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REVIEW

I-WAVE PERIODICITY TRANSCRANIAL MAGNETIC STIMULATION (iTMS) ON CORTICOSPINAL EXCITABILITY. A SYSTEMATIC REVIEW OF THE LITERATURE

D. J. KIDGELL,[a] J. MASON,[a] A. FRAZER[b] AND A. J. PEARCE[c,d]*

[a] *Department of Rehabilitation, Nutrition and Sport, School of Allied Health, La Trobe University, Bundoora, Victoria, Australia*

[b] *Institute of Sport, Exercise and Active Living, College of Exercise Science, Victoria University, Victoria, Australia*

[c] *Melbourne School of Health Sciences, The University of Melbourne, Victoria, Australia*

[d] *Centre for Design Innovation, Swinburne University of Technology, Victoria, Australia*

Abstract—Repetitive transcranial magnetic stimulation (rTMS) is an established technique that can modulate excitability of the motor cortex and corticospinal tract, beyond the duration of the stimulation itself. More recently, a newer repetitive technique, known as I-wave periodicity TMS (iTMS) has been purported to show increases in corticospinal excitability following at least 10 min of iTMS duration. The aim of this study was to use a systematic review to search the literature from January 2000 to October 2015 with regard to corticospinal outcomes following iTMS intervention. We also rated the quality of studies and assessed the risk of bias by applying the Downs and Black checklist and the Cochrane Collaboration Risk of Bias Tool respectively. From an initial yield of 144, 11 studies were included. Studies were found to be of moderate quality, however a high risk of bias was identified. Despite these issues, evidence from the studies presented in this review so far indicates that iTMS is effective in increasing corticospinal excitability. However, further studies are required from other groups to validate the findings to date. Additional research is required to reduce the variability in corticospinal excitability and also to functional outcomes along with corticospinal excitability following iTMS.

Key words: corticospinal excitability, I-wave periodicity, motor-evoked potential, repetitive transcranial magnetic stimulation, systematic review.

Contents

INTRODUCTION

The ability to alter the excitability of the motor cortex (M1) and spinal cord (corticospinal) pathway has been made possible with advances in non-invasive brain stimulation (Thickbroom and Mastaglia, 2009). In recent years, there have been a number of different non-invasive techniques including repetitive transcranial magnetic stimulation (rTMS) (Pascual-Leone et al., 1994; Fitzgerald et al., 2006), theta burst stimulation (Huang et al., 2005), repetitive paired associative stimulation (Stefan et al., 2000), and quadripulse stimulation (Hamada et al., 2007b). These techniques have demonstrated their ability to modulate the excitability of the corticospinal pathway beyond the stimulation period (Chen et al., 1997; Hummel and Cohen, 2005; Lui et al., 2012). Parallel to the

*Correspondence to: A. J. Pearce, The University of Melbourne, Victoria, Australia. Tel: +61-3-83440423; fax: +61-3-83444188.
E-mail address: ajpearce@unimelb.edu.au (A. J. Pearce).

Abbreviations: GABA, γ-aminobutyric acid; ISI, interstimulus interval; iTMS, I-wave periodicity transcranial magnetic stimulation; LTD, long-term depression; LTP, long-term potentiation; MEP, motor-evoked potential; NHMRC, National Health and Medical Research Council; NMDA, *N*-methyl-D-aspartate; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PTNs, pyramidal tract neurons; rTMS, repetitive transcranial magnetic stimulation; TES, transcranial electrical stimulation.

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development in these repetitive techniques, I-wave periodicity TMS (iTMS) has also demonstrated modulatory effects in the human corticospinal pathway. The number of publications using this technique has increased recently; therefore with the emergent awareness of iTMS, this paper initially describes the mechanisms underpinning iTMS, followed by a systematic review and qualitative analysis of the published iTMS studies to date.

Physiological bases of transcranial stimulation

Early studies by Day et al. (1989) demonstrated stimulation of the motor cortex gives rise to a series of high-frequency (~600 Hz) waves, or multiple descending volleys (Rusu et al., 2015). Both animal and human transcranial electrical stimulation (TES) studies have demonstrated the first volley, termed direct or D-wave, followed by three or four indirect waves (I-waves). Animal studies have shown that the D-wave results from direct activation of the axons of the fast pyramidal tract neurons (PTNs), whereas I-waves arise from indirect trans-synaptic activation of PTNs (Patton and Amassian, 1954). In humans, Di Lazzaro et al. (1998) demonstrated TES of the motor cortex also produces a short-latency wave analogous to D-waves previously described by Patton and Amassian (1954), followed by I-waves. However, unlike TES, TMS induces descending volleys with latencies approximately 1.0 to 1.5 ms longer than the volley recruited by electrical stimulation (Di Lazzaro et al., 1998). It has therefore been posited that TMS does not activate corticospinal fibers directly, but rather reflects repeated indirect trans-synaptic activation of corticospinal neurons via excitatory cortical interneurons or I-waves (Thickbroom et al., 2006).

Stimulation-induced modulation. Although the exact mechanisms underpinning corticospinal modulation are not exactly known in any of the stimulation paradigms, Classen and Ziemann (2003) have suggested that it is unlikely to be one single mechanism in any particular stimulation paradigm. Moreover, Classen and Ziemann (2003) postulate that with different stimulation paradigms, it is likely that the combination of mechanisms will differ, reflective of that particular paradigm. Typically studies adapting TMS interventions interpret changes in the raw motor-evoked potential (MEP) amplitude as modulations in corticospinal excitability (Hess et al., 1986; Andersen et al., 1999). Assessment of corticospinal excitability has usually been performed by measuring the amplitude of the MEP, elicited by single pulse TMS. Paired pulse TMS paradigms where two pulses, a conditioning stimulus and a test stimulus are applied to elicit an evoked potential at varying stimulation intensities, can also be used to quantify intracortical facilitation or intracortical inhibition. For example, when a subthreshold conditioning stimulus precedes the test stimulus at an interstimulus interval (ISI) between 10 and 15 ms, the MEP is facilitated and reflective of *N*-methyl-D-aspartate (NMDA) receptor activity. Conversely, using the same protocol but changing the ISI to between 2 and 5 ms produces inhibition of the test MEP, and is known as short interval intracortical inhibition (SICI), reflecting γ-aminobutyric acid ($GABA_A$) receptor activity. However, when two supra-threshold paired stimuli are delivered between 50 and 200 ms, inhibition of the test stimuli is observed. Known as long interval intracortical inhibition (LICI), this paired-pulse paradigm is through to represent $GABA_B$ receptor activity (for further discussion see Hanajima and Ugawa, 2008).

High frequency rTMS (> 5 Hz) has shown to increase MEP amplitude during and post rTMS (Pascual-Leone et al., 1994; Peinemann et al., 2004). Ziemann and colleagues (1998a,b) suggest this increased MEP amplitude occurs via neuronal property changes influencing the internal circuitry, notably through reduced GABA inhibition and altered voltage-gated Na^+ and Ca^{2+} channel-mediated mechanisms. Conversely low-frequency rTMS of 1 Hz results in reduction in excitability during (Pascual-Leone et al., 1994) and following (Touge et al., 2001) the intervention, which Fitzgerald et al. (2005) has suggested to be due to activity at both GABA and NMDA receptor systems. With theta burst stimulation, mechanisms for modulation are suggested to be long-term potentiation (LTP), observed with intermitted theta burst stimulation, or long-term depression (LTD) demonstrated via continuous theta burst stimulation (Huang et al., 2005). Similar suggestions of LTP/LTD mechanisms have also been made for repetitive paired associative stimulation due to the physiological profile of PAS-induced plasticity resembling spike-timing-dependent (Hebbian) LTP/LTD in animal models (Stefan et al., 2000). Similarly, Hamada et al. (2007b) have also suggested LTP as being the underlying mechanisms to account for the modulatory effect following quadripulse stimulation.

Safety of transcranial stimulation paradigms

There has been a significant increase in the application of non-invasive brain stimulation in both experimental studies and therapeutic treatment (Rossi et al., 2009). Generally, the safety of transcranial stimulation paradigms has been reported. However, with repetitive paradigms, such as low- and high-frequency rTMS and theta burst, there is a small risk that high-frequency rTMS and TBS paradigms can result in significant and spreading increases in excitability, that may induce seizures in healthy participants (Thickbroom et al., 2006; Rossi et al., 2009). Other potential adverse events include burning sensation (more so with electrical or direct current stimulation than TMS), syncope (although Rossi et al., 2009 suggest this is possible as an epiphenomenon and not related to brain effects), and vagal reactions in three participants following theta burst stimulation (Grossheinrich et al., 2009). Minor events commonly reported include transient headache, local pain, neck pain, and toothache, particularly with low- and high-frequency rTMS (Rossi et al., 2009). Rossi et al. (2009) reported that iTMS studies had been undertaken, and at the time of the consensus statement, no adverse effects had been reported with the iTMS technique.

I-wave periodicity repetitive TMS

Another novel patterned rTMS paradigm involves pairs of supra-threshold stimuli delivered at an ISI of 1.5 ms. As