |               Robust
   MEPchange |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+-----------------------------------------------------------
----
  Hemisphere |  -5.273922   1.748358    -3.02   0.003    -8.700641   -
1.847202
         Age |    .220899   .1200631     1.84   0.066    -.0144204
.4562183
      Gender |   3.494108    3.30978     1.06   0.291    -2.992941
9.981156
       _cons |   40.70547   7.366821     5.53   0.000     26.26676
55.14417
-------------------------------------------------------------------------
-----

-------------------------------------------------------------------------
-----
                             |               Robust
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf.
Interval]
-----------------------------+-------------------------------------------
----
Studyno: Identity            |
                  var(_cons) |   139.5504   69.44456      52.61957
370.0966
-----------------------------+-------------------------------------------
----
newPartID: Identity          |
                  var(_cons) |   532.0593   147.2917      309.2568
915.3788
-----------------------------+-------------------------------------------
----
               var(Residual) |   742.8034   195.1739      443.8315
1243.168
-------------------------------------------------------------------------
-----

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

```
Performing EM optimization:

Performing gradient-based optimization:

Iteration 0:   log pseudolikelihood = -2202.1571
Iteration 1:   log pseudolikelihood = -2202.1419
Iteration 2:   log pseudolikelihood = -2202.1419

Computing standard errors:

Mixed-effects regression                        Number of obs     =
442

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

                                                Wald chi2(3)      =
3.55
Log pseudolikelihood = -2202.1419               Prob > chi2       =
0.3143

                               (Std. Err. adjusted for 14 clusters in
Studyno)
------------------------------------------------------------------------------
-----
             |               Robust
   MEPchange |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+----------------------------------------------------------------
----
     ppTSint |  -7.076269   7.480375    -0.95   0.344    -21.73753
7.584998
         Age |   .1994886   .1260021     1.58   0.113    -.0474709
.4464481
      Gender |   2.977309   3.339325     0.89   0.373    -3.567647
9.522266
       _cons |   44.66832   8.532178     5.24   0.000     27.94556
61.39108
------------------------------------------------------------------------------
-----

------------------------------------------------------------------------------
-----
                             |               Robust
  Random-effects Parameters  |   Estimate   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

-------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     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)
-----------------------------------------------------------------------------
--------
                |               Robust
      MEPchange |      Coef.   Std. Err.      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
------------------------------------------------------------------------
--------

------------------------------------------------------------------------
-----
                             |                 Robust
  Random-effects Parameters  |   Estimate   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

-------------------------------------------------------------
               |     No. of       Observations per Group
 Group Variable |     Groups    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)
-------------------------------------------------------------------------
-----
             |               Robust
   MEPchange |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+-----------------------------------------------------------
----
     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
-------------------------------------------------------------------------
-----

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

```
Performing EM optimization:

Performing gradient-based optimization:

Iteration 0:   log pseudolikelihood = -401.55242
Iteration 1:   log pseudolikelihood = -401.55242

Computing standard errors:

Mixed-effects regression                        Number of obs     =
78

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

                                                Wald chi2(2)      =
.
Log pseudolikelihood = -401.55242               Prob > chi2       =
.

                                (Std. Err. adjusted for 3 clusters in
Studyno)
----------------------------------------------------------------------------
-----
             |               Robust
   MEPchange |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+--------------------------------------------------------------
----
       BiRMT |   .5683006   .2016816     2.82   0.005     .1730119
.9635893
         Age |   .3348599   .1559223     2.15   0.032     .0292577
.640462
      Gender |   11.97175   5.343505     2.24   0.025     1.498677
22.44483
       _cons |   6.050009   13.59681     0.44   0.656    -20.59924
32.69926
----------------------------------------------------------------------------
-----

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

-------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     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)
------------------------------------------------------------------------------
-----
             |               Robust
   MEPchange |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+----------------------------------------------------------------
----
     MonoAMT |   -.490092   .4207196    -1.16   0.244    -1.314687
.3345032
```

```
         Age |   .1233373   .0812742     1.52   0.129    -.0359572
.2826318
      Gender |   3.201804   4.477844     0.72   0.475    -5.574608
11.97822
       _cons |   63.16403   18.60141     3.40   0.001     26.70593
99.62213
------------------------------------------------------------------------------
-----

------------------------------------------------------------------------------
-----
                             |                 Robust
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf.
Interval]
-----------------------------+------------------------------------------------
----
Studyno: Identity            |
                  var(_cons) |   178.3565   101.5413      58.43668
544.3675
-----------------------------+------------------------------------------------
----
newPartID: Identity          |
                  var(_cons) |   436.5358   265.2162      132.7011
1436.036
-----------------------------+------------------------------------------------
----
               var(Residual) |   729.7473    306.515      320.3637
1662.271
------------------------------------------------------------------------------
-----

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

Performing EM optimization:

Performing gradient-based optimization:

Iteration 0:   log pseudolikelihood = -542.54893
Iteration 1:   log pseudolikelihood = -541.89134
Iteration 2:   log pseudolikelihood = -541.85954
Iteration 3:   log pseudolikelihood = -541.85928
Iteration 4:   log pseudolikelihood = -541.85928

Computing standard errors:

Mixed-effects regression                        Number of obs     =
107

-------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     Groups    Minimum    Average    Maximum
----------------+--------------------------------------------
```

```
       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)
------------------------------------------------------------------------------
-----
             |               Robust
   MEPchange |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+----------------------------------------------------------------
----
       BiAMT |  -.6226971   .3247755    -1.92   0.055    -1.259245
.0138512
         Age |   .4843482   .2664709     1.82   0.069    -.0379252
1.006622
      Gender |   9.836636   7.351436     1.34   0.181    -4.571914
24.24519
       _cons |   55.12375   12.62634     4.37   0.000     30.37658
79.87092
------------------------------------------------------------------------------
-----

------------------------------------------------------------------------------
-----
                             |               Robust
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf.
Interval]
-----------------------------+------------------------------------------------
----
Studyno: Identity            |
                  var(_cons) |   1.52e-18   6.41e-15             0
.
-----------------------------+------------------------------------------------
----
newPartID: Identity          |
                  var(_cons) |    269.623   10006.22      6.94e-30
1.05e
-----------------------------+------------------------------------------------
----
               var(Residual) |     1210.3   50865.76      2.04e-33
7.19e
------------------------------------------------------------------------------
-----
```

*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

-------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     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)
------------------------------------------------------------------------------
             |               Robust
   MEPchange |      Coef.   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
---------------------------------------------------------------------------
-----

---------------------------------------------------------------------------
-----
                              |               Robust
  Random-effects Parameters   |   Estimate   Std. Err.     [95% Conf.
Interval]
------------------------------+--------------------------------------------
----
Studyno: 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 || Studyno: || newPartID:,robust



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

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

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

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

                               (Std. Err. adjusted for 15 clusters in
Studyno)
--------------------------------------------------------------------------
-----
             |               Robust
   MEPchange |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+------------------------------------------------------------
----
      Muscle |  -2.724574   8.771385    -0.31   0.756    -19.91617
14.46703
         Age |   .1088982   .1172347     0.93   0.353    -.1208777
.3386741
      Gender |   5.613454   3.598004     1.56   0.119    -1.438504
12.66541
     BaseMEP |  -23.35856   8.339092    -2.80   0.005    -39.70288   -
7.014239
  Hemisphere |  -4.010334   1.748747    -2.29   0.022    -7.437816   -
.5828523
       _cons |   65.97491    15.2152     4.34   0.000     36.15367
95.79614
--------------------------------------------------------------------------
-----

--------------------------------------------------------------------------
-----
                             |               Robust
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf.
Interval]
-----------------------------+--------------------------------------------
----
Studyno: Identity            |
                  var(_cons) |   193.7342   84.36848      82.51254
454.8754
-----------------------------+--------------------------------------------
----
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

-------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     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)
------------------------------------------------------------------------------
-----
             |               Robust
   MEPchange |      Coef.   Std. Err.      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
------------------------------------------------------------------------
-----

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

-------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     Groups    Minimum    Average    Maximum
----------------+--------------------------------------------
        Studyno |         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)
------------------------------------------------------------------------------
-----
             |               Robust
   MEPchange |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+----------------------------------------------------------------
----
     MonoRMT |   -.349762   .3247811    -1.08   0.282    -.9863212
.2867972
         Age |   .1424259   .1185159     1.20   0.229     -.089861
.3747128
      Gender |   4.353436   4.096342     1.06   0.288    -3.675246
12.38212
     BaseMEP |  -29.64184   10.55421    -2.81   0.005    -50.32772   -
8.955958
  Hemisphere |  -5.605659   1.897601    -2.95   0.003    -9.324888    -
1.88643
       _cons |   89.87277   28.39005     3.17   0.002      34.2293
145.5162
------------------------------------------------------------------------------
-----

------------------------------------------------------------------------------
-----
                             |               Robust
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf.
Interval]
-----------------------------+------------------------------------------------
----
Studyno: Identity            |
                  var(_cons) |   282.1264   104.4826      136.5243
583.0117
-----------------------------+------------------------------------------------
----
newPartID: Identity          |
                  var(_cons) |   443.2318   111.2133      271.0516
724.786
-----------------------------+------------------------------------------------
----
               var(Residual) |   673.8053   156.6797      427.1741
1062.83
------------------------------------------------------------------------------
-----
```

```
->  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

-------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     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)
------------------------------------------------------------------------
-----
             |               Robust
   MEPchange |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+----------------------------------------------------------
----
       BiRMT |   .2470882   .3100845     0.80   0.426    -.3606662
.8548427
         Age |   .1444077   .1741899     0.83   0.407    -.1969982
.4858136
      Gender |   15.61687   4.818079     3.24   0.001     6.173611
25.06013
     BaseMEP |  -18.17106   9.119013    -1.99   0.046      -36.044   -
.2981202
  Hemisphere |  -2.415782   2.125187    -1.14   0.256    -6.581073
1.749508
       _cons |    47.3614   36.95123     1.28   0.200    -25.06168
119.7845
------------------------------------------------------------------------
-----
```

```
------------------------------------------------------------------------------
-----
                              |               Robust
  Random-effects Parameters  |   Estimate   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

-------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     Groups    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)
```

```
------------------------------------------------------------------------------
-----
             |               Robust
   MEPchange |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+----------------------------------------------------------------
----
     MonoAMT |  -.9197529   .7011269    -1.31   0.190    -2.293936
.4544306
         Age |    .192005   .1362812     1.41   0.159    -.0751012
.4591112
      Gender |   7.086305    7.54868     0.94   0.348    -7.708835
21.88145
     BaseMEP |  -37.90118   18.88504    -2.01   0.045    -74.91517   -
.8871883
  Hemisphere |  -5.014506   1.640793    -3.06   0.002    -8.230402    -
1.79861
       _cons |   113.7038    45.2527     2.51   0.012     25.01012
202.3975
------------------------------------------------------------------------------
-----

------------------------------------------------------------------------------
-----
                             |               Robust
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf.
Interval]
-----------------------------+------------------------------------------------
----
Studyno: Identity            |
                  var(_cons) |   294.2187   150.6621      107.8428
802.6928
-----------------------------+------------------------------------------------
----
newPartID: Identity          |
                  var(_cons) |   333.4856    126.739      158.3374
702.3777
-----------------------------+------------------------------------------------
----
               var(Residual) |   617.1795   188.3234      339.3748
1122.389
------------------------------------------------------------------------------
-----

->  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

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

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

                                (Std. Err. adjusted for 6 clusters in
Studyno)
-------------------------------------------------------------------------
-----
             |               Robust
   MEPchange |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+-----------------------------------------------------------
----
       BiAMT |  -.8642859   .2980498    -2.90   0.004    -1.448453   -
.2801191
         Age |   .3718181   .3588239     1.04   0.300    -.3314639
1.0751
      Gender |   8.742461    7.38026     1.18   0.236    -5.722582
23.2075
     BaseMEP |  -26.34473    6.81125    -3.87   0.000    -39.69453   -
12.99492
  Hemisphere |  -23.37366   12.19491    -1.92   0.055    -47.27525
.5279212
       _cons |   95.81923   22.85276     4.19   0.000     51.02865
140.6098
-------------------------------------------------------------------------
-----

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

-------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     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)
```

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

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



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

-------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     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)
---------------------------------------------------------------------------
-----
             |               Robust
   MEPchange |      Coef.   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 noretable

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

-------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     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)
--------------------------------------------------------------------------
-----
             |               Robust
   MEPchange |      Coef.   Std. Err.      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 noretable

Performing EM optimization:
```

```
Performing gradient-based optimization:

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

Computing standard errors:

Mixed-effects regression                        Number of obs     =
393

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

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

                               (Std. Err. adjusted for 14 clusters in
Studyno)
----------------------------------------------------------------------------
-----
             |               Robust
   MEPchange |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+--------------------------------------------------------------
----
  Hemisphere |  -.3405924   12.30545    -0.03   0.978    -24.45883
23.77765
         Age |   .5841057   .3740313     1.56   0.118    -.1489822
1.317194
      Gender |  -12.20163   8.972212    -1.36   0.174    -29.78684
5.383583
       _cons |   146.7153   18.53423     7.92   0.000     110.3889
183.0417
----------------------------------------------------------------------------
-----

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

Performing EM optimization:

Performing gradient-based optimization:

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

```
Iteration 2:   log pseudolikelihood = -2245.3709

Computing standard errors:

Mixed-effects regression                        Number of obs     =
379

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

                                                Wald chi2(3)      =
7.33
Log pseudolikelihood = -2245.3709               Prob > chi2       =
0.0621

                               (Std. Err. adjusted for 13 clusters in
Studyno)
------------------------------------------------------------------------
-----
             |               Robust
   MEPchange |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+----------------------------------------------------------
----
     ppTSint |  -31.27347   20.60984    -1.52   0.129    -71.66801
9.121077
         Age |   .4298185     .34591     1.24   0.214    -.2481526
1.10779
      Gender |  -12.51507   8.949082    -1.40   0.162    -30.05495
5.024806
       _cons |   165.8492   17.05441     9.72   0.000     132.4231
199.2752
------------------------------------------------------------------------
-----

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

Performing EM optimization:

Performing gradient-based optimization:

Iteration 0:   log pseudolikelihood = -2326.7597
Iteration 1:   log pseudolikelihood = -2326.6911
Iteration 2:   log pseudolikelihood = -2326.6911

Computing standard errors:
```

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

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

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

                                  (Std. Err. adjusted for 14 clusters in
Studyno)
-------------------------------------------------------------------------
--------
                |               Robust
      MEPchange |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
----------------+--------------------------------------------------------
-------
Neuronavigation |  -25.58969   19.30257    -1.33   0.185    -63.42203
12.24266
            Age |   .4761308   .4088646     1.16   0.244    -.3252292
1.277491
         Gender |  -13.51574   8.596723    -1.57   0.116    -30.36501
3.33353
          _cons |   167.4227   20.74099     8.07   0.000     126.7711
208.0742
-------------------------------------------------------------------------
--------

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

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

-------------------------------------------------------------
```

```
                |     No. of       Observations per Group
 Group Variable |     Groups    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)
------------------------------------------------------------------------------
-----
             |               Robust
   MEPchange |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+----------------------------------------------------------------
----
     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 noretable

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

-----------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     Groups    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)
------------------------------------------------------------------------
-----
             |               Robust
   MEPchange |      Coef.   Std. Err.      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
```

```
                                                              avg =
15.0
                                                              max =
25

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

                                (Std. Err. adjusted for 5 clusters in
Studyno)
-------------------------------------------------------------------------
-----
             |               Robust
   MEPchange |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+-----------------------------------------------------------
----
       BiAMT |   3.663754   2.684226     1.36   0.172    -1.597232
8.92474
         Age |  -.0134243   1.033459    -0.01   0.990    -2.038967
2.012118
             |
      Gender |
     Female  |  -18.24444   35.65254    -0.51   0.609    -88.12214
51.63325
       _cons |   44.28037   74.17977     0.60   0.551    -101.1093
189.67
-------------------------------------------------------------------------
-----

-------------------------------------------------------------------------
-----
                             |               Robust
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf.
Interval]
-----------------------------+-------------------------------------------
----
Studyno: Identity            |
                 var(_cons) |   8.70e-15   2.29e-12      3.6e-239
2.1e□
-----------------------------+-------------------------------------------
----
              var(Residual) |   7760.838   2052.043      4622.133
13030.91
-------------------------------------------------------------------------
-----

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

Performing EM optimization:
```

```
Performing gradient-based optimization:

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

Computing standard errors:

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

                                                Obs per group:
                                                              min =
15
                                                              avg =
26.3
                                                              max =
39

                                                Wald chi2(2)      =
.
Log pseudolikelihood = -470.62852               Prob > chi2       =
.

                                (Std. Err. adjusted for 3 clusters in
Studyno)
------------------------------------------------------------------------------
-----
             |               Robust
   MEPchange |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+----------------------------------------------------------------
----
       BiRMT |    2.52194   .4265283     5.91   0.000      1.68596
3.357921
         Age |  -.0098836   .5789575    -0.02   0.986    -1.144619
1.124852
             |
      Gender |
     Female  |  -5.543591   25.27648    -0.22   0.826    -55.08457
43.99739
       _cons |   57.58981   34.99041     1.65   0.100    -10.99014
126.1698
------------------------------------------------------------------------------
-----

------------------------------------------------------------------------------
-----
                             |               Robust
  Random-effects Parameters  |   Estimate   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
> udyno: || 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

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

                                                Wald chi2(2)      =
6.39
Log pseudolikelihood = -2294.5463               Prob > chi2       =
0.0410
```

```
                              (Std. Err. adjusted for 14 clusters in
Studyno)
----------------------------------------------------------------------
-----
             |               Robust
   MEPchange |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+--------------------------------------------------------
----
     BaseMEP |   -71.8332   28.93723    -2.48   0.013    -128.5491   -
15.11728
             |
      Gender |
     Female  |  -4.802347   8.188739    -0.59   0.558    -20.85198
11.24729
       _cons |   227.1622   34.26389     6.63   0.000     160.0062
294.3182
----------------------------------------------------------------------
-----

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

*Iterating

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

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

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

-------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     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)
-----------------------------------------------------------------------------
-----
             |               Robust
   MEPchange |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+---------------------------------------------------------------
----
         Age |  -.0014924   .4610102    -0.00   0.997    -.9050559
.902071
     BaseMEP |  -71.83875   28.90852    -2.49   0.013    -128.4984   -
15.17908
      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.ppTSint BaseMEP Gender if Protocol == 1 & Dx==0 ||
Studyno: ||
>  newPartID:,robust noretable
```

```
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

-------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     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)
-------------------------------------------------------------------------
-----
             |               Robust
   MEPchange |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+-----------------------------------------------------------
----
     ppTSint |  -33.31513   16.43076    -2.03   0.043    -65.51884   -
1.111426
     BaseMEP |  -80.82001   32.65889    -2.47   0.013    -144.8303   -
16.80976
      Gender |  -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
-------------------------------------------------------------------------
-----

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

Performing EM optimization:

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

--------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     Groups    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)
--------------------------------------------------------------------------
-----
             |               Robust
   MEPchange |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+------------------------------------------------------------
----
      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 noretable

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
```

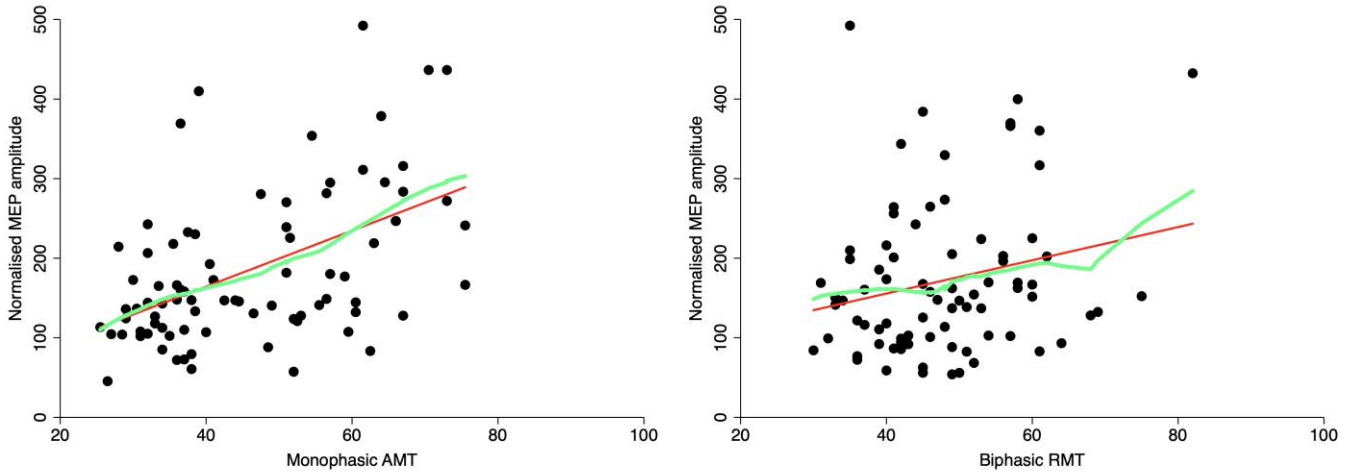
```
Computing standard errors:

Mixed-effects regression                        Number of obs     =
393

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

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

                               (Std. Err. adjusted for 14 clusters in
Studyno)
------------------------------------------------------------------------
-----
             |               Robust
   MEPchange |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+----------------------------------------------------------
----
  Hemisphere |   3.108259   11.50447     0.27   0.787    -19.44008
25.6566
     BaseMEP |  -72.00222   28.99535    -2.48   0.013    -128.8321   -
15.17237
      Gender |  -4.817496   8.170127    -0.59   0.555    -20.83065
11.19566
       _cons |   226.4826   34.17639     6.63   0.000     159.4981
293.4671
------------------------------------------------------------------------
-----






. *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 noretable

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

```
> : || newPartID:,robust noretable

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

-------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     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)
--------------------------------------------------------------------------
-----
             |               Robust
   MEPchange |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+------------------------------------------------------------
----
         Age |  -.1797049   .4539419    -0.40   0.692    -1.069415
.7100049
     BaseMEP |  -81.56248   32.36383    -2.52   0.012    -144.9944   -
18.13054
      Gender |  -4.877201   8.339107    -0.58   0.559    -21.22155
11.46715
     ppTSint |  -34.70664   16.96814    -2.05   0.041    -67.96358    -
1.44971
       _cons |   252.5945   41.95015     6.02   0.000     170.3737
334.8153
--------------------------------------------------------------------------
-----

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

```
Performing EM optimization:

Performing gradient-based optimization:

Iteration 0:   log pseudolikelihood = -2209.6575
Iteration 1:   log pseudolikelihood = -2209.6066
Iteration 2:   log pseudolikelihood = -2209.6066

Computing standard errors:

Mixed-effects regression                        Number of obs     =
379

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

                                                Wald chi2(4)      =
12.08
Log pseudolikelihood = -2209.6066               Prob > chi2       =
0.0168

                               (Std. Err. adjusted for 13 clusters in
Studyno)
-------------------------------------------------------------------------
-----
             |               Robust
   MEPchange |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+-----------------------------------------------------------
----
      Muscle |  -.5893533   22.91711    -0.03   0.979    -45.50606
44.32735
     BaseMEP |  -80.82978   32.49044    -2.49   0.013    -144.5099    -
17.1497
      Gender |  -4.487589   8.229603    -0.55   0.586    -20.61732
11.64214
     ppTSint |  -33.15798   18.77948    -1.77   0.077    -69.96508
3.649129
       _cons |    245.611   35.42306     6.93   0.000      176.183
315.0389
-------------------------------------------------------------------------
-----

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

Performing EM optimization:
```

```
Performing gradient-based optimization:

Iteration 0:   log pseudolikelihood = -2209.5734
Iteration 1:   log pseudolikelihood = -2209.5228
Iteration 2:   log pseudolikelihood = -2209.5228

Computing standard errors:

Mixed-effects regression                        Number of obs     =
379

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

                                                Wald chi2(4)      =
7.49
Log pseudolikelihood = -2209.5228               Prob > chi2       =
0.1123

                               (Std. Err. adjusted for 13 clusters in
Studyno)
----------------------------------------------------------------------------
-----
             |               Robust
   MEPchange |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+--------------------------------------------------------------
----
  Hemisphere |   3.669611   11.43856     0.32   0.748    -18.74955
26.08878
     BaseMEP |  -81.09817   32.73725    -2.48   0.013     -145.262   -
16.93434
      Gender |  -4.458662   8.230826    -0.54   0.588    -20.59078
11.67346
     ppTSint |  -33.35855   16.39337    -2.03   0.042    -65.48896   -
1.228138
       _cons |   244.6294   38.22342     6.40   0.000     169.7129
319.5459
----------------------------------------------------------------------------
-----

.
. *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

--------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     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)
--------------------------------------------------------------------------
-----
             |               Robust
   MEPchange |      Coef.   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
```

```
Computing standard errors:

Mixed-effects regression                        Number of obs     =
603

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

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

                               (Std. Err. adjusted for 26 clusters in
Studyno)
------------------------------------------------------------------------------
-----
             |               Robust
     MonoRMT |      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 noretable

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
```

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

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

                               (Std. Err. adjusted for 26 clusters in
Studyno)
-------------------------------------------------------------------------
-----
             |               Robust
     MonoRMT |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+-----------------------------------------------------------
----
  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                        Number of obs     =
603

-------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     Groups    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
```

```
Computing standard errors:

Mixed-effects regression                        Number of obs     =
603

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

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

                               (Std. Err. adjusted for 26 clusters in
Studyno)
--------------------------------------------------------------------------
-----
             |               Robust
     MonoRMT |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+------------------------------------------------------------
----
      Gender |   .8295988   .8551474     0.97   0.332    -.8464594
2.505657
         Age |   .0877955   .0250402     3.51   0.000     .0387177
.1368733
  Hemisphere |  -2.167551   .8941426    -2.42   0.015    -3.920038   -
.4150637
       _cons |    43.8205   2.032247    21.56   0.000     39.83737
47.80363
--------------------------------------------------------------------------
-----

--------------------------------------------------------------------------
-----
                            |               Robust
  Random-effects Parameters |   Estimate   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

-------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     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)
------------------------------------------------------------------------------
--------
                |               Robust
        MonoRMT |      Coef.   Std. Err.      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
```

```
-----------------------------------------------------------------------------
--------

-----------------------------------------------------------------------------
-----
                              |                 Robust
  Random-effects Parameters  |   Estimate   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

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

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

```
                                (Std. Err. adjusted for 26 clusters in 
Studyno)
---------------------------------------------------------------------------
-----
             |               Robust
     MonoRMT |      Coef.   Std. Err.      z    P>|z|     [95% Conf. 
Interval]
-------------+-------------------------------------------------------------
----
      Muscle |  -.3326077   4.704501    -0.07   0.944    -9.553259    
8.888044
         Age |    .083011   .0246176     3.37   0.001     .0347614    
.1312606
  Hemisphere |  -2.172428   .8909239    -2.44   0.015    -3.918607   -
.4262489
       _cons |   44.61384   2.055979    21.70   0.000      40.5842    
48.64349
---------------------------------------------------------------------------
-----

---------------------------------------------------------------------------
-----
                             |               Robust
  Random-effects Parameters  |   Estimate   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: 
```

```
Iteration 0:   log pseudolikelihood = -2176.1161
Iteration 1:   log pseudolikelihood = -2176.0594
Iteration 2:   log pseudolikelihood = -2176.0594

Computing standard errors:

Mixed-effects regression                        Number of obs     =
605

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

                                                Wald chi2(2)      =
13.60
Log pseudolikelihood = -2176.0594               Prob > chi2       =
0.0011

                               (Std. Err. adjusted for 26 clusters in
Studyno)
-------------------------------------------------------------------------
-----
             |               Robust
     MonoRMT |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+-----------------------------------------------------------
----
         Age |   .0830299    .024557     3.38   0.001     .0348992
.1311607
             |
  Hemisphere |
          R  |   -2.17207   .8939147    -2.43   0.015    -3.924111   -
.4200297
       _cons |   44.52302   1.914349    23.26   0.000     40.77097
48.27508
-------------------------------------------------------------------------
-----

-------------------------------------------------------------------------
-----
                             |               Robust
  Random-effects Parameters  |   Estimate   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

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

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

                                (Std. Err. adjusted for 6 clusters in
Studyno)
----------------------------------------------------------------------------
-----
             |               Robust
     MonoAMT |      Coef.   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

-------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     Groups    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)
-----------------------------------------------------------------------
-----
             |               Robust
     MonoAMT |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+---------------------------------------------------------
----
  Hemisphere |  -2.043988   1.408105    -1.45   0.147    -4.803822
.7158467
         Age |   .0876773   .0500413     1.75   0.080    -.0104019
.1857565
       _cons |   40.12775   4.312104     9.31   0.000     31.67618
48.57931
-----------------------------------------------------------------------
-----

-----------------------------------------------------------------------
-----
                             |               Robust
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf.
Interval]
-----------------------------+-----------------------------------------
----
Studyno: Identity            |
                  var(_cons) |   76.12289   49.24335      21.42294
270.4901
-----------------------------+-----------------------------------------
----
newPartID: Identity          |
                  var(_cons) |   38.35551    4.93975      29.79908
49.36883
-----------------------------+-----------------------------------------
----
               var(Residual) |   26.01736   11.17431      11.21185
60.37393
-----------------------------------------------------------------------
-----

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

Performing EM optimization:

Performing gradient-based optimization:
```

```
Iteration 0:   log pseudolikelihood = -646.28457
Iteration 1:   log pseudolikelihood = -646.28112
Iteration 2:   log pseudolikelihood = -646.28112

Computing standard errors:

Mixed-effects regression                        Number of obs      =
185

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

                                                Wald chi2(2)       =
8.51
Log pseudolikelihood = -646.28112               Prob > chi2        =
0.0142

                                (Std. Err. adjusted for 6 clusters in
Studyno)
-----------------------------------------------------------------------------
-----
             |               Robust
     MonoAMT |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+---------------------------------------------------------------
----
      Gender |   .1558349   1.916686     0.08   0.935      -3.6008
3.91247
         Age |   .0895047    .046856     1.91   0.056    -.0023314
.1813408
       _cons |   39.13461   4.358948     8.98   0.000     30.59123
47.67799
-----------------------------------------------------------------------------
-----

-----------------------------------------------------------------------------
-----
                             |                 Robust
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf.
Interval]
-----------------------------+-----------------------------------------------
----
Studyno: Identity            |
                  var(_cons) |   76.07656   47.62336      22.30515
259.4757
-----------------------------+-----------------------------------------------
----
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

-------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     Groups    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)
------------------------------------------------------------------------------
-----
             |               Robust
     MonoAMT |      Coef.   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
---------------------------------------------------------------------------
-----

---------------------------------------------------------------------------
-----
                             |           Robust
  Random-effects Parameters  |   Estimate   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
```

```
Iteration 3:   log pseudolikelihood = -968.33653

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(4)      =
35.12
Log pseudolikelihood = -968.33653               Prob > chi2       =
0.0000

                                (Std. Err. adjusted for 12 clusters in
Studyno)
------------------------------------------------------------------------
------
              |               Robust
        BiRMT |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
--------------+---------------------------------------------------------
-----
Machine_BiRMT |
     Nexstim  |   -.765736   4.473454    -0.17   0.864    -9.533545
8.002073
MagstimRapid  |   8.282471   3.746673     2.21   0.027     .9391273
15.62581
              |
          Age |   .1384992   .0656583     2.11   0.035     .0098113
.2671872
              |
       Gender |
      Female  |   2.580854   1.479766     1.74   0.081    -.3194337
5.481142
        _cons |   39.30193   2.966451    13.25   0.000     33.48779
45.11607
------------------------------------------------------------------------
------

------------------------------------------------------------------------
-----
                             |               Robust
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf.
Interval]
-----------------------------+------------------------------------------
----
Studyno: 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)
--------------------------------------------------------------------------
--------
                |               Robust
          BiRMT |      Coef.   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
--------------------------------------------------------------------------
--------

--------------------------------------------------------------------------
-----
                             |               Robust
  Random-effects Parameters  |   Estimate   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

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

                                  (Std. Err. adjusted for 12 clusters in
Studyno)
-------------------------------------------------------------------------
--------
                |               Robust
          BiRMT |      Coef.   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)
--------------------------------------------------------------------------
------
              |               Robust
        BiAMT |      Coef.   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
--------------------------------------------------------------------------
------

--------------------------------------------------------------------------
-----
                             |               Robust
  Random-effects Parameters  |   Estimate   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                        Number of obs     =
277
Group variable: Studyno                         Number of groups  =
14

                                                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)
--------------------------------------------------------------------------
--------
                |               Robust
          BiAMT |      Coef.   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
--------------------------------------------------------------------------
--------

--------------------------------------------------------------------------
-----
                             |               Robust
  Random-effects Parameters  |   Estimate   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
Group variable: Studyno                         Number of groups  =
14

                                                Obs per group:
                                                              min =
10
                                                              avg =
19.8
                                                              max =
38

                                                Wald chi2(3)      =
20.17
Log pseudolikelihood = -964.48931               Prob > chi2       =
0.0002

                                  (Std. Err. adjusted for 14 clusters in
Studyno)
--------------------------------------------------------------------------
--------
                |               Robust
          BiAMT |      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
------------------------------------------------------------------------------
--------

------------------------------------------------------------------------------
-----
                             |               Robust
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf.
Interval]
-----------------------------+------------------------------------------------
----
Studyno: 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  ||
Studyno:,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: Studyno                         Number of groups  =
14

                                                Obs per group:
                                                              min =
10
                                                              avg =
19.8
                                                              max =
38
```

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

                                  (Std. Err. adjusted for 14 clusters in
Studyno)
--------------------------------------------------------------------------
--------
                |               Robust
          BiAMT |      Coef.   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
--------------------------------------------------------------------------
--------

--------------------------------------------------------------------------
-----
                             |               Robust
  Random-effects Parameters  |   Estimate   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

```
 mixed BiAMT i.Machine_BiAMT i.Neuronavigation || Studyno:,robust

Performing EM optimization:

Performing gradient-based optimization:

Iteration 0:   log pseudolikelihood = -964.49799
Iteration 1:   log pseudolikelihood = -964.49799

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(2)      =
19.93
Log pseudolikelihood = -964.49799               Prob > chi2       =
0.0000

                                  (Std. Err. adjusted for 14 clusters in
Studyno)
--------------------------------------------------------------------------
--------
                |               Robust
          BiAMT |      Coef.   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
--------------------------------------------------------------------------
--------
```