Variability in Neural Excitability and Plasticity Induction in the Human Cortex: A Brain Stimulation Study

Abbreviated Title: Excitation and Plasticity in the Human Cortex

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Abstract

Background: The potential of non-invasive brain stimulation (NIBS) for both probing human neuroplasticity and the induction of functionally relevant neuroplastic change has received significant interest. However, at present the utility of NIBS is limited due to high response variability. One reason for this response variability is that NIBS targets a diffuse cortical population and the net outcome to stimulation depends on the relative levels of excitability in each population. There is evidence that the relative excitability of complex oligosynaptic circuits (late I-wave circuits) as assessed by transcranial magnetic stimulation (TMS) is useful in predicting NIBS response.

Objective: Here we examined whether an additional marker of cortical excitability, MEP amplitude variability, could provide additional insights into response variability following application of the continuous theta burst stimulation (cTBS) NIBS protocol. Additionally we investigated whether I-wave recruitment was associated with MEP variability.

Methods: Thirty-four healthy subjects (15 male, aged 18-35 years) participated in two experiments. Experiment 1 investigated baseline MEP variability and cTBS response. Experiment 2 determined if I-wave recruitment was associated with MEP variability.

Results: Data show that both baseline MEP variability and late I-wave recruitment are associated with cTBS response, but were independent of each other. Combined together, these variables predict 31% of the variability in cTBS response.

Conclusions: This study provides insight into the physiological mechanisms underpinning NIBS plasticity responses and may facilitate development of more reliable NIBS protocols.

Key Words: Transcranial magnetic stimulation, Theta burst stimulation, Motor evoked potential, Variability, Motor cortex

Introduction

Non-invasive brain stimulation (NIBS) can induce neuroplasticity in the human cortex that has similar characteristics to activity-dependent long-term potentiation (LTP) and long-term depression (LTD) [1,2]. NIBS-induced neuroplasticity outlasts the stimulation [3-5], is bi-directional based on pattern of stimulation [3-5], and is abolished following administration of NMDA antagonists [6]. Importantly, there are behavioural effects following NIBS. For example, inhibitory NIBS protocols applied to the motor cortex (M1) can degrade motor control [7], and facilitatory NIBS can increase the rate of learning on a ballistic motor task [8]. Inducing LTP- or LTD-like plasticity in the human motor cortex and modifying behaviour would be of clinical value for a range of neurological conditions. However, at present the effects of various NIBS protocols are highly variable [9-14]. This response variability limits the behavioural and clinical usefulness of NIBS.

Several factors contribute to NIBS response variability including age, time of day, attention, history of physical activity and genetics [15]. Additionally, inter-individual differences in the cortical network activated by NIBS can influence the response. The descending volley evoked by single pulse transcranial magnetic stimulation (TMS) consists of a series of components. The earliest of these probably reflects direct activation of the corticospinal output cells and is known as the “direct (D)-wave”. The later components have been termed “indirect (I)-waves”. The early I-waves likely reflect monosynaptic input to corticospinal neurons from layer II/III interneurons, whereas more complex oligosynaptic circuits generate the late I-waves [16]. Individuals in whom TMS is more likely to recruit late I-waves respond more strongly to several forms of NIBS [13,17]. The reason for this is unclear but Hamada and colleagues (2013) suggested that the late I-wave generating circuit might be

more sensitive to NIBS than the early I-wave generating circuit. Here, we were interested in examining whether variability in baseline motor evoked potential (MEP) amplitude could serve as an indicator of likely neuroplastic response to a NIBS protocol (continuous theta burst stimulation: cTBS). Our reasoning was as follows: the amplitude of MEPs evoked in individuals in whom TMS was more likely to recruit late I-wave generating circuits would be more variable due to the involvement of more complex networks than in individuals in which TMS was more likely to recruit less complex early I-wave generating circuitry [18]. To explore mechanisms underpinning MEP variability we used multiple TMS coil orientations to examine I-wave recruitment [13]. In summary, the aims of this study were to (1) investigate the relationship between MEP variability and NIBS (cTBS) response, and (2) explore whether I-wave recruitment profile might influence MEP variability.

Material and Methods

Subjects

A total of 34 healthy subjects (15 male) aged 18-35 years (mean age, 25.0 ± 4.9 years) participated in two experimental sessions. Potential subjects with contraindications for TMS, including metallic implants, a history of seizures and medications known to alter CNS excitability were excluded [19]. Ethical approval was provided by the University of Adelaide Human Research Ethics Committee, and all participants provided written informed consent in accordance with the Declaration of Helsinki.

Electromyography

For both experimental sessions, surface EMG was recorded from the right first dorsal interosseous (FDI) muscle using Ag/AgCl electrodes (Ambu, Ballerup, Denmark) with

electrodes positioned in a belly-tendon montage. Signals were sampled at 5 kHz (Cambridge Electronic Design 1401, Cambridge, UK), amplified with a gain of 1000, band-pass filtered (20-1000 Hz) (Cambridge Electronic Design 1902 amplifier, Cambridge, UK) and stored for offline analysis (Signal v4.09, Cambridge Electronic Design, Cambridge, UK).

Transcranial Magnetic Stimulation

Single-pulse TMS was applied with a monophasic waveform using a figure-of-eight coil (external wing diameter 90mm) connected to a Magstim 200 stimulator (Magstim Company, Dyfed, UK). For Experiment 1, the coil was positioned tangentially over the left M1, with the handle rotated posterior-laterally approximately 45° to the sagittal plane to induce a posterior-anterior current flow across the hand M1. The optimal coil position for evoking a MEP in the right FDI muscle at rest was located and marked on the scalp using a water-soluble felt tip marker. RMT for the right FDI was defined as the minimum stimulus intensity required to evoke an MEP with peak-to-peak amplitude ≥50μV in at least five out of 10 consecutive trials in the relaxed FDI.

For Experiment 2, MEPs were evoked using three different directions of current flow across the left M1 hand area. Previous studies have demonstrated that by modifying the direction of current flow it is possible to target specific populations of neurons using single pulse TMS. Posterior-anterior (PA) currents preferentially recruit early I-waves, anterior-posterior (AP) currents recruit late I-waves and lateral-medial (LM) currents at high stimulus intensities evoke D-waves [18,20-23]. In this experiment we evoked MEPs using three different coil orientations to preferentially induce current flow across the hand M1 to investigate late I-waves, early I-waves and D-waves. PA currents were elicited with the handle of the figure-

of-eight coil rotated posterior-laterally, approximately 45° to the sagittal plane. AP currents were elicited by placing the coil 180° to the PA current coil position. LM currents were elicited with the handle rotated laterally to a position 90° to the midsagittal line. Active motor threshold (AMT) was measured for PA, AP and LM currents while stimulating at the hotspot determined by PA currents, as previous studies have determined that direction of the current does not influence the position of the hotspot [22,24]. AMT was defined as the lowest intensity to evoke an MEP of ≥ 200μV in at least five out of 10 consecutive trials whilst maintaining a 5-10% maximal voluntary contraction of the FDI. Muscle contraction was monitored visually using a digital oscilloscope with participants able to monitor and adjust muscle contraction to maintain the required 5-10% MVC.

Continuous theta burst stimulation

In Experiment 1, an air-cooled figure-of-eight coil connected to a Magstim Super Rapid stimulator (Magstim Company, Dyfed, UK) was used to apply cTBS with a biphasic pulse waveform (current direction PA-AP) to the optimal site for stimulating the right FDI. The cTBS protocol consisted of 600 pulses applied in bursts of three pulses at 50Hz, repeated at 5Hz for a total of 40 seconds [3]. The intensity of stimulation was set to 70% RMT [25,26], assessed prior to cTBS application using the rTMS coil.

Experimental Protocol

For Experiment 1, subjects attended an afternoon experimental session to determine the relationship between baseline MEP variability and the response to cTBS. Subjects were seated in a comfortable chair with their right upper limb in a relaxed position. At baseline, a total of 225 MEPs were evoked over two blocks separated by a short, 2 minute rest interval.

Three stimulation intensities were used to examine whether the relationship between MEP variability and cTBS response was influenced by MEP amplitude; the intensities were 120% RMT, 150% RMT and a stimulus intensity set to produce a 1mV MEP (SI_{1mV}). The 120% RMT and SI_{1mV} intensities were selected as they are commonly used to evoke test MEPs prior to plasticity induction protocols [27-29]. The 150% intensity was used to explore the relationship between baseline MEP amplitude variability and plasticity response at larger mean MEP amplitudes. At baseline, a total of 75 TMS pulses at each of the three intensities were delivered randomly with an inter-stimulus interval of 6 sec ± 10%. Following cTBS, 50 TMS pulses at each of the three intensities were delivered randomly (with an inter-stimulus interval of 6 sec ± 10%) from 0-15 minutes following cTBS, and again at 20-35 minutes following cTBS; therefore, a total of 300 MEPs (100 MEPs for each intensity) were obtained following cTBS (and we grouped these into 5-minute blocks: 0-, 5-, 10-, 20-, 25-, 30-min post cTBS). The same stimulation intensities and inter-stimulus intervals were used at baseline and following cTBS.

Experiment 2 was conducted in the afternoon, >7 days following experiment 1. The purpose of Experiment 2 was to determine if differences between individuals in I-wave recruitment were associated with different levels of MEP variability. Subjects were seated in a comfortable chair with the lateral aspect of the distal phalanx of the right index finger positioned against a force transducer. For both AP and PA coil orientations, 20 MEPs were evoked at 110% AMT with subjects asked to relax their hand every 10 trials to avoid fatigue. For LM coil orientation, 10 MEPs were evoked at 150% AMT or 50% of maximum stimulator output (MSO), whichever was greater. Higher stimulus intensities were used for LM currents to increase the likelihood of evoking a D-wave [21]. For all three coil orientations, MEPs

were evoked with an inter-stimulus interval of 6 sec ± 10%. MEP onset latency for each trial (for all three coil orientations) was determined automatically with a custom made script to avoid assessor bias (Signal v4.09, Cambridge Electronic Design, Cambridge, UK). In each trial, the onset latency was defined as the time point where the rectified EMG signals exceeded an average plus two standard deviations of the pre-stimulus EMG level 100ms prior to the TMS pulse. AP, PA and LM onset latencies were averaged across trials for each subject. Consistent with the study of Hamada and colleagues (2013), the latency difference between LM and AP evoked MEPs was used as a measure of the relative likelihood of recruiting late I-wave input to corticospinal neurons [13].

Data analysis

Normality of data were tested with the Shapiro-Wilk test and where required, logarithmic transformations were performed. Descriptive statistics were used to report experimental variables. To characterise the response to cTBS in Experiment 1, MEP amplitudes were averaged for each stimulus intensity, subject and time point. Trials contaminated with background EMG activity during 100ms prior to the TMS pulse were excluded from the analysis. A repeated measures ANOVA (factor of 'TIME': baseline, T0, T5, T10, T20, T25, T30) was used to investigate the effect of cTBS on absolute MEP amplitude evoked at 120% RMT, 150% RMT and $SI_{1mV.}$ The association between baseline MEP variability (coefficient of variation, CV) and cTBS response (quantified as the grand average of post-cTBS time points normalised to the baseline) was investigated with Pearson correlations for MEPs evoked at 120% RMT, 150% RMT and $SI_{1mV.}$ To investigate whether RMT was associated with baseline MEP variability, we performed Pearson correlations between RMT and MEP variability for

MEPs evoked at 120% RMT, 150% RMT and $SI_{1mV.}$ To investigate whether the distribution of MEP amplitudes changed following cTBS we analysed the skewness and kurtosis of MEPs evoked at 120% RMT and SI_{1mV} before and after cTBS and tested for differences using paired t-tests. For Experiment 2, the association between AP-LM and PA-LM latency differences, and both cTBS response and variability of baseline MEPs was investigated with Pearson correlations for MEPs evoked at 120% RMT, 150% RMT and $SI_{1mV.}$ Since it could be argued that the range of MEP latencies evoked by AP currents is due to variation of MEP amplitudes evoked with this coil orientation, we correlated AP MEP amplitude and AP MEP latency. The significance level was set at $p \leq 0.05$, and SPSS software was used for all statistical analyses (IBM Corp., Released 2011, IBM SPSS Statistics for Windows, Version 20.0, Armonk, NY, USA).

Results

Experiment 1 – Baseline MEP variability and cTBS response

The average RMT was 41.3%MSO (SD 8.3). Baseline neurophysiological measures for each stimulus intensity are reported in Table 1. There was no significant effect of cTBS on absolute MEP amplitude for MEPs evoked at 120% RMT ($p = 0.12$), 150% RMT ($p = 0.15$), or SI_{1mV} ($p = 0.09$) (see figure 1). As there were no significant differences across post-cTBS time points, we calculated a grand average cTBS response value for each intensity: MEP amplitudes were normalised to baseline, and then averaged across all post-cTBS time-points. There were significant correlations between baseline MEP variability and cTBS response for 120% RMT ($r = -0.44$, $p = 0.01$) and SI_{1mV} ($r = -0.37$, $p = 0.03$), but not 150 %RMT ($p = 0.59$) (see figure 2); higher variability in baseline MEP amplitude (at 120%RMT and SI_{1mV}) was associated with a stronger response to cTBS. Although there were significant

associations between the variability and amplitude of MEPs recorded at baseline (120%RMT; r = -0.47, p = 0.01; 150% RMT; r = -0.45, p = 0.01; SI_{1mV}; r = -0.43, p = 0.01), the relationship between baseline MEP variability and cTBS response remained when controlling for baseline MEP amplitude (120%RMT; r = -0.43, p = 0.01; SI_{1mV}; r = -0.35, p = 0.03). There were no significant relationships between RMT and baseline MEP variability for MEPs evoked at all intensities (all p > 0.16). There was no significant difference in distribution of MEP amplitudes from baseline to post cTBS for MEPs evoked at 120% RMT (p = 0.44) or SI_{1mV} (p = 0.42) in both participants with high or low MEP variability (see figure 3).

Experiment 2 – I-wave recruitment and MEP variability

Mean AMT, MEP amplitude and onset latencies for PA, AP and LM coil orientations are reported in table 2. The mean AP-LM latency difference was 3.85±1.25 ms and PA-LM latency difference was 1.82±1.12 ms (see figure 4). There was a significant correlation between AP-LM latency difference and grand average cTBS response for MEPs evoked at 120% RMT (r = -0.37, p = 0.03) (figure 4), but not 150% RMT (p = 0.40) or SI_{1mV} (p = 0.27). There were no significant associations between PA-LM latency difference and cTBS response for MEPs evoked at any stimulation intensity (p > 0.54). There were no significant associations between AP-LM or PA-LM latency difference and baseline MEP variability for MEPs evoked at any intensity (all p > 0.33). There was no association between MEP amplitude evoked by AP currents and AP latency (p = 0.83). Since both MEP variability and late I-wave recruitment appear to be independent, but important, factors associated with the cTBS response measured at 120% RMT we investigated the relationship with a multiple regression. The regression model reached significance (R^2 = 0.31, *p*=0.004), indicating that MEP variability and late I-wave recruitment predict 31% of the variance in cTBS response.

Discussion

In this study we report significant inter-subject variability in the response to cTBS, which is consistent with recent reports [13,30]. Indeed, even though care was taken in controlling factors know to influence cTBS response (e.g. pre-activation and time of day) there was no significant group level cTBS response. While progress has been made in understanding the causes of response variability (for review see Ridding and Ziemann [15]), a large component of this variability remains unexplained. Here, we provide some novel insights into additional factors contributing to cTBS response variability.

Associations between I-wave recruitment, MEP variability, and cTBS response

By using different coil orientations (PA/AP) it is possible to preferentially recruit early and late I-waves. Using this approach, Hamada and colleagues [13]demonstrated a stronger cTBS response in individuals in whom TMS pulses preferentially recruited late I-waves. The current results replicate the findings of Hamada et al. [13], showing that inter-individual differences in late I-wave recruitment is significantly associated with cTBS response. Hamada and colleagues [13]suggested that the significant association between I-wave recruitment and cTBS-induced plasticity could be due to a greater sensitivity of the late I-wave generating circuit than the early I-wave generating circuit to cTBS.

Given the proposed differential sensitivity of the late and early I-wave generating circuits, we examined the relationship between the likelihood of the TMS pulse recruiting late I-waves (with LM-AP latency difference acting as a marker) and MEP variability; we hypothesised that MEPs evoked in individuals in whom TMS was more likely to recruit late I-

wave circuits would be more variable than MEPs in individuals in which TMS was more likely to recruit less complex early I-wave circuitry. However, surprisingly, we found no relationship between I-wave recruitment and MEP variability. This suggests that MEP variability is not highly dependent upon engagement of late I-wave circuits.

While there was no significant association between I-wave recruitment and MEP variability, there was a significant association between MEP variability and cTBS response; greater MEP variability at baseline was associated with a greater cTBS response. This relationship was evident for MEPs evoked by both 120% RMT and SI_{1mV} intensities. One possible explanation for this is that high MEP variability is associated with a wider distribution of MEP amplitudes; for example, in individuals with high variability, TMS might evoke more very large MEPs that are closer to the ceiling of the testable range than in individuals with low variability. This could be important because it has been reported that cTBS is more likely to inhibit near-maximal MEPs [31]. Thus it could be that, on average, individuals with high variability are more likely to respond to cTBS because they have more near-maximal MEPs. If this were the case, then we might expect these large MEPs to be inhibited following cTBS, and hence the distribution of MEP amplitudes would change. However, we show that the distribution of MEPs evoked at 120% RMT and SI_{1mV} intensities did not change following cTBS, irrespective of whether individuals demonstrated high or low baseline variability. There was no relationship between baseline variability in MEPs evoked at an intensity of 150% RMT and cTBS response. We suggest this likely reflects the reduced MEP variability when tested at this high intensity. Together, these results suggest late I-wave recruitment and MEP variability are independently associated with cTBS response. When combined, MEP variability and late I-wave recruitment predicted 31% of the cTBS response variability

in the current study. Given the extensive range of factors that contribute to variability in NIBS response [15], these two factors account for a major component of cTBS response variability.

Similarity to the relationships between movement variability and motor learning

Interestingly, there are some parallels between the current results and several recent reports examining motor learning. Greater task related baseline movement variability predicts faster motor learning [32]. Also, Teo and colleagues [8] reported that facilitatory intermittent theta burst stimulation increased movement variability on a subsequent ballistic motor learning task, and that this increase in variability correlated with learning. Movement variability allows the individual to explore motor command space and identify optimal motor patterns resulting in greater efficiency during learning. While multiple factors are likely to contribute to variability of movement output, movement execution contributes a large proportion of this variability [33]. The corticospinal system plays a key role in movement execution [34] and variability in movement likely reflects both cortical and spinal influences. Therefore, the MEP variability described here may reflect to some degree the variability seen in movements during learning. While the output measures of behavioural (learning) and neurophysiological studies (cTBS response) are clearly quite different, there might be involvement of a common physiological mechanism, namely activity dependent changes in synaptic strength.

When considering these results, it is important to acknowledge some limitations. First, we only studied a population of healthy adults using one common NIBS plasticity-inducing paradigm (cTBS). It is unclear whether these findings are generalizable to wider populations

or alternative NIBS paradigms. Second, we have only investigated one potential contributor to MEP variability. It is likely multiple, interacting factors contribute to MEP variability and further studies should seek to provide greater understanding of contributions to this variability. Third, MEP variability is likely due to both cortical and spinal effects [35-37]. We did not investigate spinal influences and so the association between MEP variability and the cortically generated cTBS response might be over or under estimated. Finally, although we took care to minimise coil movement during data collection, it is possible that random small coil movements may have contributed to the overall MEP variability. However, we consider it unlikely that this contributed to the reported association between variability and cTBS response and, in fact, may have weakened the relationship by introducing noise. The use of stereotactic navigation techniques may strengthen the findings reported in this study.

In summary, we provide evidence that MEP variability is an important influence on the cTBS response in healthy adults. Traditionally considered an unwanted characteristic of stochastic nervous system function driven by multiple intrinsic and extrinsic contributions, MEP variability may in fact be an important physiological characteristic to enhance our understanding of cortical network excitability, motor learning and NIBS response. Our results may suggest avenues for developments that improve the reliability of NIBS, for example by employing behavioural or external priming procedures to increase variability in the excitability of the corticospinal system prior to plasticity induction.

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Table and Figure Legends

Table 1: Baseline neurophysiological measures for each stimulus intensity

RMT, resting motor threshold; MSO, maximum stimulator output; mV, millivolts; CV, coefficient of variation; MEP, motor evoked potential.

Table 2: AMT, MEP amplitude and onset latency for MEPs evoked using PA, AP and LM coil orientations. AMT, active motor threshold; MEP, motor evoked potential; MSO, maximal stimulator output; PA, posterior-anterior current direction; AP, anterior-posterior current direction; LM, lateral-medial current direction.

Figure 1: Group average cTBS response for MEPs evoked at 120% RMT, 150% RMT, and SI_{1mV}. CTBS did not affect MEP amplitude for any stimulation intensity.

Figure 2: Correlation between MEP variability at baseline for MEPs evoked at A) 120% RMT, B) 150% RMT and C) SI_{1mV} and cTBS response averaged across post cTBS time points. Greater MEP variability was associated with a stronger response to cTBS for MEPs evoked at 120% RMT and SI_{1mV} intensities.

Figure 3: Distribution of MEPs evoked at baseline (top) and following cTBS (bottom) for subjects with low variability (left) and high variability (right) for MEPs evoked at SI_{1mV}. MEP amplitude was normalised to the mean baseline amplitude for each subject. There was no change in distribution of MEPs following cTBS suggesting that cTBS does not target specific networks responsible for either large or small MEPs.

Figure 4: PA-LM and AP-LM latency differences for A) individual participants and B) presented as a histogram in 0.5ms bins. The AP-LM latency difference was longer than the PA-LM latency difference. The AP-LM latency difference also appeared more variable across participants compared to the PA-LM latency difference. Figure C) presents the correlation between AP-LM latency difference as a measure of late I-wave efficiency and cTBS response averaged across post cTBS time points for MEPs evoked at 120% RMT. A stronger response to cTBS was associated with a greater AP-LM latency difference.

Tables

Table 1

	Stimulus Intensity		
	120%RMT	150%RMT	SI_{1mV}
Stimulation Intensity (%MSO, mean (SD))	49.7 (9.6)	62.3 (11.8)	50.9 (11.7)
MEP amplitude (mV, mean (SD))	1.48 (0.9)	3.05 (1.5)	1.18 (0.4)
MEP variability (CV, %, mean (SD))	64.4 (20.7)	35.6 (13.3)	66.5 (24.9)

Table 2

	AMT (%MSO)	MEP amplitude (mV)	Latency (ms)
PA	32.7 (7.4)	0.83 (0.41)	22.6 (1.7)
AP	45.1 (10.7)	0.68 (0.38)	24.5 (2.1)
LM	36.1 (8.7)	5.89 (2.41)	20.7 (1.6)

References

[1] Bliss TV, Gardner-Medwin AR. Long-lasting potentiation of synaptic transmission in the dentate area of the unanaestetized rabbit following stimulation of the perforant path. J Physiol 1973;232:357-74.

[2] Dudek SM, Bear MF. Bidirectional long-term modification of synaptic effectiveness in the adult and immature hippocampus. J Neurosci 1993;13:2910-8.

[3] Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron 2005;45:201-6.

[4] Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology 1997;48:1398-403.

[5] Berardelli A, Inghilleri M, Rothwell JC, Romeo S, Currà A, Gilio F et al. Facilitation of muscle evoked responses after repetitive cortical stimulation in man. Exp Brain Res 1998;122:79-84.

[6] Huang Y-Z, Chen R-S, Rothwell JC, Wen H-Y. The after-effect of human theta burst stimulation is NMDA receptor dependent. Clin Neurophysiol 2007;118:1028-32.

[7] Bradnam LV, Stinear CM, Byblow WD. Theta burst stimulation of human primary motor cortex degrades selective muscle activation in the ipsilateral arm. J Neurophysiol 2010;104:2594-602.

[8] Teo JTH, Swayne OBC, Cheeran B, Greenwood RJ, Rothwell JC. Human theta burst stimulation enhances subsequent motor learning and increases performance variability. Cereb Cortex 2011;21:1627-38.

[9] López-Alonso V, Fernández-del-Olmo M, Costantini A, Gonzalez-Henriquez JJ, Cheeran B. Intra-individual variability in the response to anodal transcranial direct current stimulation. Clin Neurophysiol 2015;126:2342-7.

[10] Chew T, Ho KA, Loo CK. Inter- and intra-individual variability in response to transcranial direct current stimulation (tDCS) at varying current intensities. Brain Stimul 2015;8:1130-7.

[11] Müller-Dahlhaus JF, Orekhov Y, Liu Y, Ziemann U. Interindividual variability and age-dependency of motor cortical plasticity induced by paired associative stimulation. Exp Brain Res 2008;187:467-75.

[12] Hinder MR, Goss EL, Fujiyama H, Canty AJ, Garry MI, Rodger J et al. Inter- and intra-individual variability following intermittent theta burst stimulation: Implications for rehabilitation and recovery. Brain Stimul 2014;7:365-71.

[13] Hamada M, Murase N, Hasan A, Balaratnam M, Rothwell JC. The role of interneuron networks in driving human motor cortical plasticity. Cereb Cortex 2013;23:1593-605.

[14] Vallence AM, Kurylowicz L, Ridding MC. A comparison of neuroplastic responses to non-invasive brain stimulation protocols and motor learning in healthy adults. Neurosci Lett 2013;549:151-6.

[15] Ridding MC, Ziemann U. Determinants of the induction of cortical plasticity by non-invasive brain stimulation in healthy subjects. J Physiol (Lond) 2010;588:2291-304.

[16] Di Lazzaro V, Profice P, Ranieri F, Capone F, Dileone M, Oliviero A et al. I-wave origin and modulation. Brain Stimul 2012;5:512-25.

[17] Wiethoff S, Hamada M, Rothwell JC. Variability in response to transcranial direct current stimulation of the motor cortex. Brain Stimul 2014;7:468-75.

[18] Di Lazzaro V, Oliviero A, Saturno E, Pilato F, Insola A, Mazzone P et al. The effect on corticospinal volleys of reversing the direction of current induced in the motor cortex by transcranial magnetic stimulation. Exp Brain Res 2001;138:268-73.

[19] Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Screening questionnaire before TMS: An update. Clin Neurophysiol 2011;122:1686.

[20] Day BL, Dressler D, Maertens de Noordhout A, Marsden CD, Nakashima K, Rothwell JC et al. Electric and magnetic stimulation of human motor cortex: surface EMG and single motor unit responses. J Physiol (Lond) 1989;412:449-73.

[21] Werhahn KJ, Fong JKY, Meyer BU, Priori A, Rothwell JC, Day BL et al. The effect of magnetic coil orientation on the latency of surface EMG and single motor unit responses in the first dorsal interosseous muscle. Electroencephalogr Clin Neurophysiol 1994;93:138-46.
[22] Sakai K, Ugawa Y, Terao Y, Hanajima R, Furubayashi T, Kanazawa I. Preferential activation of different I waves by transcranial magnetic stimulation with a figure-of-eight-shaped coil. Exp Brain Res 1997;113:24-32.
[23] Di Lazzaro V, Restuccia D, Oliviero A, Profice P, Ferrara L, Insola A et al. Effects of voluntary contraction on descending volleys evoked by transcranial stimulation in conscious humans. J Physiol (Lond) 1998;508:625-33.
[24] Arai N, Okabe S, Furubayashi T, Terao Y, Yuasa K, Ugawa Y. Comparison between short train, monophasic and biphasic repetitive transcranial magnetic stimulation (rTMS) of the human motor cortex. Clin Neurophysiol 2005;116:605-13.
[25] Gentner R, Wankerl K, Reinsberger C, Zeller D, Classen J. Depression of human corticospinal excitability induced by magnetic theta-burst stimulation: evidence of rapid polarity-reversing metaplasticity. Cereb Cortex 2008;18:2046-53.
[26] Goldsworthy MR, Müller-Dahlhaus F, Ridding MC, Ziemann U. Inter-subject variability of LTD-like plasticity in human motor cortex: A matter of preceding motor activation. Brain Stimul 2014;7:864-70.
[27] Pitcher JB, Doeltgen SH, Goldsworthy MR, Schneider LA, Vallence A-M, Smith AE et al. A comparison of two methods for estimating 50% of the maximal motor evoked potential. Clin Neurophysiol 2015;126:2337-41.
[28] Goldsworthy MR, Hordacre B, Ridding MC. Minimum number of trials required for within- and between-session reliability of TMS measures of corticospinal excitability. Neuroscience 2016;320:205-9.
[29] Di Lazzaro V, Profice P, Pilato F, Capone F, Ranieri F, Pasqualetti P et al. Motor cortex plasticity predicts recovery in acute stroke. Cereb Cortex 2010;20:1523-8.
[30] Goldsworthy MR, Pitcher JB, Ridding MC. The application of spaced theta burst protocols induces long-lasting neuroplastic changes in the human motor cortex. Eur J Neurosci 2012;35:125-34.
[31] Goldsworthy MR, Vallence AM, Hodyl NA, Semmler JG, Pitcher JB, Ridding MC. Probing changes in corticospinal excitability following theta burst stimulation of the human primary motor cortex. Clin Neurophysiol 2016;127:740-7.
[32] Wu HG, Miyamoto YR, Castro LNG, Olveczky BP, Smith MA. Temporal structure of motor variability is dynamically regulated and predicts motor learning ability. Nat Neurosci 2014;17:312-21.
[33] Van Beers RJ, Haggard P, Wolpert DM. The role of execution noise in movement variability. J Neurophysiol 2004;91:1050-63.
[34] Sanes JN, Donoghue JP. Plasticity and primary motor cortex. Annu Rev Neurosci 2000;23:393-415.
[35] Bergmann TO, Molle M, Schmidt MA, Lindner C, Marshall L, Born J et al. EEG-guided transcranial magnetic stimulation reveals rapid shifts in motor cortical excitability during the human sleep slow oscillation. J Neurosci 2012;32:243-53.
[36] Groppa S, Oliviero A, Eisen A, Quartarone A, Cohen LG, Mall V et al. A practical guide to diagnostic transcranial magnetic stimulation: Report of an IFCN committee. Clin Neurophysiol 2012;123:858-82.
[37] Sauseng P, Klimesch W, Gerloff C, Hummel FC. Spontaneous locally restricted EEG alpha activity determines cortical excitability in the motor cortex. Neuropsychologia 2009;47:284-8.