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A comparison of neuroplastic responses to non-invasive brain stimulation protocols and motor learning in healthy adults.

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Abstract

Non-invasive brain stimulation (NBS) techniques can induce neuroplastic changes similar to those associated with motor learning and there is evidence for the involvement of common mechanisms. Whether there are correlations between the changes induced by NBS and those associated with motor learning remains unclear. We investigated whether there was any relationship between an individual's neuroplastic responses to several different NBS protocols (continuous theta-burst stimulation (cTBS); intermittent theta-burst stimulation (iTBS); facilitatory paired associative stimulation (PAS: inter-stimulus interval 25 ms)) and whether these responses correlated with the neuroplastic response associated with a motor training (MT) task involving repeated fast-as-possible thumb abductions. Changes in motor evoked potential (MEP) amplitude were used to assess the neuroplastic response to each protocol. MEP amplitude decreased significantly following cTBS, however there was no significant change in MEP amplitude following iTBS, PAS or MT. There were no significant correlations between individuals' neuroplastic responses to any of the NBS protocols tested or between individuals' neuroplastic responses to the NBS protocols and motor learning. These results provide no support for an association between individuals' neuroplastic responses to several plasticity-inducing protocols. Although there is evidence for involvement of common mechanisms in the neuroplastic changes induced by NBS and motor learning, the results of this study suggest (1) the mechanisms mediating TBS-, PAS-, and MT-induced plasticity may only partially overlap, and (2) additional factors, including large intra and inter-subject response variability, may make the demonstration of associations between neuroplastic responses to the various protocols difficult.

1. Introduction

The human primary motor cortex (M1) is capable of both rapid, reversible plastic changes and longer-term, more permanent reorganization. The past decade has seen many groups investigate the potential of non-invasive brain stimulation (NBS) techniques to induce functionally-relevant plasticity in M1. The fundamental aim of this research is to develop NBS protocols that induce cortical changes that lead to improved performance of motor tasks, outlasting the period of stimulation, which could be used in therapy.

Current NBS techniques can induce neuroplastic changes similar to those associated with motor learning [1] and, indeed, there is evidence for the involvement of common mechanisms. Motor learning is mediated, at least in part, by changes in synaptic efficacy brought about via long-term potentiation- (LTP) and long-term depression- (LTD) like processes [20, 25, 28]. More recently, compelling evidence has emerged suggesting that the neuroplastic changes in M1 induced by NBS protocols (theta-burst stimulation (TBS) and paired-associative stimulation (PAS)) are also mediated by changes in synaptic efficacy via LTP- and LTD-like mechanisms [1, 12, 29, 32]. Furthermore, bidirectional interactions are evident between NBS-induced neuroplasticity and voluntary movement; TBS affects subsequent voluntary movements [13] and neuroplastic responses to TBS and PAS are influenced by voluntary movement prior to, and during, stimulation [8, 14, 15]. Together, these findings provide evidence for the engagement of similar processes in NBS- and motor learning-induced plasticity.

Here, we investigated whether an individual's neuroplastic responses to different NBS protocols correlate with each other and with their neuroplastic response to motor learning. LTP- and LTD-like plasticity responses in M1 were examined by measuring changes in

corticospinal excitability following motor training (MT), cTBS, iTBS, and PAS in a fully within-subject design. We hypothesised that subjects who responded strongly to one NBS protocol would also respond strongly to the other tested NBS and MT protocols.

1. Materials and methods

2.1 Subjects

Eighteen right-handed subjects (9 females; mean age 23.3 ± 2.7 years) participated in MT, cTBS, and iTBS protocols and 12/18 participated in a PAS protocol. The protocol was in accordance with the Declaration of Helsinki and approved by the University of Adelaide Human Ethics Committee. All subjects gave written informed consent prior to testing and were screened for any conditions that would contraindicate TMS.

All sessions were conducted in the afternoon to minimise time of day influences [26] and sessions were separated by ≥3 days [9, 10]. The order of protocol testing was pseudo-randomized, except for PAS which was conducted last.

2.2 Transcranial Magnetic Stimulation

Electromyographic (EMG) activity was recorded from the relaxed right abductor pollicis brevis (APB) using surface electrodes (belly-tendon configuration). The EMG signal was amplified (x1000; CED 1902 amplifier), band pass filtered (20-1000 Hz) and digitized at a sampling rate of 2 kHz (CED 1401 interface). A Magstim-200 stimulator generated single-pulse stimuli, delivered through a figure-of-eight coil (90 mm) placed tangentially to the scalp with the handle pointing backward, 45° away from the midline. Suprathreshold pulses were delivered over the left M1 to identify the optimal site for consistently evoking MEPs in the relaxed APB and this site was marked on the scalp.

Resting motor threshold (RMT) was determined in each session before and after the protocol tested; RMT was defined as the minimum intensity (as a percentage of maximal stimulator output; MSO) required to elicit MEPs in the relaxed APB ≥ 50 µV in at least 5/10 consecutive trials. The TMS intensity that elicited MEPs of ~1mV (SI_{1mV}) in the relaxed APB was determined at baseline and was used to examine changes in MEP amplitude post-intervention. Blocks of 15 single-pulse TMS trials (inter-trial interval of 7-seconds ±10%), were delivered at baseline and 0, 5, 10, 20, and 30 minutes post-intervention.

2.3 Plasticity-inducing protocols

2.3.1 Motor Training

Subjects' right arm was placed in a plastic cast secured to a board positioned across the chair. The right elbow was flexed at approximately 90° with the forearm in a semipronated position and all fingers fixed within the cast. Movement of the right thumb was not restricted in any direction. An accelerometer was secured onto the distal phalanx of the right thumb to record the acceleration of the thumb movements (abduction-adduction and flexion-extension axes).

The MT task consisted of two blocks of 225 thumb abduction movements, separated by a 5-minute break [16]. Movements were paced by a metronome at a rate of 0.25 Hz (15-minutes per block). Subjects were instructed to abduct their thumb as quickly as possible after each tone and then return their thumb to the neutral rest position. Throughout the training task, peak acceleration of each abduction movement was presented on a screen in front of the participant and verbal feedback was provided to encourage optimal performance. This motor training task has been employed in numerous other studies and induces robust motor learning in which M1 has an important role [16, 19, 27].

2.3.2   *Theta Burst Stimulation*

TBS was delivered using a Double-Cooled-Coil-System coil (70 mm, Magstim). Short bursts of three pulses were delivered at 50 Hz every 200 ms: for cTBS, bursts of stimuli were applied continuously for 40-seconds; for iTBS, 2-second bursts of stimuli were applied every 10-seconds for 190-seconds [13]. TBS intensity was set to 80% of active motor threshold (AMT); AMT was defined as the minimum intensity required to elicit a MEP in APB >200 μV in at least 5/10 consecutive trials when performing a low-level voluntary contraction of APB (10% maximal voluntary contraction). AMT was assessed following the determination of the optimal site for stimulation but prior to the determination of SI_{1mV}.

2.4 Paired Associative Stimulation (PAS)

PAS consisted of electrical stimulation applied to the right median nerve, paired with single TMS pulses applied to the optimal scalp site for stimulation of right APB. Bipolar electrodes for nerve stimulation were placed immediately proximal to the wrist crease with 30 mm between anode and cathode (cathode proximal). Electrical stimuli were 100 μs in duration. Sensory perceptual threshold was determined in each experimental session by increasing electrical stimulation in 1 mA increments until subjects reliably reported feeling the stimulus. Peripheral nerve stimulus intensity was 300% of sensory perceptual threshold and TMS intensity was SI_{1mV}. Peripheral nerve stimulation preceded TMS by 25 ms, an inter-stimulus interval shown to induce an LTP-like increase in MEP amplitude [30]. We used a shortened PAS protocol consisting of 225 pairs of stimuli delivered at 0.25 Hz (total time 15-minutes) [21]. Subjects received regular encouragement to keep their attention focused on the peripheral stimulation throughout the protocol.

2.5 Data Analysis

Individual MEP trials were excluded if EMG activity was present in the 100 ms immediately prior to TMS. The peak-to-peak MEP amplitude (mV) was measured for each trial. Assumption testing performed prior to analyses showed no assumptions were violated and data were normally distributed. One-way repeated-measures analysis of variance (ANOVA) was used to test for differences in baseline MEP amplitude, RMT, and SI_{1mV}. A paired-samples *t*-test was used to test for a difference in baseline AMT (AMT was obtained for cTBS and iTBS only).

Paired-samples *t*-tests were used to test for differences between RMT and AMT measured at baseline and again immediately after each of the protocols (AMT: cTBS, iTBS only). One-way repeated-measures ANOVA was used to test for differences in mean MEP amplitude across time for each protocol. For the MT protocol, peak acceleration of the initial abduction movement after the response tone was calculated for each trial (m/s^2). Trials within each MT block (total 225 trials) were grouped into blocks of 25 trials (i.e. nine blocks). A two-way repeated measures ANOVA was performed to test for changes in acceleration *across* the two major training blocks (two blocks of 225 trials) and *within* the two major training blocks (nine blocks of 25 trials). Two-tailed tests were used for all analyses. The coefficient of variation was calculated from mean MEP amplitude data at each time point post-intervention for each protocol (minimum and maximum values calculated at any single post-intervention time point are reported in Fig 1). Figures show standard error of the mean (SEM).

Correlational analyses were performed to examine associations between each subject's mean post-intervention MEP response (mean of all post-intervention measures: 0, 5, 10, 20, and 30-minutes post-intervention normalised to baseline MEP) following each of the protocols [10,

11]. Given the inter-subject variability in the magnitude and time at which the maximal response to NBS paradigms is seen, we performed further correlational analyses using the following response quantification variables: (1) each subject's maximal MEP response (at any time point post-intervention); (2) each subject's MEP response at 0, 5, and 10 minutes post-intervention; (3) each subject's *mean* MEP response from 0-5 minutes post-intervention and 0-10 minutes post-intervention.

3 Results

3.1 Resting motor thresholds and stimulus intensities

There were no significant differences in mean baseline RMT, AMT, and SI_{1mV} across the sessions testing the different protocols. Repeated-measures ANOVAs showed no main effect of PROTOCOL for RMT ($F_{(3,33)}=2.14$, $P>.05$), SI_{1mV} ($F_{(3,33)}=1.48$, $P>.05$), or baseline MEP amplitude ($F_{(3,33)}=2.36$, $P>.05$) and a paired-samples t-test showed no significant difference between AMT (cTBS and iTBS: $t_{(17)}=0.68$, $P>.05$).

3.2 Motor Training

Figure 1 shows mean peak acceleration of thumb abduction movements with MT and mean MEP amplitude following MT, cTBS, iTBS, and PAS. The peak acceleration of thumb abductions increased with MT, both *across* the two major training blocks ($F_{(1,17)}=22.11$, $P<.05$) and *within* the two major training blocks ($F_{(8,136)}=26.88$, $P<.05$). Furthermore, there was a significant interaction between these factors ($F_{(8,136)}=2.96$, $P<.05$) due to a greater increase in acceleration in the first than the second major training block (Fig. 1A). There was no difference between RMT measured at baseline and RMT measured immediately following MT ($t_{(17)}=0.27$, $P>.05$). Following MT, there was a small increase in MEP amplitude that failed to reach statistical significance ($F_{(5,85)}=1.78$, $P>.05$: Fig. 1B). Thirteen out of 18

subjects showed a numerical increase in MEP amplitude immediately following MT (increases ranging from 1-251%; mean increase 64%) and 14/18 subjects showed a numerical increase in MEP amplitude 5-minutes post-MT (increases ranging from 3-202%; mean increase 59%).

3.3 Theta-Burst Stimulation

The mean TMS intensity was 33% for cTBS and 32% for iTBS. There was no significant difference in RMT at baseline and immediately following TBS (cTBS: $t_{(17)}=0.62$, $P>.05$; iTBS: $t_{(17)}=1.46$, $P>.05$).

A repeated measures ANOVA showed a significant main effect of TIME for cTBS ($F_{(5,85)}=3.83$ $P<.05$). Paired-sample t-tests showed MEP amplitude was significantly decreased immediately post-cTBS ($t_{(17)}=4.25$, $P<.01$) and 5-minutes post-cTBS ($t_{(17)}=3.11$, $P<.01$), decreases of 28% and 18% respectively (Fig. 1C). Thirteen out of the 18 subjects showed a numerical decrease in MEP amplitude immediately following cTBS (decreases ranging from 19-76%; mean decrease 42%) and 15/18 subjects showed a numerical decrease in MEP amplitude 5-minutes post-cTBS (decreases ranging from 4-74%; mean decrease 27%).

Following iTBS, there was no significant change in mean MEP amplitude (Fig. 1D). A repeated measures ANOVA showed no significant main effect of TIME ($F_{(5,85)}=0.88$, $P>.05$). Eight out of 18 subjects showed a numerical increase in MEP amplitude 10-minutes post-iTBS (increases ranging from 4-200%; mean increase 62%).

3.4 PAS

The mean TMS intensity for PAS was 57%. There was no significant difference in RMT at baseline and immediately following PAS ($t_{(11)}$=0.90, P>.05). Following PAS, MEP amplitude increased numerically but a repeated-measures ANOVA showed no significant main effect of TIME ($F_{(5,55)}$=1.29, P>.05; Fig. 1E). Nine out of 12 subjects showed a numerical increase in MEP amplitude 5-minutes post-PAS (increases ranging from 13-361%; mean increase 78%).

3.5 Relationship between plasticity responses

The mean MEP response post-intervention for each protocol was used to examine potential relationships between the neuroplastic responses of individuals across the protocols. Correlational analyses showed no significant relationships between subject's mean neuroplastic responses for any of the protocols tested (Fig. 2). The results of further correlational analyses showed no significant relationships between each subject's (1) maximal MEP response, (2) MEP response at 0, 5, and 10 minutes post-intervention and (3) *mean* MEP response from 0-5 and 0-10 minutes post-intervention.

4 Discussion

The main finding reported here is that there was no association between an individual's neuroplastic responses to a variety of commonly employed NBS protocols and their neuroplastic response to a MT task. Although there is evidence for involvement of common mechanisms in NBS- and MT-induced neuroplasticity, the results of this study suggest that the mechanisms mediating TBS-, PAS-, and MT-induced plasticity may only partially overlap. Furthermore, additional factors, including large intra- and inter-subject response variability, may make the demonstration of associations in the response to these interventions difficult.

Previous studies have reported that TBS and PAS can bidirectionally modulate cortical excitability [13, 30]. In the present study we report a statistically significant decrease in MEP amplitude following cTBS, but non-significant changes in MEP amplitude following iTBS and PAS. These non-significant group responses to some NBS protocols are not entirely surprising in light of a number of recent reports highlighting the large variability in response to NBS paradigms [7, 21, 26, 31]. Indeed, a recent study showed, in 52 subjects, that on average there was no significant group response to either cTBS or iTBS [10]. These authors identified subgroups within the population ("responders" and "non-responders") and provided physiological data which predicted the likelihood that subjects would fall into these groups [10]. In this large sample, the overall response rate was ~50% for both iTBS and cTBS. In light of this result, it is not clear why MEP amplitude was significantly decreased following cTBS but not significantly facilitated following iTBS in the current study. One possible explanation is smaller variability following cTBS than iTBS; previous studies have shown smaller SEM following cTBS than iTBS [2, 13] and in the current study, the coefficient of variation was smaller for cTBS than iTBS (Fig. 1). Large response variability has also been reported in the PAS literature with MEP amplitude increases ranging from 32% [7] to 79% [23] and response rates as low as 50% [31]. In the current study, we report a (non-significant) 50% increase in MEP amplitude following PAS and a response rate of 67%, a result that falls well within the range of PAS-induced MEP facilitation reported by others. Therefore, overall the response to cTBS, iTBS, and PAS reported here is similar to other reports in the literature. The absence of significant changes in corticospinal excitability following iTBS and PAS is likely due to large inter-subject response variability [10, 24]. Several determinants of inter-subject response variability have been identified, such as age, exercise history, and genetics [24]. Although many studies do not report NBS-induced response characteristics of their sample, the increasing presence of 'non-responders' in the

NBS literature, together with the response rates of the present study, highlights the importance of understanding inter-subject response variability following NBS protocols. It is worth noting that MT appears the most effective method for increasing corticospinal excitability. It is plausible that the involvement of volition, preparation, and execution in MT but not NBS protocols contributes to the greater facilitatory effect induced by MT than NBS.

Here we showed that an individual's neuroplastic response to one NBS protocol does not correlate with their neuroplastic response to another NBS protocol (at least the protocols examined here). Given the proposed involvement of similar mechanisms in NBS-induced neuroplastic responses, this finding might appear unexpected, however, there are at least two potential explanations. First, it is plausible that the mechanisms that mediate plasticity induced by different NBS protocols only partially overlap. There is good evidence to suggest that cTBS-, iTBS-, and PAS-induced neuroplastic responses are all mediated by changes in synaptic efficacy via LTP-/LTD-like mechanisms: all induce excitability changes that outlast the stimulation period, are reversible, and determined by the temporal pattern of stimulation [13, 29, 32]. Furthermore, both TBS- and PAS-induced effects are N-methyl-D-aspartate receptor (NMDAR) dependent [12, 29]. Despite this, recent pharmacological evidence has shown that the blockade of D2 dopaminergic receptors abolished TBS-induced effects but facilitated PAS-induced effects [18, 22], suggesting that the mechanisms mediating TBS- and PAS-induced plasticity are partially distinct. Further, there is evidence to suggest that neuroplastic responses to different NBS protocols might be due to activation of different populations of synapses [6]. Indeed, Di Lazzaro and colleagues have shown that while PAS and iTBS act primarily on cortical circuits generating late I-waves [3, 4], cTBS acts primarily on cortical circuits generating I1 [5, 6]. Li Voti and colleagues [17] examined the relationship between neuroplastic responses to different NBS protocols within a group of

individuals and showed a positive relationship between the neuroplastic responses to 5 Hz repetitive TMS (rTMS) and iTBS. This suggests that 5Hz rTMS and iTBS engage common mechanisms important for short-term plasticity [17]. Relationships between multiple NBS protocols thought to be mediated by LTP-like mechanisms, however, were not examined. Here, we were unable to demonstrate a relationship between NBS-induced plasticity and that associated with performance of a simple motor learning task. It remains unknown whether associations exist between NBS-induced plasticity and other types of learning.

The absence of correlations between neuroplastic responses to the different protocols tested here could also be due, in part, to response variability. Indeed, a recent study demonstrated large variability when comparing the effects of six NBS protocols [2]. The effect of inter-subject variability on responses to NBS protocols at the group level has been discussed above. Response variability, however, is also high within individuals: Sale and colleagues [26] examined intra-subject variability with repeated PAS sessions and found no significant relationship between individual's neuroplastic responses obtained in separate sessions. Determinants of inter-subject variability are also likely to contribute to the variability observed in individuals across sessions. To determine whether true relationships exist between responses to different NBS protocols, more intra-subject variability data are necessary. It is worth noting the possibility that the absence of relationships between neuroplastic responses to the different protocols is because they do, in fact, induce plasticity via different mechanisms. We believe this explanation to be unlikely, however, given the compelling evidence that all protocols tested here are mediated by changes in synaptic efficacy via LTP- and LTD-like mechanisms [1, 12, 20, 25, 28, 29, 32].

Conclusions

Here we provide evidence that an individual's neuroplastic response to one NBS protocol is a poor predictor of their response to an alternative NBS protocol or a simple motor learning protocol. While other studies have provided evidence for the involvement of common mechanisms in the plasticity responses to the different tested NBS and motor learning protocols, the current results suggest that, if this is true, it is likely that the mechanisms only partially overlap. This, together with the large intra- and inter-subject response variability evident following NBS protocols, may contribute to the difficulty in identifying relationships between neuroplastic responses to NBS protocols and MT within individuals. This finding highlights the fact that the mechanisms mediating plasticity induced by various NBS protocols are not fully understood.

Acknowledgements

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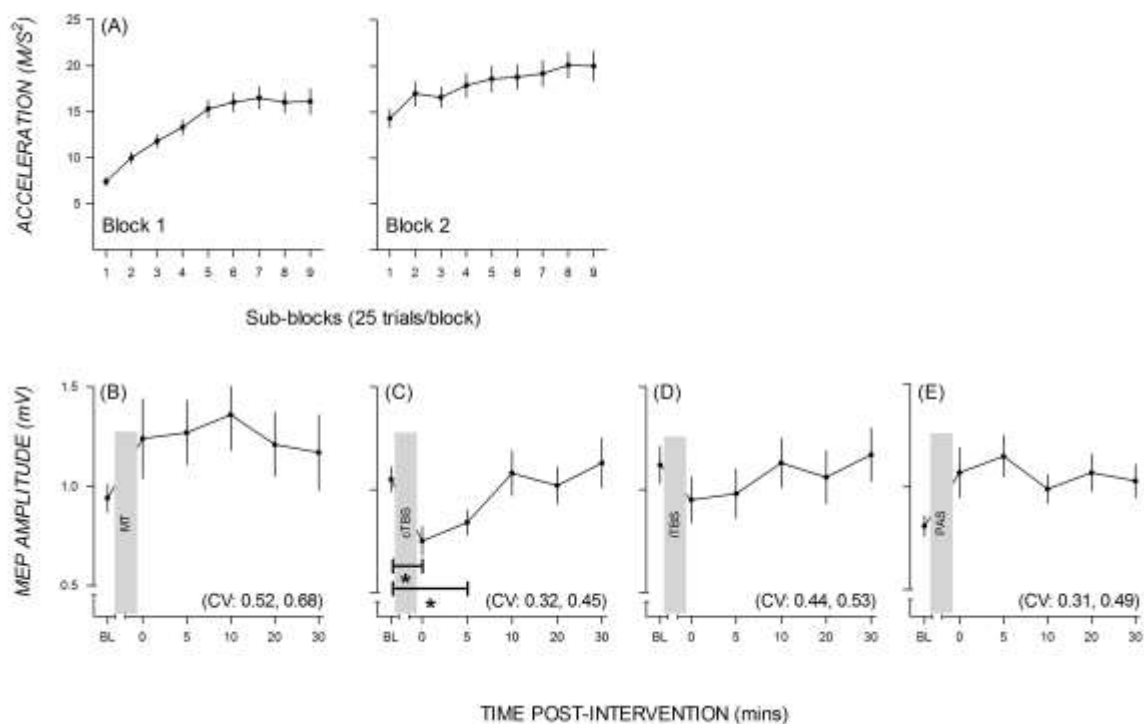
Fig. 1. Mean peak acceleration and mean MEP amplitude following MT, cTBS, iTBS, and PAS. Peak acceleration increased across training blocks (A). A numerical but non-significant increase in MEP amplitude was observed immediately following MT (B) and PAS (E). MEP amplitude decreased immediately post-cTBS, returning to baseline levels 10-minutes post-cTBS (C). MEP amplitude showed no systematic change following iTBS (D). Error bars show SEM. Minimum and maximum coefficient of variation (CV) values calculated at any single post-intervention time point are presented for each protocol.
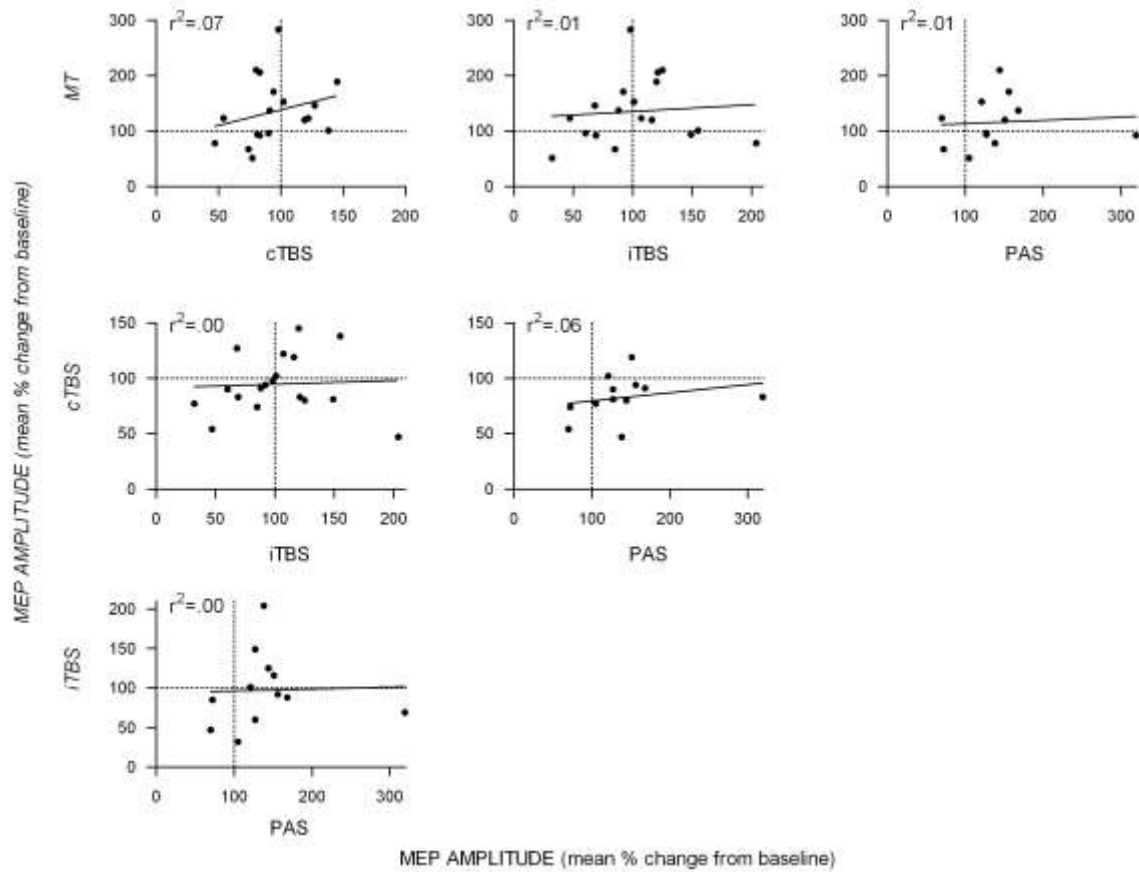
Fig. 2. Scatter diagrams showing relationships between mean MEP changes following each of the different NBS protocols.