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Functional repetitive transcranial magnetic stimulation increases motor cortex excitability in survivors of stroke

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HIGHLIGHTS

- Functional-rTMS (repetitive transcranial magnetic stimulation simultaneously delivered during a voluntary muscle contraction) promoted greater cortical excitability changes than passive-rTMS.
- Survivors of stroke had a refinement in the level of muscle activity and force fluctuations following passive-rTMS.
- Functional-rTMS preferentially modulated the agonist/primary muscle group which may have important clinical implications for stroke rehabilitation.

ABSTRACT

Objective: To determine if repetitive transcranial magnetic stimulation (rTMS) applied to the motor cortex with simultaneous voluntary muscle activation, termed functional-rTMS, will promote greater neuronal excitability changes and neural plasticity than passive-rTMS in survivors of stroke.
Methods: Eighteen stroke survivors were randomized into functional-rTMS (EMG-triggered rTMS) or passive-rTMS (rTMS only; control) conditions. Measures of short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF), force steadiness (coefficient of variation, CV) at 10% of maximum voluntary contraction, and pinch task muscle activity were assessed before and after rTMS. Functional-rTMS required subjects to exceed a muscle activation threshold to trigger each rTMS train; the passive-rTMS group received rTMS while relaxed.
Results: Significant interactions (time × condition) were observed in abductor pollicis brevis (APB) SICI, APB ICF, CV of force, and APB muscle activity. Functional-rTMS decreased APB SICI ($p < 0.05$) and increased ICF ($p < 0.05$) after stimulation, whereas passive-rTMS decreased APB muscle activity ($p < 0.01$) and decreased CV of force ($p < 0.05$). No changes were observed in FDI measures (EMG, ICF, SICI).
Conclusion(s): Functional-rTMS increased motor cortex excitability, i.e., less SICI and more ICF for the APB muscle. Passive stimulation significantly reduced APB muscle activity and improved steadiness.
Significance: Functional-rTMS promoted greater excitability changes and selectively modulated agonist muscle activity.

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) has the potential for therapeutic benefit during post-stroke rehabilitation (Lefaucheur, 2008; Machado et al., 2008; Talelli et al., 2006). Neurologic damage from stroke often reduces primary motor cortex (M1) excitability (Di Lazzaro et al., 2008), resulting in a net loss of descending excitatory input to spinal motor neurons. This neurologic origin is the dominant source of muscle weakness (Gemperline et al., 1995; Gracies, 2005; Kamper et al., 2006), and ultimately leads to upper extremity impairment. Animal and human studies have revealed the potential for undamaged adjacent regions of the cortex to con-

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tribute to recovery by functionally remodeling motor cortex representations (Adkins-Muir and Jones, 2003; Kleim et al., 2003; Nudo et al., 1990, 2001; Plautz et al., 2000). rTMS presumably modulates neural excitability of regions through its action on undamaged intracortical connections (Pell et al., 2011). Post-stroke motor behavior, therefore, is a primary target for rTMS interventions (Nithi and Mills, 2000). Initial evidence suggests that active engagement or simultaneous motor training during rTMS may enhance the efficacy of the cortical stimulation by incorporating an element of use-dependent plasticity (Bütefisch et al., 2004; Fujiwara and Rothwell, 2004; Izumi et al., 2008). Full realization of the therapeutic potential of this approach requires further identification of neurophysiologic mechanisms including changes in the ability to generate and modulate muscle activity (Hotermans et al., 2007).

Many early protocols employed a passive rTMS protocol (no active engagement by the participant during stimulation) to modulate brain excitability in both neurologically intact and stroke populations. For example, in a healthy population, 20 s of high frequency (5 Hz bursts of 3 pulses) rTMS to the hand area of primary motor cortex (M1) increased maximal grip force to a greater extent than sham stimulation or rest (Nowak et al., 2005). In survivors of stroke, Kim et al. (2006) demonstrated that a single session of rTMS (20 stimuli at 80% of RMT at 10 Hz for 8 trains) increased motor cortex excitability and enhanced motor accuracy during a sequential finger tapping task. Yozbatiran et al. (2008) demonstrated that 20 min of high-frequency rTMS (20 Hz, subthreshold) in 12 participants favorably impacted motor performance. These passive rTMS protocols modulated cortical excitability and behavioral changes following stimulation that did not require active involvement of the subject.

The use of motor training and simultaneous cortical stimulation (defined here as functional-rTMS) is supported both theoretically (Hebb, 1949; Kleim and Jones, 2008; Nudo et al., 2001) and with initial empirical evidence (Bütefisch et al., 2004; Fujiwara and Rothwell, 2004; Izumi et al., 2008). Functional-rTMS may enhance the degree of rTMS induced neural plasticity by augmenting the excitability of the motor circuits already engaged during a voluntary motor task. This represents a potential advantage of functional-rTMS over passive-rTMS. For example, Bütefisch et al. (2004) demonstrated that motor cortex rTMS paired with a motor training task enhanced motor memory in neurologically intact subjects. When coupled with muscle contractions, rTMS has been observed to facilitate agonist muscles but not antagonists in neurologically intact populations (Fujiwara and Rothwell, 2004). Izumi et al., 2008 delivered TMS synchronized with maximal effort at hand opening in survivors of stroke and demonstrated a reduction in spasticity of the forearm flexors or improved manual performance. These promising initial reports suggest the need to determine the full therapeutic potential for functional-rTMS in survivors of stroke.

Functional-rTMS may improve recovery from stroke by promoting cortical reorganization arising from increased cortical excitability and synaptic efficacy. This study sought to determine whether functional-rTMS enhances the efficacy of rTMS to increase short-term neuronal excitability and motor performance. Given that optimal control of force may be an important neuromotor outcome because it is critical for upper extremity function in survivors of stroke (Lodha et al., 2010; McDonnell et al., 2006), we evaluated force steadiness and muscle activity during a lateral pinch task in parallel with neurophysiologic measures of short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF). We hypothesized that functional-rTMS would promote greater neuronal excitatory changes in the motor cortex and improve motor performance compared to passive-rTMS. We also explored a secondary working hypothesis that functional-rTMS may preferentially modulate selective muscles, i.e., modulate the agonist muscle. As such, we considered commonly known intrinsic hand muscles that contribute to a lateral pinch task.

2. Methods

2.1. Participants

Eighteen survivors of stroke (7 women, 11 men) volunteered and provided written informed consent (Table 1 for demographics). They were 64 ± 11 years of age (range 41–86 years) and 3.6 ± 3 years post-stroke (range 0.5–14 years). All study procedures were approved by the Human Subjects Committee of Colorado State University. Participants were screened for eligibility with a health history questionnaire, Mini Mental Status Exam (Folstein et al., 1975), an evaluation of movement (see inclusion criteria), and an electroencephalogram (EEG) assessed by a neurologist to rule out evidence of epileptiform activity. Participants met these inclusion criteria, (1) unilateral clinical stroke presentation at least 6 months prior to the study, (2) ability to actively flex the shoulder approximately 30°, extend wrist and fingers, and achieve a lateral/key pinch, (3) a score of 24 or higher on the Mini Mental State Exam (Folstein et al., 1975), and (4) the ability to actively participate for approximately 2 h during the experimental sessions. Exclusion criteria were (1) medications that may lower seizure threshold, (2) history of epilepsy or seizure disorder, mass brain lesions, or epileptiform activity on screening EEG, (3) pacemaker or medication pump, metal plate in skull, metal objects in the eye or skull, or intracardiac lines, (4) history of heart disease, (5) pregnancy, and (6) younger than 21 years.

Participants completed clinical assessments to determine level of impairment and functional ability. The Fugl-Meyer Motor Assessment (FM) is a stroke-specific assessment of impairment and sensorimotor function including proprioception, movement, coordination, and reflex action of the shoulder, elbow, forearm, wrist, and hand (Duncan et al., 1983; Folstein et al., 1975). Scoring of each item is on a 3-point ordinal scale (0 = cannot perform, 1 = performs partially, 2 = performs fully) (Gladstone et al., 2002).

3. Experimental setup

Following the functional assessment, subjects were seated in a semi-reclined chair with the hemiparetic arm resting on a lap pillow. Generally, this resting position required internal shoulder rotation, elbow flexion, neutral forearm, and a slightly extended wrist. The skin was abraded and cleaned prior to the application of a pair of 8 mm surface electrodes (In Vivo Metric) in a belly-tendon arrangement on first dorsal interosseous (FDI), abductor pollicis brevis (APB), flexor pollicis brevis (FPB), and biceps brachii muscles. The electromyogram (EMG) from the FDI and APB was analyzed for the outcome measures. All EMG channels were monitored during the rTMS for safety considerations, and the FDI, APB, and FPB were used to trigger the rTMS during functional-rTMS (see below). The EMG was recorded using a PowerLab 16/30 system (sampled at 2 kHz; bandpass filtered at 10 Hz–5 kHz for the steadiness task and 1 Hz–5 kHz for the TMS outcomes). Fig. 1 displays a schematic of the protocol.

3.1. Cortical excitability testing use paired-pulse TMS

Motor cortex stimulation was delivered with a 70 mm figure-of-eight shaped coil and two Magstim 2002 stimulators connected through a bi-stimulation module (Magstim Ltd., UK). The coil was positioned with the handle pointing posterior along a sagittal axis inducing a current posterior to anterior. The stimulation area (hot spot) was determined as the point consistently producing the largest MEP amplitude in the FDI muscle. The FDI was used to determine the hot spot and resting motor threshold (RMT) for three reasons: (1) the RMT is similar to other intrinsic hand muscles