Clinical Neurophysiology 127 (2016) 2892–2897

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

Optimal number of pulses as outcome measures of neuronavigated transcranial magnetic stimulation

Won Hyuk Chang [a,b], Peter J. Fried [a], Sadhvi Saxena [a], Ali Jannati [a], Joyce Gomes-Osman [a], Yun-Hee Kim [b,c], Alvaro Pascual-Leone [a,*]

[a] Berenson-Allen Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA
[b] Department of Physical and Rehabilitation Medicine, Center for Prevention and Rehabilitation, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
[c] Department of Health Science and Technology, Department of Medical Device Management & Research, SAIHST, Sungkyunkwan University, Seoul, Republic of Korea

See Editorial, pages 2890–2891

ARTICLE INFO

Article history:
Accepted 1 April 2016
Available online 12 April 2016

Keywords:
Transcranial magnetic stimulation
Motor evoked potentials
Intracortical inhibition
Intracortical facilitation
Reliability

HIGHLIGHTS

- The minimum number of pulses for reliable amplitude and latency of motor evoked potentials was 21 and 23 in response to neuronavigated single-pulse TMS, respectively.
- The minimum number of pulses for reliable short-interval intracortical inhibition and intracortical facilitation was 20 and 25, respectively.
- Navigated transcranial magnetic stimulation might reduce the number of pulses necessary for reliable measurements.

ABSTRACT

Objective: Identify the optimal number of pulses necessary to achieve reliable measures of motor evoked potentials (MEPs) in transcranial magnetic stimulation (TMS) studies.
Methods: Retrospective data was obtained from 54 healthy volunteers (30 men, mean age 61.7 ± 13.1 years) who as part of prior studies had completed three blocks of 30 consecutive TMS stimuli using neuronavigation. Data from four protocols were assessed: single-pulse TMS for measures of amplitude and latency of MEPs; paired-pulse TMS for short-interval intracortical inhibition (sICI) and intracortical facilitation (ICF); and single-pulse TMS to assess the effects of intermittent theta burst stimulation (iTBS). Two statistical methods were used: an internal consistency analysis and probability of inclusion in the 95% confidence interval (CI) around the mean MEPs amplitude.
Results: For single-pulse TMS, the minimum number of pulses needed to achieve reliable amplitude and latency MEPs measures was 21 and 23, respectively. For paired-pulse TMS, the minimum number of pulses needed to achieve reliable sICI and ICF measures was 20 and 25, respectively. Finally, the minimum number of pulses needed to achieve reliable amplitude and latency MEPs measures after iTBS was 22 and 23, respectively.
Conclusions: This study provides guidelines regarding the minimum number of pulses needed to achieve reliable MEPs measurements in various study protocols using neuronavigated TMS.
Significance: Results from this study have the potential to increase the reliability and quality of future neuronavigated TMS studies.

* Corresponding author at: Berenson-Allen Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center, 330 Brookline Ave., Boston, MA 02215, USA. Tel.: +1 617 667 0307; fax: +1 617 975 5322.
E-mail address: apleone@bidmc.harvard.edu (A. Pascual-Leone).

http://dx.doi.org/10.1016/j.clinph.2016.04.001
1388-2457/

1. Introduction

A single transcranial magnetic stimulation (TMS) pulse of adequate intensity can induce responses in muscles that receive corticomotor input from the stimulated motor cortical area (Barker et al., 1985). The action potentials induced by TMS travel along the corticospinal tract and peripheral motor nerve, resulting in muscle responses that can be recorded as motor evoked potentials (MEPs). MEPs are widely used to assess the integrity of the corticospinal and corticobulbar motor pathways in clinical neurophysiology and examine the influence of various interventions and factors (Rossini et al., 2015). In addition, TMS can be used to investigate inhibitory and facilitatory interactions in the cortex with paired-stimuli based on a conditioning-test paradigm (Rossini et al., 2015).

A basic parameter to assess TMS-induced MEPs is the cortical motor threshold (CMT) (Groppa et al., 2012). The CMT is defined as the minimal intensity of motor cortex stimulation required to elicit a reliable MEP of minimal amplitude in the target muscle. Two kinds of CMT have been used to study TMS-induced MEPs. One is the resting motor threshold (RMT), assessed with the target muscle at rest, and the other is the active motor threshold (AMT), assessed during a slight tonic contraction of the target muscle (Groppa et al., 2012). Different procedures for determining the CMT have been described and can be used depending on the setting and the available technical support (Rossini et al., 2015). In addition, the amplitude and latency of MEPs have been used to assess corticomotor reactivity and conduction (Rossini and Rossi, 2007). However, these parameters show substantial variability and dependence on many technical factors. MEPs with the largest amplitude and shortest latency in a run of 5–6 consecutive MEPs can provide a good estimate of optimal corticomotor conduction in the clinical setting (Groppa et al., 2012). Others have advocated the use of average metrics of a block of MEPs (Jung et al., 2010; Kim et al., 2006; Vernet et al., 2014; Ziemann et al., 2001). In this approach, using a larger number of TMS pulses, while more accurate, requires more time for assessment. It also has been suggested that neuronavigation might increase the consistency of MEPs (Bashir et al., 2011; Gugino et al., 2001). However, there is no current consensus about the number of TMS pulses necessary to achieve reliable MEPs measurements.

The objective of the present study was to evaluate the optimal number of pulses to achieve reliable MEP parameters in neuronavigated TMS studies across a variety of common neurophysiological measurements in order to provide guidance for the design of experimental protocols.

2. Methods

2.1. Participants

For the present retrospective study, we used data obtained from various protocols that measured MEPs induced by neuronavigated TMS to assess corticomotor reactivity, corticospinal conduction and long-term potentiation-like plasticity in healthy participants. In all those studies, the motor hotspot had been identified as the scalp location of the TMS coil that evoked MEPs of greatest amplitude (consistent Rossini et al., 2015), but then the identified location had been marked on the individual's MRI and neuronavigation (eXimia 3.1, Nexstim Ltd., Helsinki, Finland) used to identify and consistently target the hotspot across stimulation trials.

For the present analysis we included data from a total of 54 healthy participants (30 men, mean age 61.7 ± 13.1 years). Their baseline characteristics are summarized in Table 1. The local institutional review board had approved all the trials at which data were collected, as well as this retrospective combined analysis. All participants provided written informed consent.

Table 1
Baseline characteristics of participants.

Characteristics	Values
Age (y, mean ± SD, range)	61.7 ± 13.1 (20–80)
Sex (M:F)	30:24
Handedness (right:left)	53:1
Resting motor threshold (%, mean ± SD, range)	53.9 ± 13.0 (31–83)
Active motor threshold (%, mean ± SD, range)	44.7 ± 8.9 (29–63)

Inclusion criteria for the present study were: (1) healthy participants (as evidenced by a medical examination of general health, neurologic and cognitive function); (2) age greater than 18 years.

Exclusion criteria for the present study were: (1) clinical evidence or suspicion of vascular disease including cardiovascular disease, peripheral vascular disease, stroke, or microvascular disease; (2) current or history of any neurological disorder affecting cognitive function, including dementia, epilepsy, stroke, brain lesions, or multiple sclerosis; (3) history of neurosurgical procedures or head trauma that resulted in neurological impairment; (4) current or history of major depression, bipolar or psychotic disorders, or any other major psychiatric condition; and (5) any ongoing medications with known TMS contraindications. In addition, at all source study protocols, participants with any risk factors or contraindications to TMS as per current recommendations endorsed by the International Federation of Clinical Neurophysiology (IFCN) (Rossi et al., 2009; Rossini et al., 2015) had been excluded.

2.2. Source data

In the experiments generating the source data, the following TMS methodologies and experimental protocol were used:

2.3. Experimental set-up

For single and paired-pulse stimulation, a Magstim Super Rapid Stimulator (Magstim Ltd., Withland, Wales, UK) was used to deliver biphasic pulses with current flowing in the brain in an antero-posterior and then a postero-anterior (AP–PA) direction. For intermittent theta burst stimulation (iTBS), a MagPro Stimulator (MagVenture A/S, Farum, Denmark) was used to deliver biphasic pulses with current flowing in AP–PA direction. An infrared-based MRI-guided navigation system (Nexstim Ltd., Helsinki, Finland) was used to ensure that the same cortical location was targeted in each study. During stimulation, surface electromyography (EMG) was recorded and monitored continuously online. Active electrodes were attached to the skin overlying the belly of first dorsal interosseous (FDI) muscle. A reference electrode was placed over the metacarpophalangeal joint. A ground electrode was placed over either the ulnar styloid process or the ipsilateral forearm. The EMG signals were filtered (8–500 Hz), amplified, displayed, and stored for off-line analysis. The TMS system delivered triggered pulses that synchronized the TMS and EMG systems. The participants were also monitored for drowsiness and asked to keep their eyes open throughout the experiment. Relaxation of the measured muscle was controlled by continuous visual EMG monitoring.

2.4. Single-pulse TMS

Each participant was seated in a comfortable chair with a headrest, elbows positioned at approximately 90°, and hands resting on a pillow on his or her lap. The optimal scalp location for activation of the FDI in the dominant hand was determined as the location at