Title: Can rTMS Enhance Somatosensory Recovery After Stroke?

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Abbreviated protocol

Specific Aims. There is a confluence of evidence that supports the proposed work. First, sensory recovery is a product of brain plasticity and can be achieved even in chronic stages after stroke as demonstrated by preliminary data and evidence from the literature. Second, rehabilitation therapies can be enhanced with rTMS. Both post-stroke rehabilitation and rTMS are well established methodologies in the investigators' laboratories. Third, there is limited knowledge regarding the most effective type of rTMS (facilitatory or inhibitory) that would enhance recovery of somatosensation for individuals in chronic stages after stroke. Therefore, the main objective of this study is to test the feasibility and preliminary efficacy of a novel approach to treat sensory deficits after stroke with a combination of repetitive Transcranial Magnetic Stimulation (rTMS) and peripheral arm and hand sensory therapy. We propose to address the two study Aims by testing the following hypotheses. Aim 1: Test effect of rTMS of the contralesional S1 region on sensory function Hypothesis 1a. Facilitatory rTMS of contralesional S1 produces a greater response versus sham rTMS, according to a measure of tactile discrimination. Hypothesis 1b. Facilitatory rTMS of contralesional S1 produces a greater response versus inhibitory rTMS in improving tactile discrimination. Aim 2: Characterize neurophysiological changes in response to rTMS of contralesional S1. Hypothesis 2: Repetitive TMS of the contralesional S1 region leads to functional brain changes.

Study design overview. We will enroll subjects who are at least 6 months from onset of the first ever stroke and who have residual sensory deficits. There will be 3 treatment sessions at least 7 days apart consisted of rTMS and sensory re-education therapies. Prior to the first intervention session, there will be a baseline data collection session. rTMS will target the contralesional (intact hemisphere) primary sensory region. rTMS stimulation will be either facilitatory, i.e. temporary increasing brain activity, or inhibitory, i.e. temporary decreasing brain activity. rTMS will be administered in combination with peripheral sensory therapies. The order of the sessions will be randomly assigned. All evaluations will be performed by a therapist who will be blinded to the site or the type of rTMS..

rTMS intervention. We will use a frameless stereotaxy system, Brainsight 2(Rogue Research, Inc., Montreal, QC) to perform image-guided TMS. The optimal stimulation site will be approximately 2 cm posterior to the hand motor area and to a hotspot for eliciting MEPs in first dorsal interossues (FDI) (Schneider 2010).

A Magstim Super Rapid 200[2] magnetic stimulator (MagStim Company Ltd., Wales, UK) will be used along with a flat 70 mm figure-of-eight magnetic air-cooled coil with a maximum magnetic field strength of 1.5 T (Tesla) and an average inductance of 15.5 μH. The figure-of-eight coil produces a focal stimulation point in the middle of the junction between the two circular coil elements. We will use both inhibitory and facilitatory rTMS stimulation protocols (Pleger 2006,Huang 2005). These protocols have been effectively used in achieving changes in somatosensation in healthy adults (Premji 2010,Ragert 2008). Facilitatory rTMS protocol will consist of 5Hz rTMS at 90% resting MT; a total of 1250 pulses (Pleger 2006), (Rossini 1999,Rossini 1994). Inhibitory rTMS protocol will consist of 1Hz rTMS for a total of 1200 pulses. Sham intervention will be provided using a sham coil. The active coil is a flat 70 mm figure-of-eight magnetic air-cooled coil with a maximum magnetic field strength of 1.5 T (Tesla) and an average inductance of 15.5 μH; the sham coil is identical in appearance to the active coil but has a maximum magnetic field of 0.2T and an average inductance of 2.8 μH which is well below stimulus threshold while producing similar sensory and auditory effects.

Peripheral Sensory stimulation will consist of vibratory stimulation (5 minutes), and functional neuromusclular electrical stimulation (5 minutes) of the affected arm and will be administered simultaneously after the rTMS treatments.

Aim1 (testing Hypothesis 1a and 1b) Test effect of rTMS of the contralesional S1 region on sensory function **The primary outcome** measures will be **two point discrimination**. It will be collected at 3 time points during the treatment session (once before and 2 times after the rTMS: immediately after and 1 hour after. **Two-point discrimination** will be measured with Disk-Criminator disks (Baltimore, MD) by determining subjects' ability to distinguish if the touch consisted of one or two points.

Aim 2 to test Hypothesis 2: Characterize neurophysiological changes in response to rTMS of contralesional S1.. The primary outcome measure to test Hypothesis 2 we will be **SEP** . It will be collected at 3 time points during the treatment session (once before and 2 times after the rTMS: immediately after and 1 hour after. **Somatosensory evoked potentials (SEP)**. SEP will be induced by stimulation of the median nerves at the wrist with a square pulse of 0.2ms delivered at 3Hz at an intensity of 2.5 times above sensory threshold but below pain threshold (Delberghe 1990). SEPs will be recorded with Ag-AgCl scalp electrodes placed on the scalp over S1 cortical region keeping impedance at 5kΩ (2 cm posterior to the C3 and C4 coordinate, International 10-20 system (Nuwer 1994)), referenced to a frontocentral Fz electrode and grounded with a clavicular electrode. Location of the scalp electrodes will be digitized with Brainsight system (Rogue, Montreal) for later coregistration with the TMS data. SEP will be acquired with a Neuroscan system (Compumedics, Charlotte, NC) at a sampling rate of 1kHz using a 10 DC gain and band filtered(low pass 40 Hz, high pass 0.1 Hz, notch at 60 Hz). SEP data will be collected in blocks of 500 epochs. The N20/P30 components will be identified based on their latency and polarity and their peak-to peak amplitude measured. N20 is a negative peak within a primary sensory receptive region at 20 ms following peripheral nerve stimulus (Allison 1989,Lueders 1983). We expect to find changes in the amplitude and possibly latency of N20/P25 SEP component (Premji 2010).

Inclusion criteria

- Medically stable and at least 6 months after first ever stroke
- Cognition sufficiently intact to give valid informed consent to participate (Etchells 1999)
- Ability to follow two stage commands
- Impaired but not absent ability to feel touch, vibration, movement of affect arm
- Sufficient endurance to participate in the study
- Age > 18

Exclusion Criteria

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- More than one ischemic strokes or stroke affecting both sides
- Significant neglect for those with left-sided deficits
- Acute or progressive cardiac, renal, respiratory, neurological disorders or malignancy.
- Any psychiatric diagnosis or active psychological condition
- Presence of implanted medical devices such as cardiac pacemakers and defibrillators, intrathecal drug delivery pumps, or spinal cord, vagus nerve or similar stimulators, or cochlear implants
- Presence of metallic hardware that would be in close contact with the TMS discharging coil such as intracranial implants, aneurysm clips, plates, electrodes

- Past history of seizures or unexplained loss of consciousness
- Family history of medication refractory epilepsy
- History of substance abuse within the last 6 months
- Chronic sleep deprivation, ongoing untreated sleep disorder
- Concurrent ototoxic medication (aminoglycodides, cisplantine)
- Pregnancy or pregnancy planning during the study period
- Currently taking medications or substances that lower the threshold for onset of seizure: imipramine, amitriptyline, doxepine, nortriptyline, maprotiline, chlorpromazine, clozapine, foscarnet, ganciclovir, ritonavir, amphetamines, cocaine (MDMA, ecstasy), phencyclidine (PCP, angel's dust), ketamine, gamma-hydroxybutyrate, alcohol, theophylline.
- Individuals will be excluded if they recently stopped taking the following drugs within the past 6 months: alcohol, barbiturates, benzodiazepines, meprobamate and chloral hydrate.
- Inability to understand English
- Unavailable to participate in the study

Statistical Analysis Plan. The outcome measures for the aims are typical longitudinal data. Linear mixed models (LMM) will be fitted for the data. LMM is a generalization of the standard linear model, permitting the data to exhibit correlation and nonconstant variability.