Journal of Electromyography and Kinesiology 25 (2015) 754–764

Contents lists available at ScienceDirect

Journal of Electromyography and Kinesiology

journal homepage: www.elsevier.com/locate/jelekin

Reproducibility of transcranial magnetic stimulation metrics in the study of proximal upper limb muscles

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ARTICLE INFO

Article history:
Received 5 January 2015
Received in revised form 11 May 2015
Accepted 29 May 2015

Keywords:
Transcranial magnetic stimulation
Reliability
Primary motor cortex
Proximal muscles
Corticospinal
Motor evoked potential

ABSTRACT

Objective: Reproducibility of transcranial magnetic stimulation (TMS) metrics is essential in accurately tracking recovery and disease. However, majority of evidence pertains to reproducibility of metrics for distal upper limb muscles. We investigate for the first time, reliability of corticospinal physiology for a large proximal muscle – the biceps brachii and relate how varying statistical analyses can influence interpretations. *Methods*: 14 young right-handed healthy participants completed two sessions assessing resting motor threshold (RMT), motor evoked potentials (MEPs), motor map and intra-cortical inhibition (ICI) from the left biceps brachii. Analyses included paired *t*-tests, Pearson's, intra-class (ICC) and concordance correlation coefficients (CCC) and Bland–Altman plots. *Results*: Unlike paired *t*-tests, ICC, CCC and Pearson's were >0.6 indicating good reliability for RMTs, MEP intensities and locations of map; however values were <0.3 for MEP responses and ICI. *Conclusions*: Corticospinal physiology, defining excitability and output in terms of intensity of the TMS device, and spatial loci are the most reliable metrics for the biceps. MEPs and variables based on MEPs are less reliable since biceps receives fewer cortico-motor-neuronal projections. Statistical tests of agreement and associations are more powerful reliability indices than inferential tests. *Significance*: Reliable metrics of proximal muscles when translated to a larger number of participants would serve to sensitively track and prognosticate function in neurological disorders such as stroke where proximal recovery precedes distal.

1. Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive neurophysiologic technique to measure excitability of cortices and their output pathways in the brain. It is most popular use concerns the study of physiology of the primary motor cortex (M1) and emergent corticospinal projections. By measuring the amplitude of evoked motor potentials (MEPs) in muscles in response to TMS, one can estimate corticospinal excitability and output devoted to the muscle (Baker, 1985; Barker et al., 1987; Liepert et al., 2000; Rossini et al., 1994; Bastani and Jaberzadeh, 2012). The entire corticospinal output projecting to the muscle can also be plotted as what is commonly referred to as the motor map. Finally, TMS can be used to determine parameters of cortico-cortical physiology that shape corticospinal excitability and output, such as intra-cortical inhibition (ICI), which represents the influence of cortical interneurons (Kujirai et al., 1993). Because of its ability to define even subtle changes in motor cortical and corticospinal physiology, TMS is fast becoming popular in clinical applications. Hundreds of studies in neurologic populations such as stroke and spinal cord injury attribute time-varying change in TMS metrics to physiologic mechanisms underlying disease and recovery (Stinear et al., 2007; Trompetto et al., 2000; Liepert et al., 2000; Wittenberg et al., 2003). However, to ensure that TMS can indeed serve as a clinical tool to track longitudinal processes, it is first critical to understand test–retest reliability of its metrics in healthy individuals (Malcolm et al., 2006; Pourtney

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http://dx.doi.org/10.1016/j.jelekin.2015.05.006
1050-6411/

and Watkins, 2000; Christie et al., 2007; Doeltgen et al., 2009; De Vet et al., 2006; Mills and Nithi, 1997; Kimiskidis et al., 2004).

At this time, several different studies have reported that TMS metrics are generally reliable. However, the majority defines reliability of metrics for distal muscles of the upper limb (Christie et al., 2007; Kamen, 2004; Livingston and Ingersoll, 2008; Malcolm et al., 2006; McDonnell et al., 2004; Carroll et al., 2001; Bastani and Jaberzadeh, 2012). Distal muscles have been the muscles of choice because they are afforded with prominent cortical representations and substantial corticospinal projections (Malcolm et al., 2006; Kamen, 2004; Brasil-Neto et al., 1992). Thus, they are extremely responsive to TMS such that MEPs are easy to acquire and are sufficiently large to study (van Kuijk et al., 2009; Roick et al., 1993; Cantello et al., 1992; Rossini et al., 1994; Mills and Nithi, 1997). Test–retest reliability of metrics for proximal muscles is, however, lacking. Proximal muscles are often as relevant as distal in tracking neurologic recovery; stronger proximal muscles typically serve to compensate for poor dexterity (Canning et al., 2000). In addition, in neurological conditions, such as stroke and cervical spinal cord injury, the recovery pattern generally shows restoration of proximal function before distal, which supports a majority of the acute, and sub-acute recovery, and initial functional independence (Colebatch et al., 1990; Rudhe and van Hedel, 2009). Therefore, understanding reliability of TMS metrics for proximal muscles becomes a priority for realizing its indication for clinical use.

van Kuijk et al. (2009) have compared TMS metrics between a proximal muscle (biceps brachii) and a distal intrinsic muscle of the hand (abductor digiti minimi, ADM). They have concluded that corticospinal physiology for biceps brachii shows high inter-individual variability compared to that for ADM. Their finding raises an important question – does the high inter-subject variability of TMS metrics predispose proximal muscles to poor test–retest reliability? To answer this, for the first time, we investigate reproducibility of several key TMS metrics defining parameters as corticospinal excitability and output, ICI, and physiology of motor maps for biceps brachii. Our emphasis is novel because proximal muscles are typically less studied than distal owing to the challenge in assaying with TMS. For instance, fewer cortico-motor-neuronal projections that are spread over a relatively wider area (Brasil-Neto et al., 1992), we have recently reported, render their MEPs small and extremely variable (Plow et al., 2013, 2014). Along similar lines, examining reliability of all major metrics is important, because in the study of distal muscles, a divergence is identified, where certain measures are more reliable than others (Malcolm et al., 2006).

Since, to the best of our knowledge, our study remains the first to explore test–retest reliability of TMS metrics for a large, proximal muscle, it is critical for us to compare interpretations across all-standard and novel methods of reliability analyses. Therefore, our emphasis is also novel because unlike prior studies (van Kuijk et al., 2009) we relate how varying statistical methods of test–retest reliability can influence interpretations of stability of outcomes. By knowing which metrics are most reliable for proximal muscles and which statistical tests aide in establishing reliability, would improve planning and design of longitudinal studies tracking recovery and prognosticating upper extremity function in clinical populations.

2. Methods

2.1. Subjects

Twenty young (23 ± 4.02 years, 10 females), healthy participants were enrolled. All subjects were right-hand dominant, confirmed by the Oldfield handedness test (Oldfield, 1971), and were not involved in any systematic upper limb training for a period of 5 years before enrollment. Exclusion criteria were established based on contraindications to TMS (Rossi et al., 2009) and were intended to remove any confound of neurological or musculoskeletal condition affecting upper limbs. All subjects provided informed consent prior to participation. The Institutional Review Board of the Cleveland Clinic approved the experimental protocol.

2.2. Overview of procedures

We conducted a pilot study assessing the test–retest reliability of several of the key TMS metrics defining cortico-cortical and corticospinal physiology for the left biceps brachii muscle. Subjects underwent two identical sessions, namely Test 1 and Test 2, separated by at least eight weeks (Fig. 1), wherein they were asked to refrain from any training or intervention in the interim to ensure that differences in measures from the tests were mainly related to TMS methodology. Within each session, single-pulse and paired-pulse TMS were applied to the right hemisphere for studying metrics for left biceps brachii. We chose to investigate metrics for the non-dominant, left biceps brachii, because this study was part of a larger study evaluating the weaker left arm in healthy young versus an aged population (Plow et al., 2014), where the differences in corticospinal excitation between young and old were most accentuated on the left side in right-handed participants.

2.3. TMS procedures

Participants were seated in a chair with both arms resting in slight shoulder abduction (~10°), elbow flexion (90°), and forearm in neutral position, between pronation and supination. TMS was applied using a figure-of-eight coil (70 mm diameter) connected to one or two Magstim devices (200^2 and Bistim device, Magstim Co., Dyfed, UK). The coil was held tangential to the scalp with the handle oriented backwards and laterally at 45° from the midsagittal axis, which is approximately perpendicular to the central sulcus and M1, and is believed to optimally stimulate the corticospinal tracts (Di Lazzaro et al., 2004). The position of the coil was guided by frameless stereotaxy (Brainsight, Rogue Research Inc., Montreal, Canada) using a magnetic resonance imaging (MRI) template as a reference. Each subject's head was registered to the MRI template using defined cranial landmarks, to ensure the coil position and orientation was realized with respect to that of the MRI template (Ruohonen and Karhu, 2010).

Surface electromyography (EMG) electrodes (Ag/AgCl, 45 mm diameter) were positioned over the middle of the muscle belly of the left biceps brachii. A bipolar montage was used while a reference electrode was placed over the acromion. MEP signals were amplified, band-pass filtered (10 Hz–2 kHz), digitized (4 kHz; PowerLab 4/25T, AD Instruments Inc., Colorado Springs, CO), and stored on a computer for offline analysis (Scope, version 4.0.8).

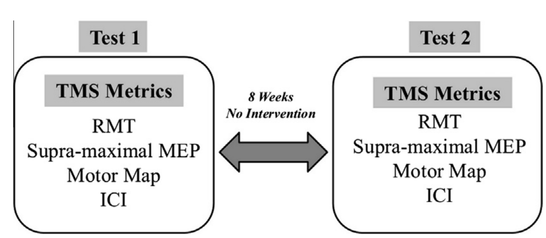

Fig. 1. The schematic representation shows the flow of procedures for the test–retest reliability paradigm. TMS was performed in each session (test 1 and test 2) to obtain the following test metrics – RMT, supra-maximal MEP, motor map and ICI.