Clinical Neurophysiology 118 (2007) 1815–1823

www.elsevier.com/locate/clinph

Pattern-specific role of the current orientation used to deliver Theta Burst Stimulation [☆],[☆☆]

P. Talelli [*], B.J. Cheeran, J.T.H. Teo, J.C. Rothwell

Institute of Neurology, University College London (UCL), UK

Accepted 11 May 2007

Abstract

Objective: To evaluate the role of current direction on the after-effects of Theta Burst Stimulation (TBS) delivered with a biphasic Magstim 200^2 stimulator.

Methods: Inhibitory (cTBS) and excitatory TBS (iTBS) were delivered over the motor cortex of healthy individuals using reversed and standard current orientations (initial current in the antero-posterior direction) at 80% and 100% of their respective active motor thresholds (AMT). The after-effects on the MEP amplitude were measured for 25 min. The effects of the most effective reversed cTBS paradigm on intracortical inhibition (SICI) and facilitation (ICF) were also tested.

Results: Reversing the current direction reduced AMT by 26% ± 2%. Compared to standard cTBS, reversed cTBS induced stronger and longer-lasting inhibition of corticospinal excitability when delivered at 100% AMT_{rev}. SICI was reduced after $\text{cTBS}_{100\%\text{revAMT}}$ while ICF was unchanged. The after-effects of reversed iTBS were quite variable regardless of the intensity.

Conclusions: cTBS applied with antero-posterior current is more effective in suppressing subsequent MEPs than conventionally orientated cTBS when the *absolute* stimulation intensity is similar. On the contrary, posterior current orientation reduces the efficacy of iTBS.

Significance: The current direction may affect the power of inhibitory and excitatory TBS in opposite ways; this should be considered in order to optimise the after-effects of biphasic RTMS.

Keywords: Repetitive transcranial magnetic stimulation; Theta Burst Stimulation; Biphasic pulses; I-waves; Inhibition; Facilitation

1. Introduction

Since the initial observations of Day et al. (Day et al., 1989) a wealth of evidence has accumulated that different populations of neurones in the hand area of the human motor cortex can be activated selectively by different orientations of TMS pulse. Thus, monophasic pulses that induce currents in the posterior–anterior direction selectively recruit I1 excitatory inputs to corticospinal neurones; only at higher intensities are other inputs, such as the I3 input, recruited. In contrast, anterior–posterior induced currents tend to excite preferentially I3 inputs at low intensities and I1 inputs at higher intensities. Latero-medial pulses tend to recruit D-waves better than any other orientation (Di Lazzaro et al., 2001, 2003; Hanajima et al., 1998). Finally, recruitment of inhibitory effects responsible for short interval intracortical inhibition (SICI) appears to be insensitive to current direction (Ziemann et al., 1996).

These initial observations were all made using single pulse stimulation. However, in recent years there has been growing interest in applying repetitive TMS (rTMS) because repeated stimulation leads to effects on cortical function that outlast the period of stimulation. Given that a pulse of TMS potentially activates any neural element at the site of stimulation, it seems likely that any effect that is produced will involve a mixture of changes in different

---

[☆] The work has taken place at the Institute of Neurology.

[☆☆] Disclosure: The authors have reported no conflicts of interest.

[*] Corresponding author. Address: Institute of Neurology, Sobell Department of Motor Neuroscience and Movement Disorders, Queen SQ, Box 146, London WC1N 3BG, UK. Tel.: +44 020 7837 3611x4468; fax: +44 020 7278 9836.

E-mail address: p.talelli@ion.ucl.ac.uk (P. Talelli).

1388-2457/$32.00
doi:10.1016/j.clinph.2007.05.062

pathways. This may well be one reason for the variation in responses of individual subjects to periods of rTMS (Maeda et al., 2000).

Given this reasoning it seems possible that different orientations of rTMS may lead to different patterns of after-effects, depending on which neurones are preferentially activated by each stimulus pulse. A recent study by Tings et al. (Tings et al., 2005) investigated the effects of suprathreshold 5 Hz rTMS on the amplitude of the MEP evoked by each of the rTMS pulses. rTMS was given using either a monophasic or a biphasic stimulator. For monophasic rTMS, facilitation was prominent with posterior–anterior pulses whereas MEPs were suppressed (at least over the first 30 pulses of a sequence) with reversed, antero-posterior pulses. No such difference was seen for biphasic rTMS, which was less effective. A similar conclusion about the superior effectiveness of monophasic pulses in suprathreshold rTMS was reported by Sommer et al. (Sommer et al., 2002) (1 Hz rTMS) and by Arai et al. (Arai et al., 2005) (3 Hz rTMS).

In all these cases it was postulated that the relative lack of effect of biphasic rTMS over monophasic rTMS was due to the fact that biphasic pulses tend to recruit different populations of neurones less selectively than monophasic pulses. However, because the MEP changes were so small, no conclusions could be reached over whether they would be influenced by changing the direction of the biphasic rTMS pulses. Despite their name, biphasic stimulator pulses are directionally selective, even when the orientation is rotated by 180°. For example, contrary to what happens with monophasic pulses, initially antero-posterior biphasic pulses are more efficient in recruiting corticospinal output than initially posterior–anterior pulses (Mills et al., 1992; Kammer et al., 2001). This is because with biphasic pulses, maximum nerve polarisation is induced during the reverse, rather than the initial phase of current (Davey and Epstein, 2000; Maccabee et al., 1998). Moreover, most rTMS studies use biphasic stimulator pulses, because it is energy-efficient. Indeed high frequencies of rTMS of 25 Hz or more can only be produced at present by biphasic stimulators.

The question we address in this paper is whether the orientation of biphasic rTMS has any significant effect on the after-effects that occur. We chose the new "theta burst" protocol devised by Huang et al. since it has been shown to have long-lasting after-effects and involves very high frequencies that can at present be delivered only by biphasic stimulators (Huang et al., 2005).

2. Materials and methods

2.1. Subjects

A total of 18 right-handed healthy individuals (mean age 29.6 ± 3.9, nine males nine females) were enrolled after giving informed consent. All experimental procedures were approved by the local Ethics Committee.

2.2. Experimental set-up

During the experiments subjects were sitting comfortably in an armchair with their eyes open. EMGs were recorded via Ag/AgCl electrodes placed over the right first dorsal interosseous (FDI) using a belly-tendon montage. Signals were filtered (30 Hz–10 KHz) and amplified (Digitimer 360, Digitimer Ltd., Welwyn Garden City, Herts, UK) and then stored on computer via a Power 1401 data acquisition interface (Cambridge Electronic Design Ltd., Cambridge UK). Analysis was carried out using Signal Software (Cambridge Electronic Design).

2.2.1. Transcranial magnetic stimulation

The primary motor cortex of the left hemisphere was stimulated. Two figure-of-eight coils (Magstim Co., Whitland, Dyfeld, UK) with the same diameter of 70 mm were used for the experiments. One of them was connected to a monophasic Magstim 200 or to two Magstim 200 via a Y-shaped cable (all Magstim Co., UK). This was used to define the motor hot-spot and to assess the after-effects of TBS on corticospinal and intracortical excitability. The second coil was connected to a biphasic stimulator, i.e., a Super Rapid Magstim package (Magstim Co., UK), and was used to deliver TBS. This was a reversing-current coil which allows reversing the direction of the current induced in the brain by alternating between two connecting cables, one "standard" and one "reversed", without changing the actual positioning of the coil (Fig. 1). The motor hot-spot was defined as the location where TMS consistently produced the largest Motor Evoked Potential (MEP). The coil was held at an angle of 45° away from the midsagittal line with the handle pointing backwards. With this positioning the current induced in the brain is almost perpendicular to the central sulcus and runs directed postero-anteriorly with monophasic stimulators and biphasic (initial phase) stimulators. Hence, with the current-reversing coil the second depolarising phase of the current in the brain is directed antero-posteriorly (AP) when the "standard" connecting cable is used and postero-anteriorly (PA) with the "reversed" connecting cable (Fig. 1). Previous experiments have shown that the direction of the current does not significantly influence the position of the hot-spot (Sakai et al., 1997; Arai et al., 2005). To avoid confusion and for the sake of simplification the term "current" will refer to the current induced in the brain by the initial phase of the biphasic pulse. Postero-anterior current direction will be referred to as "standard", while antero-posterior current direction will be "reversed".

2.2.2. Theta Burst Stimulation

Theta Burst Stimulation (TBS) consists of repeating bursts of stimuli. Each burst consists of three stimuli repeating at 50 Hz; bursts are repeating at 5 Hz. The nature of the after-effects differs according to the stimulation pattern. A continuous train of 100 bursts (300 stimuli), named continuous TBS (cTBS), given over the primary motor