Edith Cowan University

Research Online

1-1-2022

Transcranial magnetic stimulation to assess motor neurophysiology after acute stroke in the United States: Feasibility, lessons learned, and values for future research

Yi-Ling Kuo

David J. Lin

Isha Vora

Julie A. DiCarlo

Dylan J. Edwards
Edith Cowan University, d.edwards@ecu.edu.au

See next page for additional authors

Authors

Yi-Ling Kuo, David J. Lin, Isha Vora, Julie A. DiCarlo, Dylan J. Edwards, and Teresa J. Kimberley

Contents lists available at ScienceDirect

Brain Stimulation

BRAIN STIMULATION

Transcranial magnetic stimulation to assess motor neurophysiology after acute stroke in the United States: Feasibility, lessons learned, and values for future research

Check for updates

Transcranial magnetic stimulation (TMS) has been widely applied in both basic and clinical neuroscience since its introduction in 1985. In addition to its potential therapeutic value for exciting or inhibiting neural circuits [1], TMS can be used to investigate corticomotor excitability (CME), which is a key aspect of voluntary movement [2]. For example, single-pulse TMS can elicit electrical signals, which propagate along descending motor pathways and are recorded as motor evoked potentials (MEP) in target muscles. After stroke, TMS-evoked MEPs have been used to assess the integrity of the descending corticospinal tract (CST) and prognosticate upper limb function [3,4]. Assessment of MEP presence (MEP+) or absence (MEP-) in the affected hand muscle (i.e., first dorsal interosseus (FDI)) at 5–7 days post-stroke is proposed to estimate long-term upper limb function with an MEP+ response predictive of better motor outcomes [5,6]. However, assessment of acute stroke MEP status has yet to be implemented in the United States (US). Performing TMS testing during a poststroke acute hospital stay is challenging, particularly in the US healthcare system where hospital stays are 3.9–6.7 days on average [7] and literature provides little guidance on implementation. Further, the dichotomous categorization of MEP+/MEP- may estimate the CST integrity in an over-simplified way [4,8]. It is possible that other neurophysiologic measures assessed by TMS may be complementary biomarkers to characterize pathophysiology and assist estimates of motor function, but the feasibility of collecting these data in an acute hospital setting has not been well described.

Our primary aim was to develop a feasible process for collecting TMS-evoked responses at bedside, acutely post-stroke in a US hospital. The secondary aim was to assess the potential utility of additional TMS-evoked responses to better characterize neurophysiology in acute stroke. We discuss the necessary coordination, setup, and the lessons learned to facilitate the use of this potentially important tool. TMS measures collected include bilateral resting motor threshold (RMT, measuring CME) [1], cortical silent period (cSP, measuring intracortical inhibition) [9], and ipsilateral silent period (iSP, measuring interhemispheric inhibition) [10]. These measures reflect excitatory and inhibitory processing of the primary motor cortices (M1) with a single-pulse TMS.

Implementing bedside TMS assessment requires close interdisciplinary coordination. An onsite coordinator approaches poststroke individuals within the first few days after admission to screen for contraindications, obtain informed consent, and communicate with TMS investigators who subsequently make every effort to complete the TMS assessment prior to patient discharge.

Between August 2019 and June 2021, 61 people enrolled in a prospective cohort study – The Stroke Motor reHabilitation and Recovery sTudy (SMaHRT; NCT03485040) – at the Massachusetts General Hospital were screened for eligibility. Forty-six people consented and 30 people completed the TMS assessments. Sixteen individuals were not able to receive TMS due to medical complications or acute illness (N = 7), discharge before testing could occur (N = 7), withdrawal due to surgery (N = 1), or testing impacted by COVID-19 restrictions (N = 1). The participants were 4.9 ± 1.7 days (range: 2–8 days) post first-onset ischemic stroke.

The methodology for TMS assessment was as follows. A transportable cart equipped with a single-pulse TMS unit, a 70-mm figure-of-eight remote coil (The Magstim Company Ltd, UK), and a neuronavigation system (BrainSight, Rogue Research Inc., Canada) was used to wheel into a ward for bedside assessment (Fig. 1). The participants were positioned upright either in a bedside chair or long-sitting in bed. The investigators cleaned the skin to place a subject tracker (for neuronavigation) on the forehead and surface electrodes on bilateral FDI muscles to record electromyography (EMG). A participant's head was co-registered into a T1 template scan with neuronavigation to guide the search of hotspot in the M1. The assessment procedures of each hemisphere (ipsilesional hemisphere first) are described below.

1. FDI Hotspot Localization and MEP+/MEP- Determination. MEP+ was defined as any visible and consistent EMG response above the background activity (typically >20μV) and occurring 25–40 milliseconds post-stimulus at an intensity up to 100% maximum stimulator output (MSO). For those whose MEP could not be elicited at rest, a voluntary contraction was performed to generate background EMG activity to again attempt to obtain an MEP.

2. RMT Determination (%MSO). The TMS Motor Threshold Assessment Tool (MTAT 2.0) was used to determine RMT defined as ≥50μV [1]. MTAT was used due to the speed of threshold determination with minimal number of pulses. If MEP could only be elicited during active contraction, an active motor threshold was not determined, but the individual was categorized as MEP+.

3. cSP (contralateral to the stimulated hemisphere) and iSP (ipsilateral to the stimulated hemisphere) Measurements. Two silent period measures were obtained simultaneously (intensity = 130% RMT) with bilateral FDI contraction [9,10]. If

size = 0.5). The ipsilesional/contralesional ratio of iSP was 0.9 ± 0.3, indicating a moderate effect of imbalanced interhemispheric inhibition (Supplementary Table 2).

A transportable TMS cart and efficient interdisciplinary communication enable comprehensive, bedside TMS assessment to occur in between complex medical patient needs during acute hospitalization in a US-based hospital. Corticomotor excitability and inhibition may help illuminate the dynamic and poorly understood pathophysiology in acute stroke. The outlined process will enable future research on identifying TMS-derived biomarkers for motor function prognosis in stroke.

Author contributions

Conceptualization: YLK, DJL, DJE, and TJK. Funding acquisition: DJL and TJK. Coordination and data collection: YLK, IV, JAD, and TJK. Data analysis: YLK, DJL, IV, and TJK. Manuscript writing: YLK, DJL, IV, JAD, DJE, and TJK.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2021.12.001.

References

[1] Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. Clin Neurophysiol 2015;126:1071–107. https://doi.org/10.1016/j.clinph.2015.02.001.
[2] Cortes M, Black-Schaffer RM, Edwards DJ. Transcranial magnetic stimulation as an investigative tool for motor dysfunction and recovery in stroke: an overview for neurorehabilitation clinicians. Neuromodulation 2012;15:319–25. https://doi.org/10.1111/j.1525-1403.2012.00459.x.
[3] Rosso C, Lamy JC. Prediction of motor recovery after stroke: being pragmatic or innovative? Curr Opin Neurol 2020;33:482–7. https://doi.org/10.1097/WCO.0000000000000843.
[4] Kim B, Winstein C. Can neurological biomarkers of brain impairment Be used to predict poststroke motor recovery? A systematic review. Neurorehabilitation Neural Repair 2017;31:3–24. https://doi.org/10.1177/1545968316662708.
[5] Stinear CM, Byblow WD, Ackerley SJ, Smith MC, Borges VM, Barber PA. PREP2: a biomarker-based algorithm for predicting upper limb function after stroke. Ann Clin Transl Neurol 2017;4:811–20. https://doi.org/10.1002/acn3.488.
[6] Smith MC, Ackerley SJ, Barber PA, Byblow WD, Stinear CM. PREP2 algorithm predictions are correct at 2 Years poststroke for most patients. Neurorehabilitation Neural Repair 2019;33:635–42. https://doi.org/10.1177/1545968319860481.
[7] Jackson G, Chari K. National hospital care survey demonstration projects: stroke inpatient hospitalizations. Natl Health Stat Report 2019;1–11.
[8] Lundquist CB, Nielsen JF, Arguissain FG, Brunner IC. Accuracy of the upper limb prediction algorithm PREP2 applied 2 Weeks poststroke: a prospective longitudinal study. Neurorehabilitation Neural Repair 2021;35:68–78. https://doi.org/10.1177/1545968320971763.
[9] Chen M, Summers RLS, Goding GS, Samargia S, Ludlow CL, Prudente CN, et al. Evaluation of the cortical silent period of the laryngeal motor cortex in healthy individuals. Front Neurosci 2017;11:88. https://doi.org/10.3389/fnins.2017.00088.

Fig. 1. A transportable cart equipped with a TMS unit, a 70-mm figure-of-eight remote coil, and a neuronavigation system. A reconstructed brain image with real-time feedback of coil location was used to guide the stimulation in the primary motor cortex. This cart can be wheeled into a ward and this setup allows TMS assessments to occur acutely at the bedside.

cSP or iSP were not visible, stimulus intensity was increased until cSP or iSP was observed, up to 100% MSO.

Demographics and TMS data are presented in Supplementary Table 1. Testing required approximately 30–40 minutes to complete all measures in both hemispheres. There were seven individuals defined as MEP-. Among the 23 MEP+ individuals, eight had no RMT given the standard 50μV criteria (i.e., MEP<50μV at 100% MSO). Medians of the RMT were 48% (ipsilesional) and 44% (contralesional) (95% confidence interval (CI) of difference: 5.1, 4.9; effect size = 0.007). Since the silent period requires muscle contraction, data were unavailable in some individuals with severe hemiparesis due to inability to perform active contraction. Medians of the cSP were 245.7 ms (ipsilesional) and 169.8 ms (contralesional) (95% CI of hemisphere difference: 30.7, 121.0; effect size = 1.2). The ipsilesional/contralesional ratio of cSP was 1.5 ± 0.5, indicating a strong effect of greater ipsilesional intracortical inhibition. Medians of the iSP were 40.7% (ipsilesional) and 52.3% (contralesional) (95% CI of difference: 17.2, 0.3; effect

[10] Kuo Y-L, Dubuc T, Boufadel DF, Fisher BE. Measuring ipsilateral silent period: effects of muscle contraction levels and quantification methods. Brain Res 2017;1674:77–83. https://doi.org/10.1016/j.brainres.2017.08.015.

Yi-Ling Kuo

Department of Physical Therapy Education, SUNY Upstate Medical University, Syracuse, NY, USA

David J. Lin

Center for Neurotechnology and Neurorecovery, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Isha Vora

Department of Rehabilitation Sciences, MGH Institute of Health Professions, Boston, MA, USA

Julie A. DiCarlo

Center for Neurotechnology and Neurorecovery, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Dylan J. Edwards

Moss Rehabilitation Research Institute, Philadelphia, USA

School of Medical and Health Sciences, Edith Cowan University, Joondalup, Australia

Teresa J. Kimberley[*]

Center for Neurotechnology and Neurorecovery, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Department of Rehabilitation Sciences, MGH Institute of Health Professions, Boston, MA, USA

Department of Physical Therapy, MGH Institute of Health Professions, Boston, MA, USA

[*] Corresponding author. 36 1st Avenue, Boston, MA, 02129, USA.
E-mail address: tkimberley@mgh.edu (T.J. Kimberley).