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Inter-individual Variability in Response to Non-invasive Brain Stimulation Paradigms

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ABSTRACT

Background: Non-invasive Brain Stimulation (NIBS) paradigms are unique in their ability to safely modulate cortical plasticity for experimental or therapeutic applications. However, increasingly, there is concern regarding inter-individual variability in the efficacy and reliability of these paradigms.
Hypothesis: Inter-individual variability in response to NIBS paradigms would be better explained if a multimodal distribution was assumed.
Methods: In three different sessions for each subject ($n = 56$), we studied the Paired Associative Stimulation (PAS_{25}), Anodal transcranial DC stimulation (AtDCS) and intermittent theta burst stimulation (iTBS) protocols. We applied cluster analysis to detect distinct patterns of response between individuals. Furthermore, we tested whether baseline TMS measures (such as short intracortical inhibition (SICI), resting motor threshold (RMT)) or factors such as time of day could predict each individual's response pattern.
Results: All three paradigms show similar efficacy over the first hour post stimulation – there is no significant effect on excitatory or inhibitory circuits for the whole sample, and AtDCS fares no better than iTBS or PAS_{25}. Cluster analysis reveals a bimodal response pattern – but only 39%, 45% and 43% of subjects responded as expected to PAS_{25}, AtDCS, and iTBS respectively. Pre-stimulation SICI accounted for 10% of the variability in response to PAS_{25}, but no other baseline measures were predictive of response. Finally, we report implications for sample size calculation and the remarkable effect of sample enrichment.
Conclusion: The implications of the high rate of 'dose-failure' for experimental and therapeutic applications of NIBS lead us to conclude that addressing inter-individual variability is a key area of concern for the field.

Introduction

Non-invasive brain stimulation (NIBS) paradigms remain the principal tool to probe and modulate cortical plasticity in the awake human cortex. The effects of NIBS manifests as an increase or decrease in cortical excitability, as measured by the change in amplitude of motor evoked potentials (MEPs), that outlasts the period of stimulation [1–3]. Moreover, NIBS-induced changes in cortical excitability may be sub-served by mechanisms similar to those of NMDA receptor (NMDAR) dependent long-term potentiation (LTP) or long-term depression (LTD), the synaptic currency by learning occurs and memory is encoded [4–6]. This characteristic has underpinned the application of NIBS as a therapeutic adjunct, for example in rehabilitation after neurological diseases such as stroke [7–9].

As a result this broad utility, there has been a proliferation the number of NIBS protocols and proposed applications of each protocol. The most established protocols to increase cortical excitability (by recent citation records) are excitatory paired associative stimulation (PAS) [10], anodal transcranial direct current stimulation (AtDCS) [3] and intermittent theta burst stimulation (iTBS) [11].

Despite the widespread adoption of the NIBS protocols, there appears to be little consensus (or data) regarding the relative

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merits of each protocol with regards to efficacy (in terms of the magnitude or duration of the aftereffects) [12–14]. Recently, studies have also questioned the reliability (percentage of subjects that respond as expected) of PAS and TBS when analyzed with an 'intention to treat'-like approach (i.e. where the study sample was not enriched by omitting subjects that did not show the expected response), and reported significant inter-individual variability in the response for these paradigms [15,16]. To date, there are no studies reporting a similar lack of efficacy or significant inter-individual variability in the response to tDCS. However, knowledge of the efficacy, time course of effects and reliability (or failure-rate) for each individual NIBS protocol is crucial for the sample size calculation, choice of NIBS paradigm, design and analysis of experiments.

In this study we compared the efficacy and reliability of the three most established excitatory NIBS protocols (PAS_{25}, AtDCS and iTBS) on excitatory and inhibitory intracortical networks, in the same cohort of 56 subjects. We hypothesized that inter-subject variability could be explained if the response to NIBS was not unimodal, and therefore cluster into distinct populations. If distinct patterns of response were found, we wished to test if baseline TMS measures, change in inhibitory interneuronal activity or response to another NIBS paradigm could predict the pattern of MEP amplitude response for each individual.

Methods and materials

Subjects

The experiments were approved by the Ethics Committee of University of A Coruña. A total of 56 Caucasian subjects (6 women; 53 right-handed), aged between 19 and 24 years (mean age ± SD: 20.52 ± 1.52) were recruited for this study after giving written informed consent. Subjects were screened for contraindications to TMS [17] (no neurological (including a past medical history of head injury or seizures), psychiatric or other significant medical problems). Each subject participated in all three stimulation protocols.

General procedure

The order of stimulation sessions (for each protocol) was counterbalanced (to avoid an ordinal effect) and sessions for each subject were at least one week apart (to avoid cumulative effects). Each individual subject took part in all three sessions at the same time of day. 36% of the subjects were tested in the morning.

EMG recordings

Electromyographic (EMG) traces were recorded via Ag–AgCl, 9 mm diameter surface cup electrodes, from the right first dorsal interosseous (FDI) muscle. Signals were filtered (30 Hz–2 kHz) with a sampling rate of 5 kHz and amplified with a Digitimer D360 amplifier (Digitimer Ltd., Welwyn Garden City, Hertfordshire, UK), and then recorded using SIGNAL software (Cambridge Electronic Devices, Cambridge, UK).

TMS procedure

TMS were delivered through a figure-of-eight coil with outer diameter of 70 mm (Magstim Co., Whitland, Dyfeld, UK) over the left motor cortex. The coil was held with the handle pointing backwards and laterally to evoke an anteriorly directed current in the brain, and was optimally positioned to obtain MEPs in the contralateral FDI. Single and paired pulses were delivered from a monophasic Magstim BiStim.

For all three protocols, baseline and outcome data was collected in an identical fashion (see Fig. 1). For all the protocols, we first localized the "hotspot" (defined as the point on the scalp at which single pulse TMS elicited MEPs of maximal amplitude from the right FDI) and established the resting motor threshold (RMT) (minimum stimulation intensity over the motor hotspot, which elicit an MEP of no less than 50 μV in 5 of 10 trials in the relaxed FDI) and active motor threshold (AMT) (intensity necessary to evoke a 200 μV MEP while subjects maintained approximately 10% contraction of the FDI). Active motor thresholds were obtained with both the BiStim and Super Rapid Magstim packages in the case of iTBS protocol (AMT and AMT_r, respectively, and in this order).

For the baseline, we recorded 20 MEPs (at SI_{1mV}) and SICI measures. After each protocol, 12-MEPs amplitude (inter-trial interval 5 s, vary 10%) was measured at 5-min intervals for 60 min. Two blocks of SICI (10 test stimulus (TS) and 10 conditioned stimulus (CS) each, randomized) were recorded at minute 6 and minute 46 post-stimulation.

SICI was measured using the technique described by Kujirai et al. (1993) [18] – a subthreshold conditioning stimulus at the 80% of AMT [19] precedes a TS by 2 ms [20]. The mean peak-to-peak amplitude of the conditioned MEP was expressed as a percentage of the mean peak-to-peak amplitude of the unconditioned MEP.

Paired associative stimulation (PAS_{25})

PAS consisted on 200 electrical stimuli (at 300% of the perceptual threshold (PT)) over ulnar nerve at the right wrist, paired with TMS pulses (interstimulus interval of 25 ms) over the left hemisphere FDI hotspot at a rate of 0.25 Hz (total protocol duration approximately 13 min). Subjects were asked to count the number of stimuli given to ensure their attention did not vary.

PAS protocols commonly pair ADM and ulnar nerve or APB and median nerve. We opted to use a less frequently employed PAS protocol, pairing FDI and ulnar nerve, in order to record the FDI muscle across all three NIBS protocols. Although the ulnar nerve innervates the FDI, the ulnar nerve does not supply the cutaneous area over FDI. However, several studies have reported that this protocol induces significant changes in MEP amplitude [12,21]. We acknowledge this may impact the direct comparison with previous studies and interpretation of PAS_{25} protocol results as no direct comparison has been made between these PAS protocol variants.

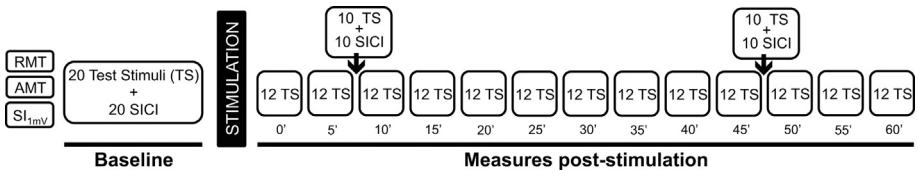

Figure 1. Common Protocol for each NIBS session. Resting Motor Threshold (RMT), Active Motor Threshold (AMT), Stimulus intensity to elicit a 1 mV (SI_{1mV}) peak to peak amplitude motor evoked potential (MEP) were recorded. 20 Baseline MEP's (at SI_{1mV}) and SICI measures were recorded. After each protocol was delivered, MEP amplitude was measured at 5-min intervals for 60 min. Two blocks of SICI were recorded at minute 6 and minute 46 post-stimulation.