Brain Stimulation 10 (2017) 588–595

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Variability in neural excitability and plasticity induction in the human cortex: A brain stimulation study

Brenton Hordacre [a], Mitchell R. Goldsworthy [a, b], Ann-Maree Vallence [c], Sam Darvishi [d], Bahar Moezzi [e], Masashi Hamada [f], John C. Rothwell [g], Michael C. Ridding [a, *]

[a] The Robinson Research Institute, School of Medicine, The University of Adelaide, Adelaide 5005, Australia
[b] Discipline of Psychiatry, School of Medicine, The University of Adelaide, Adelaide, Australia
[c] School of Psychology and Exercise Science, Murdoch University, Murdoch 6150, Australia
[d] School of Electrical and Electronic Engineering, The University of Adelaide, Adelaide 5005, Australia
[e] Computational and Theoretical Neuroscience Laboratory, School of Information Technology and Mathematical Sciences, University of South Australia, Mawson Lakes 5095, Australia
[f] Department of Neurology, Graduate School of Medicine, University of Tokyo, Tokyo 113-8655, Japan
[g] Sobell Department of Motor Neuroscience and Movement Disorders, UCL Institute of Neurology, Queen Square, London WC1N 3BG, United Kingdom

ARTICLE INFO

Article history:
Received 1 August 2016
Received in revised form
9 November 2016
Accepted 3 December 2016
Available online 9 December 2016

Keywords:
Transcranial magnetic stimulation
Theta burst stimulation
Motor evoked potential
Variability
Motor cortex

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; 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.

1. 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

* Corresponding author. The Robinson Research Institute, School of Medicine, The University of Adelaide, 77 King William St, North Adelaide, 5006, Australia.
E-mail address: michael.ridding@adelaide.edu.au (M.C. Ridding).

http://dx.doi.org/10.1016/j.brs.2016.12.001
1935-861X/

[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 whom 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.

2. Material and methods

2.1. Subjects

A total of 34 healthy subjects (15 male) aged 18–35 years (mean age, 25.0 ± 4.9 years) participated in two experiments. 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.

2.2. Electromyography

For both experiments, 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).

2.3. Transcranial magnetic stimulation

Single-pulse TMS was applied with a monophasic waveform using a figure-of-eight coil (external wing diameter 90 mm) 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. Rest motor threshold (RMT) for the right FDI was defined as the minimum stimulus intensity required to evoke an MEP with peak-to-peak amplitude ≥50 μV 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 ≥200 μV 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.

2.4. 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 50 Hz, repeated at 5 Hz for a total of 40 s [3]. The intensity of stimulation was set to 70% RMT [25,26], assessed prior to cTBS application using the rTMS coil.

2.5. 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 min 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 1 mV 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 s ± 10%. Following cTBS, 50 TMS pulses at each of the three intensities were delivered randomly (with an inter-stimulus interval of 6 s ± 10%) from 0 to 15 min following cTBS, and again at 20–35 min following cTBS; therefore, a total of 300 MEPs (100 MEPs for each intensity) were obtained following cTBS (and we grouped these into 5-min 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.