Medical University of South Carolina
Protocol

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Study Title: **NEURAL CIRCUITRIES OF MOTOR LEARNING AS A TARGET TO MODULATE SENSORIMOTOR RECOVERY AFTER STROKE**

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A. SPECIFIC AIMS

Experience-dependent plasticity in neural networks is generally appreciated as a resource for recovery, but no interventional approach exists to prevent maladaptive plastic processes (e.g., resulting in learned disuse of the paretic hand)[1]. The problem is that the mechanisms that drive maladaptive plasticity during sensorimotor recovery are still incompletely understood[2]. Additionally, it remains an open question to what degree plastic changes during recovery and sensorimotor learning share common neural circuits[3,4]. Imaging and electrophysiological evidence support learning stage-specific dynamics (e.g., in early/late encoding, consolidation) within circuits of cortical and subcortical regions that engage in distinct types of motor learning (e.g., implicit, explicit) in the intact nervous system[5–7].

Despite increasing evidence for stroke-related neural network disruptions to predict impairment in many behavioral domains[8], we still have a limited understanding of how brain lesions impact the dynamics within learning circuits and how this relates to maladaptive plastic changes. First data shows altered functional network characteristics suggesting deficient communication between task-relevant regions that are potentially linked to deficient integration of new (to be learned) information in stroke[9,10]. A separate line of research indicates a lesion-induced reorganization of the motor executive functional network connectivity that reflects the restoration of motor function[11,12].

A more comprehensive understanding of the interaction between a focal lesion and the dynamics within neural networks during sensorimotor learning will yield important information about the capacity to integrate new information and potentially avoid maladaptive mechanisms. While this is particularly relevant in the early phase post-stroke, during which these plastic changes supposedly develop[2], investigating the chronic phase in a first step will allow including biomarkers of recovery as covariates into the analysis of network alterations.

So far, the fields of sensorimotor rehabilitation research and motor-learning-related network science have not been integrated sufficiently[13] but primarily conducted in isolation, thus rendering an inclusive view impossible. Additionally, suitable paradigms that systematically differentiate types of motor learning and learning stages have not been implemented systematically for populations with sensorimotor deficits, which precludes the identification of specific network dynamics and their relevance to sensorimotor recovery.

Bringing together longstanding expertise in stroke rehabilitation, kinematic analyses of complex behavior, and advanced neuroimaging, Dr. Heise and the multi-professional COBRE team are uniquely positioned to advance the field of learning research as a diagnostic tool in the context of stroke rehabilitation. Dr. Heise (PI) combines expert knowledge in studying dynamics of complex motor control and learning using neurophysiological, neuroimaging techniques, and non-invasive brain stimulation in healthy and neurological populations[14–17], with longstanding clinical experience in the field of stroke rehabilitation.

We still do not know enough about how a focal lesion impacts the dynamics within brain circuits that govern motor learning and how this relates to maladaptive plastic changes. Filling this knowledge gap builds the basis for designing interventions that causally target experience-dependent maladaptive changes which negatively impact the patient's recovery (e.g., leading to disuse of the paretic hand). With this JI project, we will generate pilot data serving as the first evidence for motor learning-related network dynamics in the chronic phase after stroke (aim 1) and their link with biomarkers of recovery of upper-extremity sensorimotor function (aim 2).

AIM 1 To characterize motor learning (ML)-related neural network dynamics in the presence of a focal lesion, we will use a representational statistical modeling approach[18] to describe learning-related connectivity changes based on task-based functional magnetic resonance imaging (fMRI) in stroke survivors (≥6 months post-lesion, stroke group SG) and healthy volunteers of comparable age and gender (control group, CG). Functional connectivity patterns will be modeled throughout the acquisition phase to capture the temporal trajectory of encoding-related network changes.

AIM 2 To understand the association between ML-related network dynamics and biomarkers of recovery, we will comprehensively describe upper-extremity sensorimotor functioning and impairment for the individuals in the SG and statistically integrate these biomarkers of recovery with the ML-related network dynamics within a separate representational model.

B. BACKGROUND AND SIGNIFICANCE

Recovery of upper extremity function remains dissatisfying for the majority of stroke survivors with sensorimotor impairment[19], which represents a major hindrance to independence in daily life[20]. Within the field of rehabilitation research, learning mechanisms have long been a major area of interest because they are considered one key player in functional recovery. This basic premise goes back to seminal work that established the brain's capacity to change in response to environmental stimuli and learning, i.e., experience-dependent plasticity[21,22].

However, it is evident that plasticity does not have purely beneficial effects on recovery[3] but that also negative consequences such as learned disuse of the paretic hand can be observed[1].

The proposed JI project implements a conceptually and methodologically innovative approach to characterize stroke-related alterations within functional circuits that govern sensorimotor learning and their link to recovery. The completion of this project will set the stage for the PI's planned next steps. Altered network dynamics during learning in the SG will provide network-informed targets for non-invasive brain stimulation to further investigate their modifiability and behavioral relevance. Additionally, they justify the longitudinal investigation of network dynamics within learning circuits during the development of maladaptive plastic changes longitudinally in the early phase after stroke.

C. PRELIMINARY STUDIES

The project describes a pilot study and serves as a proof-of-concept to generate preliminary data to support the planned follow-up R01 proposal.

D. RESEARCH DESIGN AND METHODS (including data analysis)

D1. OVERVIEW OF STUDY STRUCTURE AND PROCEDURES

D1.1 Sample Size Rationale & Recruitment Feasibility.

Before the main study described below, a short series of pilot experiments is planned to iteratively test the experimental paradigm with the goal to assure feasibility of all experimental procedures for varying levels of motor-functional capacity in the stroke group.

Initial pilot phase. For this initial phase, which precedes the main study, we anticipate recruiting a maximum of N=40 volunteers (patients and controls) to iteratively test and optimize the paradigm (the learning task) for use in the MRI environment.

Main study. Target recruitment will include N=25 stroke survivors in the chronic phase (≥6 months after index lesion, stroke group) and N=15 healthy volunteers of comparable gender, age range and education level (control group). There will be no overlap with individuals of the initial pilot phase. Based on previous work, we anticipate that with these sample sizes it will be sufficient to determine the feasibility and effect sizes for the planned follow-up R01 application (also see Sample Size Justification below).

Recruitment. This study will recruit from the Registry for Stroke Recovery (RESTORE-Pro#00037803, IRB approved 9/6/14) which is a research tool sponsored by the National Institutes of Health (NIH) Center of Biomedical Research Excellence (COBRE) in Stroke Recovery with participants consented for future contact to support stroke recovery research conducted at MUSC. Trained RESTORE staff will query the registry for potential volunteers and provide the Principal Investigator (PI) or a member of the research team with the contact information of subjects who meet their criteria. Since these patients have already consented to being contacted for future research, the PI or a member of the research team will contact potential volunteers to further screen for potential enrollment. Contact will be sought via the preferred option indicated by the patient in the registry, e.g., via phone or email.

Recruitment of patients is feasible as it will happen in collaboration with the QBAR Core therapist team and capitalizing on the RESTORE database with over 800 participants, potentially eligible for this study. Volunteers for the control group will feasibly be recruited through the same channel and from spouses of patients and word-of-mouth to assure comparability concerning age, gender, and confounding variables such as education level. In addition, the potentially interested people will be accessed through flyers distributed digitally through MUSC information screens, the online platform Yammer.com, as well as through the MUSC Wellness Center.

Participants. For the initial pilot phase and the main study, chronic stroke survivors (time since stroke greater than or equal to 6 months) will be recruited. Acute stroke survivors (time since stroke less than 6 months) are excluded to minimize confounding from the spontaneous recovery of cognitive functioning.

D1.2 Participant Inclusion Criteria.

For all participants: Adult volunteers (age ≥18 years) with right-hand dominance[23] will be recruited for the stroke and control group.

Stroke-specific inclusion criteria are defined as (1) ischemic or hemorrhagic lesion with (2) subcortical or cortical tissue involvement, and (3) in the chronic phase (>6 months) after their index lesion, (4) voluntary whole-hand grip force (MRC, Medical Research Council scale for muscle force ≥2[24]) and repeated release (standardized as a reduction of 50% of maximum voluntary contraction measured with a dynamometer).

D1.3 Participant Exclusion Criteria.

For all participants: Any contraindication for MRI scanning is a general exclusion criterion irrespective of group. Primary intracerebral hematoma or subarachnoid hemorrhage, bi-hemispheric ischemic strokes, other concomitant neurological disorders affecting motor or cognitive function (e.g., dementia); moderate to severe global aphasia; visual impairment that precludes completion of scanner tasks; presence of any MRI risk factors such as an electrically, magnetically or mechanically activated metal or nonmetal implant including cardiac pacemaker, intracerebral vascular clips or any other electrically sensitive support system; pregnancy as the effect of MRI on the fetus is unknown; history of seizure disorder; claustrophobia; substance use disorder; psychotic disorders; moderate to severe traumatic brain injury

Stroke-group specific exclusion criteria are defined as: Primary intracerebral hematoma, or subarachnoid hemorrhage; bi-hemispheric or cerebellar strokes; other concomitant neurological disorders affecting upper extremity motor function; documented history of dementia before or after stroke; severe aphasia, particularly of receptive nature (NIHSS Language subsection ≥2[25]) affecting their ability to understand the purpose of the study and give informed consent; uncontrolled hypertension despite treatment; intake of tricyclic anti-depressants or neuroleptic medication.

D1.4 Procedures

Telephone Eligibility Screening (session 0). Potential participants of the stroke group will be pre-screened for eligibility regarding level of upper-extremity sensorimotor function and to exclude moderate or severe cognitive impairment. In lack of a validated phone proxy tool, we will use a questionnaire-based interview to estimate the level of sensorimotor function in a standardized and reproducible way (Appendix 1). Individuals reporting minimal voluntary whole-hand grip and release control will be invited for further assessment of in- and exclusion criteria if additionally identified as cognitively *unimpaired*, *ambiguous*, or *mildly impaired* by the Telephone Interview for Cognitive Status (TICS)[26,27]. Eligibility for MR imaging is screened (MRI safety screen). Individuals who are able to complete these tasks demonstrate intact decision-making capacity. Individuals identified by the TICS as *moderately* or *severely impaired* will not be invited. The telephone screening will be done by a member of the administrative member of the research team who is trained to perform the questionnaire-based interview. To ensure to recruit only eligible participants for the patient group, telephone eligibility screening needs to be performed prior to obtaining informed consent. Data generated during this initial phone interview for participants not included in the study, will not be stored. Data of participants who are recruited and consented will be stored with the participant's data under the participant's study identification number after removal of identifiable information (name, contact details).

In-person Eligibility Screening (session 0). In cases in which in-person screening is feasible, e.g., if potential participants are already at the study site and have expressed interest in participating in this study, potential participants will be pre-screened based on the same information as in the telephone screening. One exception is the cognitive screening, which will be done with the Montreal Cognitive Assessment (MoCA)[36] instead of the Telephone Interview for Cognitive Status (TICS)[26,27]. In these cases, no TICS data will be collected.

Informed Consent (session 1). Informed consent can be obtained in a written fashion by one of the members of the study team. Participants will be provided with ample time to review the consent document prior to discussion with a member of the study team. The nature of the study will be explained by a member of the study team in lay terms. If the participant or control agrees to participate in the study, they will sign and date the informed consent and HIPAA forms (or combined consent/HIPAA if applicable). They will also be informed that they may choose to withdraw from the study at any time. Participants will be informed that their decision regarding participation will not affect their clinical care in any way. A copy of the signed informed consent and HIPAA will be provided to participants.

Alternatively, electronic consent (eConsent) will be obtained through the REDCap system. A member of the research team will reach out to the participant by phone to provide details of the study. If the participant agrees to participate, a link to the REDCap eConsent will be provided to the participant via a hyperlink (text or email), and a member of the study team will review the consent document over the phone or via videoconferencing with the participant. The participant will electronically sign the eConsent and submit the REDCap survey. The study team member will then electronically sign the eConsent and print a PDF of the document. The signed PDF willl be emailed or mailed to participants for their records. eConsent will be implemented at sites that support this method of consent.

Multi-System Assessment (session 2). Following consent, participants of both groups will be assessed regarding their neuro-cognitive and emotional functioning to further assure eligibility. Handedness (for participants of the stroke group this relates to pre-morbid status) will be assessed with the Edinburgh Handedness Inventory[23].

In addition, participants of the stroke group undergo the assessment of their upper-extremity sensorimotor functioning as well as the evaluation of stroke-related quality of life (SIS-3.0[20,28]). General severity of stroke-related symptoms will be quantified with the NIH Stroke Scale (NIH-SS)[29,30]. The NIH-SS will be performed by the PI or research staff certified for testing the NIH-SS.

Physical Assessment of upper-extremity sensorimotor functioning. To comprehensively characterize a broad range of upper extremity sensorimotor control, a test battery will be used that captures the non-/low-functional up to fine-motor impairment level. Passive and active range of motion and movement-associated pain of the paretic upper extremity will be evaluated with the upper-extremity section of the Fugl-Meyer Assessment (UEFMA)[31]. To characterize grasp, grip, pinch, and gross-motor functioning with relevance to activities of daily living, the Action Research Arm Test will be used (ARAT)[32,33]. To quantify dexterity of individual finger movements, the Nine-Hole Peg Test (9HPT)[34,35] will be used. To quantify maximum voluntary contraction (MVC) and repeated contraction/release of contraction, a digital dynamometer will be used. All physical examination will be performed by a study therapist trained in standardized testing of upper-extremity function.

Neuro-Cognitive and emotion Assessment. To further ensure eligibility, an in-person session will take place. Following consent, the Montreal Cognitive Assessment (MoCA)[36] will be completed. Participants will complete computerized cognitive tests from the NIH Toolbox[39] (30-40 minutes). Each of these tests has been extensively normed compared to traditional neuropsychological measures. Tests from different batteries will be utilized in this study to optimize a comprehensive but efficient, reliable, and minimally burdensome subset of tests for chronic stroke patients. Participants of the SG presenting with aphasic symptoms will also complete the bedside Western Aphasia Battery (WAB)[37], to measure levels of aphasia that would preclude valid assessment in all other domains. Similarly, participants will complete the Virtual Reality Lateralized Attention Test (VRLAT)[38] if suspected of presenting with neglect symptoms.

The Patient Health Questionnaire-9 Item (PHQ-9)[41] will be administered to screen for depression and anxiety as these are relevant confounders for learning and memory.

All neuro-cognitive and emotion assessment will be performed by trained personnel and overseen by a licensed clinical psychologist (Dr. Lisa McTeague).

Sleep and vigilance screening. General sleep quality is quantified with the Pittsburgh Sleep Quality Index (PSQI)[43] once in session 2. Sleep duration and quality of the night preceding each individual experimental session are assessed with the respective items of the St. Mary's sleep questionnaire[44]. Before the task training and retest sessions, self-perceived vigilance is evaluated with the Stanford Sleepiness Scale (SSS)[45] and additionally quantified objectively with the psychomotor-vigilance task (PVT)[46]. Except PSQI, all of the above-mentioned sleep and vigilance screening assessments are performed on both experimental sessions (session 3 and 4). All sleep and vigilance screening will be performed by the PI or a member of the research team.

Additional Questionnaires will be used to collect information about the participant's demographics including age, gender, level of education in addition to medication intake (Appendix 2).

To reduce the burden for those participants who have participated in a study at the Stroke Recovery Research Center involving the same standardized assessments and questionnaires and consented to data sharing, we will use the already available data if these have been collected within ≤30 days.

Two-layered Learning Task (sessions 3 and 4). We will adapt an established sequence learning paradigm[47,48] for the use in patients with sensorimotor impairment of the upper extremity. Two layers of implicit sequential information (Figure 1) are implemented in the experimental paradigm through visual stimuli on a computer screen to distinguish the two modes of implicit learning. Behavior is captured with whole-hand grip-force transducers (the hand-held interface) requiring minimal active range of motion and voluntary muscle force.

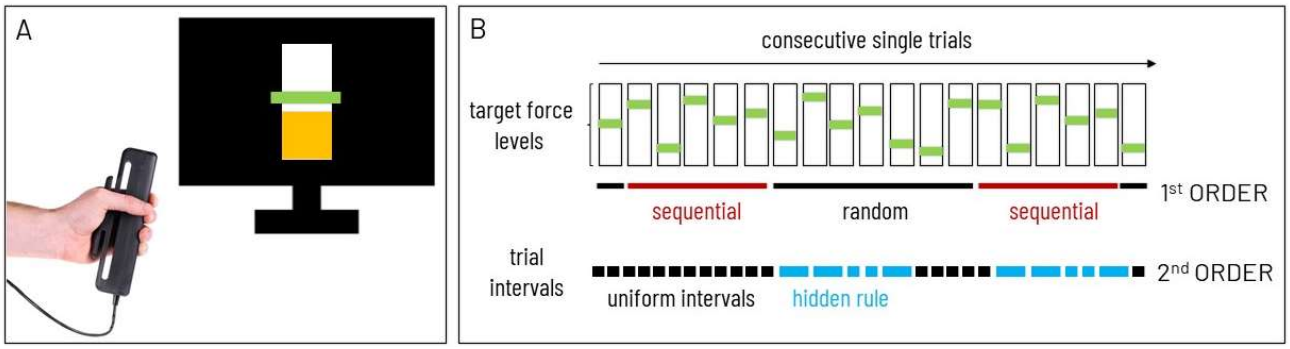

Figure 1 *Behavioral paradigm and participant flow. A) Experimental set-up showing visual stimuli with imperative cue (green) and force feedback (yellow) to implement the stimulus-response mapping of cue positions and input force level scaled relative to individual*

The force will be defined relative to maximum voluntary contraction for each hand separately. This allows even low-functioning participants to perform the task with the paretic hand. The participants will receive the instruction to follow the imperative cue by adjusting their own grip force. Feedback will be provided about the actual grip force in real-time. Force adjustment happens in stepwise increments of the relative force, which allows to induce two different implicit learning modes. Specifically, the volunteers will learn the association between visual cue and individual force level (1st order) within standard serial reaction time task[49], in which a sequence of force levels is provided repetitively and contrasted with random force levels. In addition, they will learn the hidden rule, i.e., the 2nd order sequence that can occur among both, the first-order sequential and the random force levels. This hidden regularity will be implemented through the sequential variation of cue intervals comparable to a morse code that occurs among otherwise uniform intervals. Based on the recorded muscle force (1000Hz sampling rate), the behavioral outcome (temporal/spatial accuracy) is monitored continuously throughout the learning phase. This procedure makes it possible to differentiate performance in the two learning modes. Furthermore, as left and right hand will be tested, it will be possible to estimate the impact of hand-dominance and side of lesion (non-/paretic hand) on the learning capacity for each learning mode.

Imaging Parameters (sessions 3 and 4). Scanning will take place at the Center for Biomedical Imaging on the Siemens 3T Prisma. Functional and structural scanning parameters are detailed in the **NI Core**. High-resolution structural, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted (DWI), and arterial spin labeling (ASL) perfusion imaging will use in-house standard sequences and will be collected from all participants in session 3. The task-based fMRI sequence will be optimized for an event-related design with a TR of 2 seconds. For the resting-state data, a TR of 0.8 seconds will be used. Task-based and resting-state imaging will be collected in session 4 with varying protocols for participants of SG and CG as described in the timeline below and explicitly detailed in the information and consent form. All MRI sequences will be accompanied by electrical recording of physiological signals from the upper body (e.g., electrocardiogram, electrodermal analyses) to support processing of MRI data and for secondary analyses examining relationships between autonomic nervous system dysfunction, brain, and behavioral outcomes.

D2. TIMELINE

Participants of both groups (stroke, control) will undergo the same protocol, which includes 4 sessions (outlined in the table below).

Session Number	Task Description	Location at Medical University of South Carolina	Approximate Time Commitment
0	**Telephone Eligibility Screening** • Sensorimotor function screening (Appendix 1) • Cognitive screening (TICS[26,27]) • MRI Safety Screen	Via telephone	30 minutes
1	**Consent**	Stroke Recovery Research Center or remotely through electronic consent	20-30 minutes
2	**Multi-system Assessment** All participants • Pregnancy Test • EHI[§] • Questionnaires (Appendix 2)[§] • Neuro-Cognitive and emotion Assessment Stroke group • physical Assessment of upper-extremity sensorimotor functioning • NIH-SS	Stroke Recovery Research Center or partly remotely[§]	3 – 3.5 hours

	• SIS§		
3	**MRI scanning and task familiarization** • MRI Safety Screen • Sleep and vigilance screening <u>MRI sequences:</u> • FLAIR • DWI • ASL • T2* weighted sequence (resting-state) • Physiological recordings <u>Learning task:</u> • Task familiarization (in the mock scanner)	Center for Biomedical Imaging	2 – 2.5 hours
4	**MRI scanning during task practice** MRI Safety Screen Sleep and vigilance screening <u>MRI sequences:</u> • High-resolution T1 weighted • T2* weighted sequence (task-based) during task practice • Physiological recordings	Center for Biomedical Imaging	2 – 2.5 hours

D3. DATA ANALYSIS

D3.1 Sample Size Justification.

Given the scarcity of pilot data on stroke and control participants and fMRI-based dynamic connectivity during motor learning, justification has to be based on our best estimates and regarded with some caution. One of the primary goals of this project is to determine effect sizes for the follow-up grant proposal. For changes to latent connectivity characteristics induced by implicit motor learning (pre/post evaluation), empirically obtained effect size estimates were derived from the average effect size of published studies involving participants with chronic stroke[9] and healthy volunteers[50]. Consequently, sample sizes of 25 and 15 in the stroke survivors and healthy volunteers will allow us to estimate the for the main effect of time (pre/post learning) the within-group effect sizes can be expected to be in the range of 0.33 - 0.52 at 90% confidence level.

D3.2 Analysis Plan.

Imaging Preprocessing. Data will be processed by the CBI Computational Core led by Dr. Hesheng Liu. Preprocessing parameters for the task-based fMRI data will be optimized to fit the requirements of the representational similarity analysis (RSA, described below), specifically smoothing will be reduced to allow for better multivariate pattern detection. Resting-state fMRI data will undergo in-house standard preprocessing.

For the learning task-based data, a general linear model (GLM) will be fitted to each individual's data serving as the basis for the representational similarity analysis (RSA). In addition to the regressors of interest (matched to the onset time of each regressor of the event-related design of the learning-paradigm: 1st and 2nd order sequence force cues, random force cues) six motion parameters will be included as nuisance covariates. Estimated beta-values will be extracted from the GLM for each stimulus and run for each region of interest (ROI) within subject. For each ROI, a neural matrix will be created by correlating (Pearson) the multi-voxel patterns between all possible combinations of pairs of stimuli of the learning task condition and then averaged across subjects within group (first-order RSA[51]). In the second step, group-averaged matrices (only the upper diagonal elements) will be vectorized and correlated (Pearson) for all possible combinations of ROI pairs (second-order RSA[51]), which will allow to investigate the representational similarity between ROIs i.e., the clustering/networks of ROIs, with regard to the between-condition similarity in multi-voxel activation patterns.

For the resting-state data, the connectivity analysis will be used to identify physiological biomarkers for recovery and potential predictors for learning efficiency. For this purpose whole-brain resting-state network fluctuations, based on BOLD signal time courses, will be extracted for cortical and subcortical ROIs. Nuisance regression will be performed to account for the effects of motion on functional connectivity (including six translation and rotation parameters from the motion correction transformation, average CSF, white matter, and whole-brain time courses, as well as the first derivatives, squares, and squared derivatives of each of these confound predictors[52]. To extract the dynamic modulation of connectivity over time, time courses will be divided into sub-blocks of multiples of the TR to allow capturing slow-frequency fluctuations by approximating the frequency envelope of the hemodynamic response at the given TR with the highest possible temporal precision. Connectivity will be quantified as the magnitude-squared coherence[53,54] between each pair of ROI for each sub-block of time[55]. Network characteristics and their temporal dynamics will then be analyzed with dynamic network statistics following the approach given in reference[55].

D3.3 Consideration of Sex as a Biological Variable.

While this study will not be sufficiently powered to reveal sex differences, in planned follow-up analyses we will utilize sex as a covariate, as well as age, race, and ethnicity.

D3.4 Potential Challenges and Solutions.

We expect that network definition across participants of the stroke group with varying lesion size and location will be methodologically challenging. Therefore, we will pursue a ROI-based approach in a first step, and we will take an exploratory approach to investigate the influence of lesion location and size on whole-brain networks. As RSA methodology benefits from large sample size, this pilot work includes the conventional univariate analysis of connectivity in its analysis pipeline. The implementation of the RSA analysis pipeline is one of the main purposes of this pilot study even though the results may not provide sufficient power for generalizability.

E. PROTECTION OF HUMAN SUBJECTS

We are committed to conducting safe research that favors benefits over risks. The following sections describe how we will attend to safety and ethical issues involved in conducting the proposed research.

E1. RISKS TO THE SUBJECTS

a. Human Subjects Involvement and Characteristics

As described in section D1, the target sample of the main study will include a total of N=25 adult stroke survivors in the chronic phase, N=15 neurologically healthy adult volunteers, in addition to max. N=8 participants for the initial pilot phase (max. N=4 for stroke and control group).

Inclusion of Women and Minorities.

There is a relatively equal ratio of male to female stroke patients in South Carolina. In the duration of this project, forty (N=25 stroke group, N=15 control group) individuals will be enrolled. Consequently, 50% women will be assigned to each group. There will be no exclusion criteria with respect to ethnic background. Demographic data from the US Census Bureau (2016 estimates.) indicates the sex, race and ethnicity distribution in South Carolina as follows: 51.5% female, 48.5% male; 68.5% white persons not of Hispanic origin, 27.5% Black or African American, 0.5% American Indian and Alaska Natives, 1.6% Asian persons; with 5.5% persons of Hispanic origin). The goal in the proposed study is to construct a participant pool that matches population proportions in South Carolina. (2016; https://www.census.gov/quickfacts/SC). Consequently, we will seek to enroll a minimum of 31.5% minority representation per group. As necessary, advertisements will be placed in newspapers and radio stations with primarily African-American or Hispanic readership and audience.

Comfort and reliability considerations:

During the administration of some of the neuropsychological assessments, the participants' verbal responses will be audio recorded for quality control purposes.

- Video recording of sensorimotor functional tests

During all in-person sessions, snacks and water will be offered between testing administrations in order to improve energy, limit fatigue, and promote comfort. Furthermore, multiple breaks will be offered.

Finally, participants will be given the option to schedule sessions on the same day, with a break, if additional visits/travel would be burdensome.

b. Sources of Materials

Data collected from all participants will include responses to diagnostic interview, neuropsychological assessment, questionnaire responses, structural and functional brain images, behavioral performance from scanner tasks, heart rate, respiration, demographic information, health/medication information (to determine experiment counter-indicators), contact information for scheduling appointments, personal address and other information for processing payment, and related information for the sole purpose of research and ensuring participant safety. Additionally, consent forms and HIPAA forms will be collected.

c. Potential Risks

Risks of in-person visits due to COVID-19

The option to remotely complete some of the sub-tests of the multi-system assessment (session 2), as for example the MoCA, the Stroke Impact Scale, the Edinburgh Handedness Inventory, and the BDI will be given to participants if they are unable to physically come to the Stroke Research Center for the time being, such as due to COVID19 precautions. Phone calls or video conferencing through Microsoft Teams, Zoom (with HIPAA approved license using single sign-on, or Doxy.me will be utilized to properly administer and oversee the completion of these assessments.

MRI risks.

There is a serious risk that MRI could move iron-containing objects in or around the face or head, which could in the process possibly harm the person. As such, these contraindications will be thoroughly screened at intake and at each scan. Participants are thoroughly screened to prevent metal being brought into the MR environment and are asked to change clothes into MR safe (no zippers, buttons, etc.) clothing before entering the MR chamber. In

the absence of risks related to metal, exposure to magnetic field strengths used in the present study is not shown to be a significant health risk. Electrodes used for physiological recordings are MRI safe, however may result in mild irritation to skin at the placement sites where adhesive is present.

Risks to an unborn fetus from exposure to the MRI field strength used in the proposed research (3 Tesla) are unknown. Therefore, pregnant females and those who may become pregnant (unwilling to follow study restrictions limiting chances of conception) will not be allowed to participate. Participants will be asked to lie still and awake for up to 1.5 hours in the scanner and this can occasionally result in soreness, stiff back, etc. Participants will be queried approximately every 10 minutes about their comfort. All investigators and research assistants running participants in imaging center are thoroughly trained in MR safety yearly as a requirement to run scans.

Claustrophobia.
Some emotional discomfort may be anticipated due to the enclosed nature of the MRI. Participants will be screened and encouraged not to participate if he/she has a history of claustrophobia. To minimize participant distress and to ensure comfort and consistent communication with the experimenters and PI during all scans, participants will be queried between each imaging sequence. Procedures are interrupted or terminated when a patient reports or the experimenters and/or PI suspect undue stress.

Risks related to questionnaire- and clinical assessment.
Participants may experience an exacerbation of symptoms by being asked to discuss their histories and/or filling in questionnaires about their mood and health status. Testing will be performed by a licensed clinical psychologist. In the event of a participant becoming agitated or experiencing an exacerbation of symptoms, the testing psychologist will lead the participant in relaxation exercises and debriefing until subjective distress reduces to a comfortable level.

Loss of confidentiality.
Despite efforts to maintain participants' anonymity and confidentiality, there is always some minimal risk of people other than the study investigators gaining access to protected health information.

E2. ADEQUACY OF PROTECTION AGAINST RISKS

The PI and all members of the research team will complete MUSC training in human subjects protection in research. The protocol will include and follow guidelines for protection of participants in research. Additionally, all potential research participants will be informed of their rights as an experimental participant.

a. Recruitment and Informed Consent

Measures taken to limit risk of coercion during recruitment and consent procedure. Participants will be recruited through the COBRE CTTR Core and RESTORE database and contacted through their preferred channel indicated in the registry (e.g., phone or email) to introduce the study and suggest participation. Potential participants will be invited to ask questions until they are satisfied and can make a decision to proceed or not with the phone screen. If the potential participant agrees to continue, a phone screen will be conducted to determine eligibility for the next phase (the assessment of cognitive, motor and emotional functioning) of the study. This screening session serves to assure the participants' ability to read, verbalize understanding of the content discuss, make an informed decision about participation, and sign informed consent documentation. During recruitment care will be given to assess that participants are not coerced and are not motivated solely due to financial remuneration to limit the risk of recruiting primarily socioeconomically disadvantaged individuals.

Informed Consent. If the potential participant passes the pre-screen and decides to come in for the assessment of cognitive, motor and emotional functioning, a signed informed consent will be necessary before beginning assessments. Time will be given between information and consenting to make a decision about participation. Potential participants will be encouraged to discuss the study with a person they trust (e.g., spouse or adult children) before making a decision about participation. E-consent will be an option if the participant is not able to come into the laboratory for consenting. The e-consent will be emailed through REDCap and approved research personnel will go through the e-consent with the participant over the phone or over video conferencing. The participant will receive a copy of the signed e-consent by email from the research personnel. The coordinator will offer to send the

consent form to the participant in advance to provide ample time for review. The consent form describes the study procedures and ensures participants of the confidentiality of their responses. The consent form further reminds participants that they have the option to withdraw from the study at any time and will receive proportional payment or they can refuse to answer certain questions and continue in the study with full compensation. The consent form contains thorough descriptions of the research protocol (physical and neuropsychological assessment, MRI, clinical interview, etc.) including the procedures, benefits and risks, compensation, right to nonparticipation, review processes, emergency medical treatment, financial responsibility, and privacy issues. The content of the consent will be verbally explained to the participant and the participant will be asked to raise any questions and concerns. If the person requests a waiting period, then one will be given. If the person desires to consent immediately, then the person will provide consent immediately.

b. Protection against Risk

Tracking Participant Comfort/Wellbeing.

If there are adverse effects during the laboratory sessions, the PI and/or research assistant will terminate the study, provide a debriefing, and contact PI or staff clinician (if PI is not present) for further assistance and follow-up for the participant. Only trained psychiatrists, psychologists and research staff will administer the subject screenings, assessments, and perform MRI scanning. These professionals will be sensitive to possible signs of subject fatigue or distress. Breaks from testing will be allowable, and the testing sessions may also be rescheduled. Upon study completion, participants will be fully debriefed on the rationale for the study. As part of the debriefing, each participant will also be given the opportunity to ask questions about the study and will be given the contact information of the PI.

Strategies to Ensure Comfort and Retention.

1) We will maintain communication. Specifically, the research coordinator will be in constant communication with participants. The coordinator will ensure the eligibility of the participant, safety of the participant, adherence to tasks, and contentment of the participant, throughout the study duration. The coordinator will explain all expectations and study details and re-explain throughout the study duration. In addition, upcoming visits will be reminded through phone calls or other communication methods of each participant's preference. Change of schedule will also be accommodated and coordinated by the study coordinator. 2) Participants' time and effort spent on research will be remunerated by the participation payment according to the payment schedule. 3) To maximize participants' convenience, a waiting area is provided in the lobby of the CBI with convenient access to the restrooms. Participants' parking is also accommodated in a parking lot adjacent to the research building. 4) We will ensure that our staff is well educated about the protocol and procedures by training and observing all procedures at least quarterly.

Staff Safety Training.

All research staff personnel will successfully complete IRB Certification training (CITI and GCP certification) and will be as forthcoming as possible with participants. Additionally, research staff will receive safety training in MRI by Center for Biomedical Imaging staff at MUSC.

Confidentiality.

All data except for the consent forms and HIPAA forms will be de-identified at the time of data recording. All electronic data will be stored in a password-protected research server that is accessible to study personnel only. The server is backed up every day and maintained 24/7 by IT specialists. All paper data with personally identifiable information including the consent forms and HIPAA forms will be stored in a key-locked cabinet in a key-locked room that is accessible to the study personnel only. Other paper data without personally identifiable information including testing sheets documenting testing sequences and notes will also be stored in a cabinet in a key-locked room that is accessible to study personnel only.

Screening Measures & Emergency Room.

Participants will be thoroughly screened for MRI eligibility multiple times (initial phone contact, intake interview, and again at each MRI scanning session). In the event of adverse effects related to MRI scanning, safety coordinators and medical staff have been trained how to quickly address any emergencies that may arise.

Close monitoring of participant stress and wellbeing will take place over all experimental sessions.

Physiological Recording Equipment.
Physiological recording devices meet all standards for non-invasive, scanner compatible materials.

Incidental findings
Incidental findings that may be uncovered from the MRI scan will be communicated directly to the participant immediately as they are found and explained by the investigator.

E3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

There may be no direct benefits from participating in this study.

E4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

With the precautions in place to select participants, we expect a very low risk of adverse events in our proposed participant cohort. This is relative to the substantial benefit in better understanding the effect of a focal lesion on neural network dynamics during sensorimotor learning in chronic stroke. Thus, the potential benefits for basic research and the expected findings' implications for the future design of targeted treatment for post-stroke sensorimotor rehabilitation likely outweighs the mild discomfort, risks of more serious outcomes, and time spent by participants enrolled in the proposed research.

E5. SUBJECT SAFETY AND MINIMIZING RISKS (Data and Safety Monitoring Plan)

E5.1 Safety Training.

The applicant along with the research assistant assisting with the scans will have taken first aid and CPR certification courses to assess and respond to participant emergencies within and outside of the scanner before beginning the study. Before any investigator or assistant is allowed to enter the scanner room, they are required to take an extensive MRI safety course (with annual refresher courses) that cover powering down (or quenching) the magnet for patient safety and with established procedures for expediting participant contact with emergency medical personnel, should the need arise. These courses are run by the MUSC Center for Biomedical Imaging and are a prerequisite for obtaining privileges to book and use scanner time.

E5.2 Medical Emergencies.

Emergency responding in the scanner is facilitated by having at least two research staff running a scan (applicant and research assistant as well as the MR technologist). In the event of an emergency, one of these individuals remains with the participant and undocks the scanner bed from the magnet bore. This bed can easily be wheeled out of the scan room to facilitate speedy access to arriving emergency medical personnel. The second researcher calls 9-1-1 from the scanner suite and gives details of the participant's level of medical distress and location. Next, this person goes out to the front of the scanner building to flag down arriving emergency personnel and to direct them to the participant. These guidelines are in full agreement with Center for Biomedical Imaging safety protocols.

E5.3 Ethical Research Practices.

Ethical guidelines for clinical research will be followed strictly and all information obtained in the study will be kept strictly confidential. The PI and all research staff and mentors will be responsible for and will comply with mandated reporting rules. All researchers will be obligated to demonstrate that they have remained abreast of all guidelines and rules related to the Health Insurance Portability and Accountability Act (HIPAA). Each member of the research staff will complete focused training on each task for which they are responsible and will perform ongoing quality control for others performing similar work.

E5.4 Data Monitoring Procedures.

The PI and/or study coordinator will produce quarterly administrative reports describing study progress including accrual, demographics, and participants' status. Reports will describe adherence to inclusion/exclusion criteria and the study protocol in addition to any unanticipated problems in the category of risks to participants or others as well

as any adverse events. All collected data will be obtained for research (and participant safety) purposes only. MRI data will be processed biweekly to entail consistent quality and scanner characteristics.

E5.5 Data and Safety Monitoring Board.

Data will be monitored on a bi-annual basis with respect to subject safety issues throughout the award period. The data and safety monitoring plan will include an internal Data Safety Monitoring Committee (DSMC), an external Data and Safety Monitoring Board (DSMB), and the Institutional IRB. The purpose of the DSMC, DSMB, and IRB are to ensure the safety of participants and the validity and integrity of the data.

E5.6 Data Safety Monitoring Committee (DSMC).

The internal DSMC will consist of the PI and co-investigators/consultants on the proposal. The functions of the DSMC will include: 1) providing scientific oversight; 2) reviewing all adverse effects or complications related to the study; 3) monitoring enrollment; 4) reviewing summary reports relating to compliance with protocol requirements; and 5) providing advice on resource allocation. The DSMC will meet quarterly and as necessary by telephone. The recommendations of the DSMC will be reviewed and the PI will take appropriate corrective actions as needed.

E5.7 Data and Safety Monitoring Board (DSMB).

A DSMB will be established and will consist of professionals at MUSC with appropriate expertise, who are willing to participate and who do not have any conflicts of interest. The DSMB will include: 1) one expert in the area of MR imaging, 2) a physician with expertise in chronic stroke, 3) a stroke rehabilitation specialist (physical or occupational therapist). The DSMB will meet on an annual basis. The DSMB will perform the following activities:

- Review the research protocol and plans for data and safety monitoring.
- Evaluate the progress of the intervention, including periodic assessments of data quality and timeliness, participant recruitment, enrollment, and retention, participant risk versus benefit, integrity of the intervention, and other factors that can affect study outcome.
- Consider factors external to the study when interpreting the data, such as scientific or clinical developments that may impact the safety of study participants or the ethics of the study.
- Make recommendations to the internal DSMC and MUSC IRB for continuation or termination of the project.
- Protect the confidentiality of study data and monitoring.

The DSMB will have the authority to temporarily or permanently discontinue the project if it perceives that harm is occurring due to the intervention. The DSMB will meet with the internal DSMC yearly to review adverse event reports, patient complaints if any, and enrollment rates. Data will be provided at these meetings by the investigators on key variables that may indicate harm. The DSMB will also review the elements of the plan to manage emergencies.

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G. APPENDIX

Appendix 1: Pre-Screening Telephone Questionnaire.

Appendix 2: Demographic, Education, Medication Questionnaire.