Clinical Neurophysiology 126 (2015) 1024–1032

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

Timing of motor cortical stimulation during planar robotic training differentially impacts neuroplasticity in older adults

Crystal L. Massie [a,1], Shailesh S. Kantak [b,a], Priya Narayanan [c], George F. Wittenberg [d,c,a,*]

[a] Physical Therapy and Rehabilitation Sciences Department, University of Maryland School of Medicine, Baltimore, MD 21201, USA
[b] Moss Rehabilitation Research Institute, Elkins Park, PA 19027, USA
[c] Department of Neurology, University of Maryland School of Medicine, and Maryland Exercise and Robotics Center of Excellence, Veterans Affairs Medical Center, Baltimore, MD 21201, USA
[d] Geriatrics Research, Education & Clinical Center, Veterans Affairs Medical Center, Baltimore, MD 21201, USA

See Editorial, pages 853–854

ARTICLE INFO

Article history:
Accepted 20 June 2014
Available online 16 September 2014

Keywords:
Transcranial magnetic stimulation
Motor control
Neuroplasticity
Reaching
Aging
Rehabilitation

HIGHLIGHTS

- Altering the timing of stimulation during a reaching intervention changes the direction and extent of plasticity.
- Non-invasive brain stimulation may be a catalyst to promote plasticity in older adults.
- Robotic reaching plus stimulation facilitated a rapid plastic response that was maintained during the intervention and for a short time period following the intervention.

ABSTRACT

Objective: The objective was to determine how stimulation timing applied during reaching influenced neuroplasticity related to practice. Older adult participants were studied to increase relevance for stroke rehabilitation and aging.
Methods: Sixteen participants completed 3 sessions of a reaching intervention with 480 planar robotic movement trials. Sub-threshold, single-pulse transcranial magnetic stimulations (TMS) were delivered during the late reaction time (LRT) period, when muscle activity exceeded a threshold (EMG-triggered), or randomly. Assessments included motor evoked potentials (MEP), amplitude, and direction of supra-threshold TMS-evoked movements and were calculated as change scores from baseline.
Results: The direction of TMS-evoked movements significantly changed after reaching practice ($p < 0.05$), but was not significantly different between conditions. Movement amplitude changes were significantly different between conditions ($p < 0.05$), with significant increases following the LRT and random conditions. MEP for elbow extensors and flexors, and the shoulder muscle that opposed the practice movement were significantly different between conditions with positive changes following LRT, negative changes following EMG-triggered, and no changes following the random condition. Motor performance including movement time and peak velocity significantly improved following the training but did not differ between conditions.
Conclusions: The responsiveness of the motor cortex to stimulation was affected positively by stimulation during the late motor response period and negatively during the early movement period, when stimulation was combined with robotic reach practice.
Significance: The sensitivity of the activated motor cortex to additional stimulation is highly dynamic.

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* Corresponding author at: Baltimore VAMC, Univ. of Maryland, 655 W, Baltimore St., Rm 12-047, Baltimore, MD 21201, USA. Tel.: +1 410 706 4456; fax: +1 410 605 7913.
E-mail address: gwittenb@grecc.umaryland.edu (G.F. Wittenberg).

[1] Department of Occupational Therapy, Indiana University School of Health & Rehabilitation Sciences, Indianapolis, IN 46202 USA.

http://dx.doi.org/10.1016/j.clinph.2014.06.053

1. Introduction

Neurorehabilitation efforts have focused on intense structured interventions to promote neuroplasticity because stroke is a leading cause of long-term disability world-wide. Robotic rehabilitation devices assist massed practice of upper extremity movement at high repetition rates (Lo et al., 2010; Conroy et al., 2011). They can also be used to change the learning environment, e.g., provide assistance or resistance to the motor task or train new mappings for movement to environmental effect (Krebs et al., 1998; Stein et al., 2004; MacClellan et al., 2005). Non-invasive brain stimulation such as transcranial magnetic stimulation (TMS) has been used to enhance neuroplasticity by modulating the neurophysiologic state and/or motor output (Cohen et al., 1998; Bütefisch et al., 2004; Kluger and Triggs, 2007; Chen and Udupa, 2009). There is an obvious potential synergy in combining TMS and repetitive motor practice using a robotic rehabilitation device.

A number of studies have demonstrated the potential to facilitate neuroplasticity with intense, repetitive training paradigms (Classen et al., 1998; Giacobbe et al., 2011). Classen et al. (1998) established that 30 min of brisk, repetitive practice of thumb movements in the direction opposite of the TMS-evoked movements changed the direction of the evoked movement. Similar work has been done at the wrist and elbow, but the greatest effects appear to be more distal (Krutky and Perreault (2007); Giacobbe et al., 2011). While these studies contributed to unveiling the principles of use-dependent plasticity for neurohabilitation, TMS also has been considered as a method to enhance neuroplasticity. Bütefisch et al. (2004) demonstrated the potential to increase training-dependent effects when TMS was applied to the motor cortex synchronously with some of the practiced thumb movements. This is therefore a proof-of-principle for facilitating neuroplasticity with intense motor training and TMS; however, this work has been largely isolated to a single degree-of-freedom in the distal upper extremity and the influence of the precise timing of stimulation has not been systematically investigated.

Extending this line of work to the upper extremity has begun through systematic steps to address important questions and has relied heavily on robotic training devices. First, TMS-evoked movements in the upper extremity as an outcome measure for neuroplasticity has been established (Jones-Lush et al., 2010; Lewis et al., 2012). Intense robotic reaching training facilitated plasticity in TMS-evoked upper extremity movements when reaches were practiced in a direction opposite of the initial evoked movement (Kantak et al., 2013). Further, TMS delivered at different times during practiced reaches modulated motor performance with improvements observed when TMS was delivered during the late reaction time (LRT) period (Massie et al., 2013b). A remaining question is how the *timing of stimulation during intense reaching practice* impacts the extent and type of neuroplasticity.

Applications of TMS could improve the efficacy of robotic reaching interventions, based on the rationale that a single TMS pulse delivered with precise timing in relation to the reaching movement will modulate the degree of neuroplasticity. We hypothesized that stimulation delivered during the LRT period would facilitate plasticity when compared to stimulation synchronized with muscle activity onset. The rationale was that spike-timing dependent plasticity is positive when presynaptic activity precedes postsynaptic (Stefan et al., 2000), while presynaptic activity following postsynaptic activity can result in long-term depression. The importance of stimulation timing delivered within 100 ms of movement onset has been demonstrated by Thabit et al., 2010, showing that pre-movement stimulation resulted in positive plasticity whereas stimulations that followed the activation of muscles had less effect. This time period (within 100 ms of movement onset) is a critical window of opportunity for cortical stimulation to influence voluntary movement, and comparing the pairing of stimulation with the onset of muscle activation (EMG triggered) with a late pre-movement period (150 ms prior to movement onset) has not been systematically studied. Because the optimization of timing applies to many types of motor rehabilitation, the results of this study will aid clinical researchers in the development of better therapeutic interventions that couple repetitive practice and other methods that affect brain activity, including non-invasive brain stimulation, virtual reality or other methods, with a goal of enhancing useful neuroplasticity for survivors of stroke.

2. Methods

Participants: sixteen neurologically-intact participants (9 female; 7 male) were recruited for this study and provided informed consent in a protocol approved by the University of Maryland Institutional Review Board and the local Veterans Administration Research Committee. Participants ranged in age from 47 to 75 (mean 64.7 ± 8.7) years and were not taking medications known to affect cortical excitability. Further, they had no history of seizures, treatment with antiepileptic medication, implanted electronic devices, implanted metal in the head, or any other contraindications to TMS.

Experimental setup: Participants completed 3 separate sessions with a minimum of 24 h between sessions. The order of the visits was determined using a Latin square approach. The experimental protocol was the same for each visit except the timing of stimulation delivery during the training as described below. Surface electromyography (EMG) electrodes (B+L Engineering) were applied in bipolar montage to the muscle belly of biceps, triceps, anterior deltoid, and posterior deltoid muscles. Electrode placement was verified by confirming specificity of the EMG signal during voluntary contractions, and data were collected at 2000 Hz with a custom LabView program. Participants were comfortably seated at a planar rehabilitation robotic device (Interactive Motion Technologies, Inc., Cambridge, MA, USA) as depicted in Fig. 1A. The dominant hand and forearm rested in the cradle of the robot with the starting position of the hand at midline approximately 20 cm from the edge of the table. This ensured consistent arm configuration within sessions and minimized differences between subjects. TMS coil placement over the contralateral primary motor cortex was guided with a stereotaxic device (Brainsight, Rogue Research, Montréal, Canada). We determined the movement hotspot as the location that elicited the largest TMS-evoked movements of the arm and hand as recorded by the movement of the robotic handle. The threshold was determined as the lowest intensity to elicit TMS-evoked movements of at least 1 mm in 5 of 10 consecutive stimulations. For participants whose threshold was above 100% of maximal stimulator output but in whom movements could be elicited at lower intensities, a movement threshold of 100% was used.

Assessments were completed at 5 time points during each session (see initial, post 1, post 2, etc. in Fig. 1B). TMS was used to elicit movements and corresponding motor evoked potentials (MEP) as outcome measures using a stimulation intensity of 120% of the movement threshold. Ten stimuli were delivered at rest to record the movement amplitude and direction evoked by TMS stimulation (Magstim 200, Oxford, UK). The direction angle was calculated as a vector to the end-point of the robot handle at the point of peak velocity (PV) (see Fig. 1A). The distance of the handle from the origin at that time point was calculated as a measure of the amplitude of the evoked movement. MEP data from the four muscles of interest were simultaneously collected with peak-to-peak amplitudes measured, then averaged across 10 trials. The muscles were grouped as agonists/antagonists based on the *training direction* (forward reaching had triceps and anterior deltoid as agonists