Noninvasive brain stimulation to evaluate neural plasticity after stroke

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Research Plan:

This pilot project will recruit a sample of 30 individuals with subcortical stroke aged 18-85 in the chronic phase of recovery with mild-moderate impairment of arm function (Fugl-Meyer upper extremity motor score[1] of less than 61) and 30 healthy controls. In testing sessions at the Neural Plasticity Research Laboratory (NPRL), participants will undergo: 1) noninvasive targeting of cortical locations by stereotactic neuronavigation using TMS, 2) a paired associative stimulation (PAS) protocol using noninvasive stimulation 3) EEG recording during TMS and, 4) arm motor function assessments. Participants may also be asked to complete a single magnetic resonance imaging (MRI) session prior to testing in the NPRL. Up to 5 testing sessions will be performed. The duration of each session will be less than 3 hours.

Inclusion Criteria. Individuals aged 18-85 with a middle cerebral artery stroke will be recruited. Individuals will have a first time stroke that affects the corona radiata and/or internal capsule. Stroke in these regions is common, comprising 34% of the total population[2]. Individuals in the healthy control group will be matched for handedness, gender, age (within 5 years) and education (within 2 years) to each participant in the stroke group.

Exclusion Criteria. Any participant will be excluded if they: 1) are outside the age range of 18-85; 2) show signs of dementia (score < 24 on the Montreal Cognitive Assessment);[3] 3) have aphasia (score < 13 on the Frenchay Aphasia Screen);[4] 4) have a history of head trauma, a major psychiatric diagnosis, neurodegenerative disorder or substance abuse; or 5) report contraindications to TMS.

TMS procedures:

During TMS assessment, stereotactic neuronavigation will be conducted in real-time using the BrainSight system to localize stimulation over the motor representation of the hand bilaterally using a standard brain template (Figure 1). Subjects will be seated comfortably in a reclining chair during the TMS-EEG assessment. The target muscle for stimulation will be the abductor pollicis brevis (APB). Active motor threshold (% of maximum stimulator output) for the APB representation in M1 will be determined bilaterally using standard protocols[5]. All stimulation parameters fall within published safety guidelines[6].

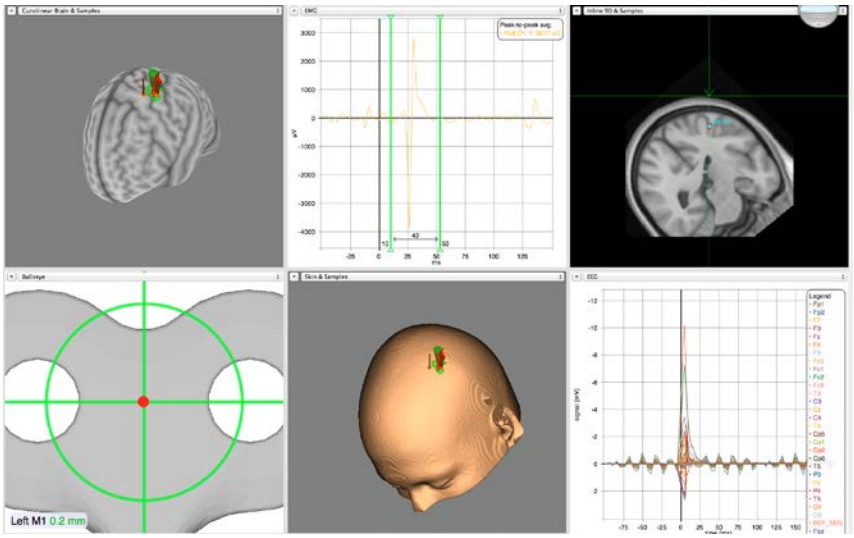

Figure 1. Real-time integration of EEG, TMS, EMG and MRI template information using BrainSight system.

Median nerve stimulation

TMS-evoked responses can be modulated when paired with a preceding peripheral nerve stimulus. When peripheral stimulation is applied 20-25ms prior to cortical stimulation, a

reduction in cortical excitability is observed, termed short-afferent inhibition (SAI)[7,8]. Stimulation of the median nerve will be performed using a bipolar bar electrode affixed to palmar aspect of the forearm proximal to the crease of the wrist bilaterally. Stimuli will be delivered 23ms prior to the TMS pulse with 0.1ms rectangular pulses at an intensity to evoke a 1mV response in the APB.

Paired associative stimulation (PAS) protocols to induce transient shifts in cortical excitability:
TMS pulses can be paired with another stimulation pulse at a particular interstimulus interval (ISI) in order to elicit transient changes in synaptic plasticity in humans. For example, long-term potentiation (LTP, a feature of synaptic plasticity) can be measured in humans using a technique termed PAS, which combines TMS and electrical stimulation of the median nerve, to excite the motor cortex (M1).[8] TMS pulses over M1 can also be combined with TMS pulses delivered over other cortical regions in a 'cortico-cortical' (cc)PAS paradigm to also induce local LTP-like effects.[9] For each PAS session, individuals will either receive traditional PAS, ccPAS or a sham stimulation intervention. Regardless of PAS group, each participant will receive 180 paired stimuli delivered at 0.25Hz for a total PAS duration of 12min. The ISI will depend on PAS condition. For traditional PAS, median nerve stimuli at 300% of the perceptual threshold will be applied 25ms prior to TMS delivery over the ipsilesional (stroke) or non-dominant (control) cortex. For ccPAS, the interstimulus interval will range from 5-15ms depending on site of stimulation[9-11].

EEG recording of TMS-evoked cortical responses:
EEG data will be recorded using a 64-channel TMS-compatible electrode cap (Easy Cap)[12]. Signals will be collected at 2000Hz (impedance: <5kΩ, low-pass filter: 0.1-500Hz) during pre- and post-TMS stimulation epochs (-100ms to 200ms) (Figure 3). Fifty suprathreshold (120% AMT) TMS pulses will be applied to M1 while the subject is seated quietly with eyes open[13,14]. This procedure will be conducted bilaterally at each assessment timepoint (Pre-PAS, Post-PAS 0', Post-PAS 30', Post-PAS 60'). Peripheral auditory and somatosensory stimulation effects will be minimized to avoid EEG artifact[15]. Data epochs (−1000 to 4000 ms with respect to TMS delivery) will be extracted for subsequent imaginary phase coherence analysis (IPC). Post-TMS coherence values between electrodes overlying M1 bilaterally (C3 and C4) will be calculated within the beta frequency range (15 to 30 Hz)[16]. These IPC values will be used to index local M1 excitability and connectivity with the contralateral homotopic region[17,18]. Differences in single-channel evoked potentials in the TMS alone will be calculated to consider the effect of afferent peripheral input on TMS-elicited cortical responses.

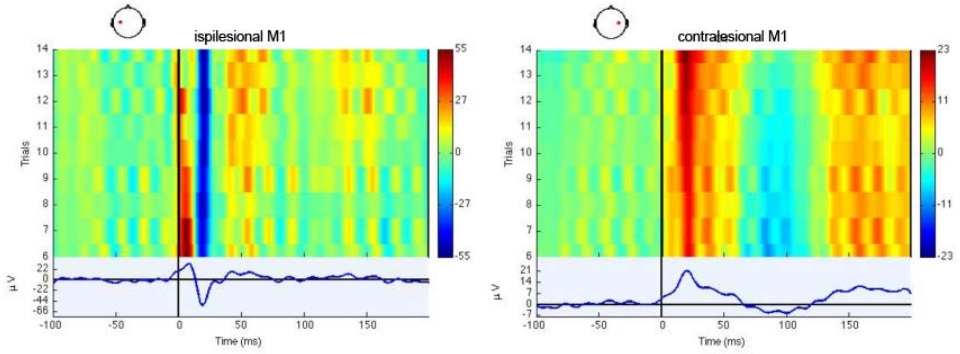

Figure 2. Example of TMS-evoked EEG data recorded from stimulated (iM1) and non-stimulated (cM1) cortical regions.

Motor function assessment:
In the stroke group, arm function will be evaluated by the Wolf Motor Function Test (WMFT), shown to be a valid and reliable test of arm function in stroke[19]. In both groups, hand-held dynamometry will be used to measure grip strength and manual dexterity will be indexed by the Nine-hole Peg Test (9HPT)[20]. These assessments will be carried out by a licensed physical therapist (M.R.B) prior to completing the PAS protocol. The serial reaction time task (SRTT) will be performed at each assessment time point to evaluate motor skill performance. The SRTT involves pressing a key that corresponds to a target square positioned on a screen in front of the participant as quickly and accurately as possible. The response time for repeated and random sequences will evaluate SRTT performance.

MRI acquisition: Scanning will be conducted at Emory University at the Center for Systems Imaging on a Siemens 3T Trio whole-body MRI scanner. A high-resolution T_1 scan (TR = 7.4ms, TE = 3.7ms, flip angle $\theta = 6°$, FOV = 256mm, 160 slices, 1 mm thickness, scan time=3.2min) will be performed without contrast. The study team will have direct and immediate access to the data using Emory University's secure network server.

Statistical Plan:
To address the hypothesis that PAS induces LTP-like plasticity in both individuals with stroke and healthy controls, a three-way group (stroke, control) x condition (real PAS, sham PAS) x time (Pre-PAS, Post-PAS 0', Post-PAS 30', Post-PAS 60') analysis of variance (ANOVA) will be performed for the primary dependent measures (IPC and WMFT time).
For the analysis, an alpha = .05 will be used and simple effects analyses will be performed for significant interaction effects.

Power analysis:
To ensure we have sufficient statistical power for our proposed aims, we used a combination of our standalone TMS data collected in participants with chronic stroke and TMS-EEG data collected to evaluate interhemispheric connectivity in young, healthy individuals[16]. To detect a hemispheric difference in iSP ratio of 0.06 with a common σ=0.11, b=0.8, a sample size of 27 subjects is required. In order to measure differences in TMS-evoked EEG responses in the hemisphere opposite the site of stimulation with a mean difference: 430μV.msec, common σ=288μV.msec, b=0.8, a sample size of 4 subjects is required. Due to the increased measurement variability in stroke, we chose a necessary sample size of n=30/group.

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