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| **Date Initially Completed:** 4/16/12 **or Date Updated:** 10/07/16 | | | **IRB # (if known):** HN 4404 |
| ***Protocol Title:*** | Visual feedback therapy for treating individuals with hemiparesis following stroke | | |
| **Protocol Version/ Date:** | This form serves as the Protocol. | | |
| **Sponsor:** | NIH | | |
| **Investigator:** | Steven Jax | **Email:** | jaxs@einstein.edu |

**Please carefully review and complete each section of this form. If your study already has a separate protocol (e.g. developed by a sponsor or submitted as part of a grant application), you have the option to reference the section and page numbers of that protocol where appropriate in this form. PLEASE NOTE: many of the questions below are looking specifically for what will be happening locally to protect participants. This information is generally not found in a protocol written for multiple sites.**

**NOTE: Depending on the nature of your research, certain sections below may not be applicable. Indicate "N/A" as appropriate. You must provide a response for each section. DO NOT DELETE SECTIONS OR LEAVE SECTIONS BLANK.**

**Keep an electronic copy of this form. You will need to modify this form when making changes to the protocol.**

**1) Protocol Abstract (*Briefly (in 250 words or less) describe the study in language understandable to a layperson. Include a brief description of the study purpose, target disease/condition if applicable, key eligibility criteria, and main study interventions*):** Each year in the United States 550,000 people develop upper-extremity movement deficits after stroke (hemiparesis). The recent success of mirror therapy (MT) is notable because it is a simple treatment for hemiparesis, and may be feasible for home use. MT uses a standard mirror to create a compelling illusion in which movements of the unimpaired limb appear as if they are being made by the impaired limb. We propose to complete a randomized placebo-controlled clinical trial of home-based MT with a target enrollment of 100 chronic stroke patients. The therapy will consist of a standardized set of hand, wrist, and elbow movements completed in two daily 30-minute sessions, 5 times per week for 4 weeks. Patients assigned to the placebo treatment (identical therapy with an opaque divider rather than a mirror) will be crossed over to receive MT after a three month follow-up. The therapy will be performed by the participant within his/her home. This project will have two phases. The first phase, to be completed at Einstin, will include all of the behavioral testing . The second phase, to be completed at the University of Pennyslvania, will be limited to MRIs and CTs and will be completed under a separate IRB protocol at the University of Pennsylvania with Dr. Coslett at the site PI.

**2) Project Objectives and Hypotheses:** The first goal of the study will be to determine whether a home-based form of MT is an effective treatment of hemiparesis. The second goal will be to determine the optimal dosing of MT by including weekly measures of improvement. The third goal will be to understand individual differences in the efficacy of mirror therapy. Previous MT studies have not reported, or lacked the power to test, why some patients benefit from MT and others do not, even though significant individual differences have been reported. Our use of a large sample of patients will allow us to assess predictors of therapeutic benefit.

## 3) Background/Significance of Research (*Provide the scientific or scholarly background and rationale for the research based on the existing literature (include references). Describe relevant prior experience and gaps in current knowledge. Describe any relevant preliminary data. Explain the significance of the research in terms of why it's important and how it will add to existing knowledge.*):

A.1. Hemiparesis in patients with stroke

Every year 550,000 people in the United States develop problems making arm and hand movements because of a stroke. Of those with deficits, 30% - 60% fail to ever recover adequate usage of the limb [1]. The consequences of these impairments are profound, and stroke patients rate the return of upper-extremity functioning as a high priority [2]. Motor deficits also lead to negative psychological and social outcomes such as depression and withdrawal [3]. Beyond the impact on individuals, stroke patients place a significant burden on the health care system, with stroke-related medical and disability costs totaling $62.7 billion each year in America alone [4].

Motor deficits in stroke patients are most clearly observed in the limb opposite the lesioned hemisphere (hemiparesis) and affect the distal portions of the limb such as the hand more significantly than proximal portions such as the shoulder [5]. Previous studies show that these deficits are caused by damage to the corticospinal tract, including the primary motor cortex and internal capsule, as well as cortical areas such as the premotor and supplementary motor areas [6, 7]. In addition to motor production problems, non-motor deficits such as poor limb sensation and pain contribute to limited use of the paretic limb [8]. Treating these motor and non-motor deficits is especially difficult in chronic patients [1]. Improvement for most chronic patients is also hindered by limited medical insurance coverage for long-term therapy, leading many to receive little to no therapy in the chronic stage.

Empirically validated treatments for hemiparesis are varied and include strength training [9], functional task practice [9], bilateral training [10] and electrical stimulation [11]. To date, the single therapy with the greatest amount of empirical validation is constraint-induced movement therapy (CIMT), which combines restraint of the unimpaired limb and intense practice using the impaired limb under the supervision of a therapist (typically 10 6-hour sessions over two weeks [12]). A common feature of almost all of these therapies is that they require a significant amount of therapist involvement, a burden that is becoming increasingly problematic due to cost concerns. Motivated by the decreasing availability of therapist time, there has been considerable recent interest in the use of robotic training to both reduce reliance on therapists as well as increase the number of movement repetitions within therapy sessions (e.g. [13]). These benefits, however, come at the expense of the significant initial cost to acquire the robotic device.

A.2. Mirror therapy

The recent success of mirror therapy (MT) for treating hemiparesis in stroke patients is notable because it does not require a significant investment in equipment. Originally developed as a treatment for phantom limb pain (for review, see [14]), MT involves the patient being seated at a table in front of a vertically-oriented mirror. The patient places her unimpaired arm on the reflective side of the mirror and her impaired arm behind the mirror so that it is not visible. Using this setup, the patient only sees the unimpaired arm in the mirror. However, when the mirror is placed midway between the two limbs, movements of the unimpaired limb (viewed in the mirror) appear in the same location as the impaired limb. Thus, the MT setup creates a compelling illusion in which movements of the unimpaired arm appear as if they are being made by the impaired arm behind the mirror [16].

The illusory visual feedback of the perceived impaired limb moving like the unimpaired limb is the basis for MT's therapeutic benefit. Although only visual feedback is directly modified in the therapy, the results of several case studies [17, 18], a small-sample study without a control group [19], and three randomized control trials with moderate sample sizes (40,40, and 36 patients; [15, 20, 21]) indicate that MT produces a benefit for stroke patients that is comparable to other therapies. For example, both MT and a briefer version of CIMT produce an approximate 20% increase in FIM score, a common measure of functional independence in activities of daily living (ADLs) and the only outcome measure that has been reported for both therapies [20, 22]. The benefit of MT is especially noteworthy given its methodological simplicity and the potential for use in the home. Informal case studies [17] and one RCT with 20 treated patients [21] have reported improvement in paretic limb functioning with home-based mirror therapy, a finding that is consistent with a recent report that home-based CIMT may be as effective as therapist-administered CIMT [23].

We propose to complete the largest randomized clinical trial of home-based mirror therapy. The therapy will consist of a standardized set of hand, wrist, and elbow movements completed in two 30-minute sessions per day, 5 times per week for 4 weeks. Patients

assigned to the placebo treatment (identical therapy with an opaque divider rather than a mirror) will be crossed over to receive MT after a three month follow-up. To date 7 patients have completed the proposed therapy regimen in a pilot study, and overall the results were encouraging. Patients showed an average improvement (relative to baseline) of 27% and 24% on the Wolf Motor Function test and Jebsen Hand Function test, respectively, two functional tests of simulated ADL performance. Even greater improvements were observed at the impairment level, with average improvement on grip force, pinch force, and finger tapping being 63%, 58%, and 43%, respectively. If the results of the full trial match those of the pilot study, home-based MT would be a meaningful advancement in the cost of hemiparesis rehabilitation.

Reduced medical costs could also come from more efficient therapist utilization. Because the therapeutic benefits of rehabilitation often decrease over time, it would be worthwhile to know the balance between treatment dosing and treatment benefit. To date little is known about the dosing of MT because only one study [18] has measured therapeutic benefit at multiple time points during treatment (in contrast to only before and after 4 or 6 weeks of treatment in previous RCTs [15, 20, 21]). Stevens and Stoykov [18] reported that two chronic stroke patients given 12 1-hour sessions of MT improved most rapidly after 3 sessions (the first assessment point) and showed relatively minor improvement in the following 7 sessions (the second assessment point). These case studies suggests that reducing dosage of MT could still lead to a clinically significant improvement in functioning. The proposed study would inform the issue of MT dosing by measuring outcomes after each week of treatment in a large sample of patients. Our pilot study results indicate that most of MT's therapeutic benefit may occur within the first two weeks of treatment. In this study we administered three impairment level tests (grip force, pinch force, finger tapping) as well as the Jebsen test after each week of therapy. Average improvement was 21%, 44%, 46%, and 47% for weeks 1-4, respectively. Although additional data are clearly needed to further support this claim, these initial results suggest that reduced therapy dosing may be nearly as therapeutic as longer courses of treatment.

Previous tests of MT indicate that its benefit is not limited to movement production. For example, the use of MT for the treatment of pain following limb amputation and complex regional pain syndrome [14] suggest that it can quickly and significantly reduce pain (e.g., from a mean visual-analogue score of 70/100 to 10/100). Limb pain is also a common consequence of stroke [8], and data from one of our pilot study patients who experienced pain in her hand reported a significant reduction in pain following MT (from 80/100 to 19/100). In addition to pain, one MT RCT [15] found significant improvements in both sense of touch and hemispatial neglect, a disorder Drs. Buxbaum and Coslett (two co-investigators) have significant experience studying and treating [24-29]. Patients with neglect, more commonly observed after right than left hemisphere damage, are more impaired than patients without neglect on measures of disability, have poorer motor function than patients without neglect, have longer rehabilitation hospitalizations, and after hospital discharge are rated as more burdensome to family members, even after controlling for scores on tests of functional independence [24]. In addition to its potential for treating hemiparesis, our trial will test whether MT reduces symptoms of pain, decreased touch sensitivity, and hemispatial neglect by including tests of these functions at each weekly screening.

B.1. Understanding individual patient differences in treatment response

A critical, but often understudied, issue in rehabilitation is predicting individual patient differences in treatment response. As reviewed in section A.1, a wide range of therapies exist for the treatment of hemiparesis, and several recent RCTs comparing two active treatments have reported equivalent benefits at the group level [9, 30, 31]. It would be clinically valuable to understand the characteristics of patients who do and do not respond to each therapy given the magnitude of these individual differences. For example, in a recent RCT of MT for chronic stroke patients [20], improvement in the Brunnstrom scale outcome measure ranged from 0% to 33% (estimated from two standard deviation above and below the mean of 16.5% improvement). Information about predicted individual differences would be useful for clinicians when deciding the course of treatment most likely to benefit the patient.

We assert that individual differences in response to MT are predictable through an understanding of the mechanisms responsible for MT's therapeutic benefit. The assembled team composed of researchers trained in the basic science of sensorimotor control (Dr. Jax) and its application to stroke patients (Drs. Jax, Buxbaum, and Coslett) is uniquely positioned to address this issue. The project is innovative because it will test competing predictions regarding the mechanism of MT by utilizing individual differences in lesion location and the integrity of four sensorimotor processes that may underlie MT's benefit. As an overview, we will first discuss the four sensorimotor processes that may underlie the mechanisms of MT's benefit (B.2), and then proceed to a summary of the

neural substrates that subserve these processes (B.3). Following this will be a discussion of the behavioral tasks we will use as convergent validity tests of the neuroanatomic predictions (B.4). Finally, we will summarize all of these predictions in Table 1.

B.2. Proposed mechanisms of MT

Understanding the mechanisms of MT requires an understanding of how the perceptual-motor system functions. A wealth of research on perceptual-motor control indicates that accurate movement production relies on cyclical interactions between descending muscle commands and ascending sensory feedback. That is, during movement the motor system produces a descending signal to the muscles which is based on a prediction about the sensory and motor consequence that signal will have [32]. After this signal is sent, ascending sensory signals, primarily from vision and proprioception, detect the effect of the descending signal and whether that ascending signal matched what was predicted before movement initiation [33]. Any mismatch between the predicted and observed sensory signals is then used to modify the motor system so that the prediction is more accurate in the future. Using this framework, let us consider the step-by-step progression of sensorimotor processing that takes place when a patient attempts to move both limbs in parallel using the MT setup (the instruction given during MT).

The cycle begins when descending signals to each limb are produced primarily by the contralateral primary motor cortex, with the signal coming from the lesioned hemisphere being insufficient to produce accurate movement (because stroke disrupts either the signal itself or the descending pathways). With a slight temporal delay, ascending sensory feedback from both proprioception and vision are received. Visual information is processed to determine how the limb configuration changed because of the descending signals. This processing is a form of action observation. A significant recent finding in the field of neuroscience is the discovery that the same neural populations that are active during action observation are often active during action production ("mirror neurons"; [34]). Clearly, not all forms of action observation are beneficial because stroke patients spend their entire post-stroke lives observing the unimpaired actions of others without making significant improvements. Observing one's own actions during MT is different from observing someone else's actions because only one's own motor system has access to the specific signals that were sent to both the impaired and unimpaired arm. Because of the mirror, the action observation feedback matches the signal sent to the unimpaired arm and not the impaired arm. Thus, one mechanism for MT's therapeutic benefit may be a form of Hebbian-like learning ("what fires together wires together") in which the action observation system in the intact hemisphere, which controls the unimpaired arm, becomes more strongly associated with the signals sent to the impaired limb. Subsequent movement production with the impaired limb may therefore be more reliant upon the action observation system in the intact hemisphere. Alternatively, the action observation system may only be responsible for recognizing more abstract aspects of action. Consistent with this claim, mirror neurons often respond primarily to the goal of an action rather than how the action is executed [36]. The therapeutic benefit of action observation proposed above would require that the action observation system is able to contribute to a more detailed level of action production than simply understanding the action's goal. Thus, action observation may not be the primary mechanism of MT's therapeutic benefit. Testing these competing predictions about the role that action observation plays in MT will be done by comparing a patient's MT benefit to that patient's accuracy on an action observation task unrelated to MT (see C.13).

In addition to action observation, proprioceptive feedback is relied upon during MT. The most obvious prediction is that poor proprioception would lead to poor response to MT, just as it does in other therapies [37]. This outcome would be logical because proprioception is the only source of sensory feedback about the hidden impaired limb during MT (since vision of that limb is blocked). The perceptual-motor system may require some form of feedback to recognize that the movement of the impaired limb does not match the visual feedback, and thus the system must modify the motor command to more closely match the visual feedback about the unimpaired arm. Without that feedback, adjustment of the perceptual-motor system might not occur. The alternative, and more counter-intuitive, prediction is that intact proprioception might disrupt MT. Our reasoning is that MT sets up a conflict between the proprioception signal coming from the impaired arm and the visual feedback about the mirror-reflected unimpaired limb. The presence of a veridical proprioception signal from the impaired arm may disrupt the effects of the false visual feedback. Support for this second prediction comes from other studies in which proprioceptive feedback is actively suppressed when the to-be-learned task involves a conflict between vision and proprioception [38]. If this counterintuitive prediction is verified, it would be especially noteworthy because poor proprioception often leads to poor recovery with standard therapies. Advancing a therapy that would benefit patients who respond poorly to other therapies is particularly innovative and significant. The proposed study will be able to differentiate between these two possibilities by using a behavioral assessment of proprioception to determine whether disrupted proprioception is associated with greater or reduced benefit of MT (see C.13).

Thus far we have focused on the separate processing of vision and proprioception, although it has long been known that these two sources of feedback are eventually integrated to form a unitary representation of the body's configuration. The distinction between the proprioceptive feedback account above and the visual-proprioception integration account presented below is that the second account concerns a later stage in sensory processing. Thus, assuming that some proprioception is present, the integration of vision and proprioception may be disrupted. The "odd" feeling when neurologically-intact participants experience the illusion induced by the mirror may result from the mismatch identified by comparing the two sensory signals. Disrupting this comparison may affect if and how strongly one experiences the MT illusion. Experiencing the illusion may be a necessary, but not sufficient, requirement of MT's benefit because the detection of a mismatch may initiate changes to the sensorimotor system to correct the mismatch. Informal reports from the use of MT in the Right Hemisphere Stroke Center of MossRehab, directed by Dr. Buxbaum (a co-investigator), indicate that MT with patients who fail to initially experience the illusion rarely leads to significant improvement. Alternatively, there may be no relationship between the illusion induced by MT and the motor production benefit. Dissociations between perception and action have been previously reported. For example, visual illusions can affect the visually perceived lengths of two lines much more than the movement to grasp those same lines [39]. Across patients we will use the results of two visual-proprioception integration tests (self-report rating of initial sensation of the mirror illusion; Parson's task) to see if these tests predict MT's benefit.

Finally, a previous study of MT [18] hypothesized that removing visual feedback of the impaired arm causes the perceptual-motor system to try to fill in that information using motor imagery. Given that other forms of motor imagery can be therapeutically beneficial, the authors proposed that motor imagery was similarly beneficial in MT. Data from a later RCT of mirror therapy calls this claim into question [20]. When MT was compared to the same therapy with a covered mirror, the results clearly indicated that MT benefited patients while the covered mirror therapy did not. However, in both forms of therapy vision of the impaired limb was blocked, and thus motor imagery would be called upon in both. We will test whether MT's benefit is predicted by motor imagery ability (see C.13 for details).

In summary, we will test competing predictions about the mechanism of MT by utilizing individual differences in the integrity of four sensorimotor processes (action observation, proprioceptive feedback, visual/proprioceptive integration, and motor imagery) that may underlie MT's benefit .

B.3. Neural substrates of sensorimotor processes required for MT

The neural substrates of the four sensorimotor processes mentioned above have been identified from a variety of sources including single-cell recordings in non-human primates as well as neuroimaging, TMS, and brain-damaged patients in humans. Space considerations prevent a detailed presentation of existing evidence, but we have reviewed this literature and developed a consensus of the neural substrates of proprioceptive feedback [40-44], action observation [45-53], visual-proprioception integration [54-56], and motor imagery [54, 57-67]. This review is summarized in Table 1. We note that the specific neural regions listed in Table 1 are based on incomplete, and often conflicting, results. To avoid relying too strongly upon the limitations of previous studies when trying to understand individual differences in MT response, we will use whole-brain voxel-based lesion-symptom mapping (VLSM) analyses to determine how lesion location affects the benefit of MT. VLSM will allow us to determine which areas of the brain are most predictive of MT's benefit without limiting our analyses to those predicted areas.

B. 4. Converging evidence between lesion location and other behavioral tests

In addition to making predictions about the integrity of the four processes that may underlie MT's benefit based on lesion location, we will measure performance on confirmatory behavioral tests to (1) provide further evidence about the neural substrates of these functions and (2) allow clinicians to have simple behavioral tests to predict individual differences in MT response without having to rely on lesion location information. All behavioral tests have been previously used in our labs. For action observation, we will use a test that involves viewing sequentially presented video pairs of actions, with the patient making same/different judgments about the actions [68]. For proprioceptive feedback, we will use the RASP [69], a standard clinical measure of proprioception that will also be a primary outcome measure . For visual-proprioceptive feedback, we will use a visual-analogue scale of initial mirror illusion sensation (rate how strongly it feels as if the arm you see in the mirror is actually the arm behind the mirror) and a simple judgment task (Parson's task [70]) that has been shown to require integration of visual and proprioceptive input. In this task, patients judge whether a visually presented hand is a left or right hand. These judgments are affected by the orientation of the participant's own hand, suggesting the decision is based on the seen and felt position of the body. We will have patients make verbal judgments while we systematically manipulate the orientation of the patients' hand. Finally, motor imagery will be assessed using consistency

on a grasping imagery task [71] in which patients report how they imagine they would grasp a handle (overhand or underhand) and compare the imagined results to their actual grasping of an object. Table 1 summarizes the preceding three sections.

| PROCESS | NEURAL SUBSTRATE | CONFIRMATORY BEHAVIORAL TEST |
|---|---|---|
| Action observation | IFG, IPL, pMTG | Spatial action recognition task |
| Proprioceptive feedback | SI, SII | RASP |
| Visual-proprioceptive integration | IPL, BA5 | Parson's task, screening questionnaire |
| Motor imagery | IPL, BG, PM | Imagined grasping |

Key: inferior frontal gyrus (IFG), inferior parietal lobe (IPL), posterior middle temporal gyrus (pMTG), primary sensory cortex (SI), secondary sensory cortex (SII), Brodmann area 5 (BA5), basal ganglia (BG), premotor (PM)

## 4) Setting of the Human Research:

a. Indicate all AEHN locations where the human research will be conducted (check all that apply):

- ☐ Tabor Rd campus
- ☒ Elkins Park campus
- ☐ Belmont Center for Comprehensive Treatment
- ☐ Center One
- ☐ Montgomery campus
- ☒ Other: please specify – University of Pennsylvania (for completing MRIs and CTs)

b. Indicate if human research will be conducted at external location(s) overseen by the AEHN investigator (e.g. private physician office, collaborating hospital/university)

- ☒ Yes (Complete Appendix B: External Site Approvals on Application for Human Research)
- ☐ No

## 5) Resources available to conduct the Human Research:

a. Target population (e.g. Adult subjects with a diagnosis of Type II diabetes for greater than two years":
Adult stroke surviors (age 21-85) with moderate hemiparesis (Fugl-Meyer score of 10-50)

b. **For prospective studies:**

i.) Total number of subjects planned to be enrolled in the study at AEHN site(s): 140 screened in single session, with target of 100 meeting inclusion criteria for the full treatment study

ii) For multi-site projects, please indicate total number of subjects planned to be enrolled in the study at all sites: Of the 100 participants that will meet inclusion criteria for the full treatment study, approximately 60 will be recruited to the brain imaging (including both MRI and CT) study conducted at U. Penn. The rest will have already received brain scans through their

participation inin MMRI sponsored studies included the Moss Research Registry and conducted via the "Cognition and Action" or "Language and Aphasia" laboratories.

iii) Describe access to a population that would allow recruitment of the targeted number of subjects (***i.e. how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit? )*** : Patients and controls will be recruited from the Moss Research Registry; the requisite approval has been obtained from Registry Coordinator. The registry contains medical records of patients who have already agreed to participate in studies, allowing us to pre-select patients based on the likelihood of meeting inclusion criteria. Patients will also be recruited using a flyer distributed by therapists in the clinical programs at MossRehab and by the research staff to participants in stroke support groups in the Philadelphia metropolitan area.

c. **For retrospective studies:**

i.) Estimated number of charts to be reviewed: N/A

ii.) Time period of interest for data being collected **(e.g. *Subjects who had XX procedure between 6/1/00 and 6/1/05*:** N/A

d. Describe the number and qualifications of the study team members, their experience in conducting research, their knowledge of the local study site(s), culture, and society: Dr. Jax, the Primary Investigator, has been conducting research at MRRI for 7 years. Co-Investigators are Institute Scientists or fellows at MRRI. Research Assistants and Assessors will have a minimum of 2 years experience conducting research in undergraduate school and/or at MRRI. Consultants have significant experience in providing either scientific or technical assistance.

e. Describe the time that the investigator and other study team members, if applicable, will devote to conducting and completing the study within the anticipated study period ***(e.g. 10% of PI's time and full-time coordinator)***: The PI (Jax) will devote 24 hours per week for the duration of the study. Co-Investigators will devote 4 hours per week. Research Assistants will devote a combined total of 40 hours per week, and the assessors will each devote 8 hours per week. Consultant will provide time as needed.

f. Describe the plan for ensuring that all investigators/staff assisting in this research are adequately informed of: 1) the protocol, including revisions to protocol and other study specific changes, 2) investigational product information if applicable, and 3) study related duties and functions: New research personnel are informed of the protocol, as well as study related duties and functions through a research training manual developed under the supervision of the PI (Jax). In addition, existing staff members conduct in-person trainings and exercises with new staff. Staff members are kept up-to-date on any revisions to the protocol or study related duties/functions at the weekly lab meetings, led by the PI (Jax).

g. Describe the facilities available to conduct this research: A dedicated, private, testing room in the Medical Arts Building of the Elkins Park campus will be used for all assessments.. The testing room is outfitted with videotaping and coding equipment. There is also a dedicated office for research assistants to complete recruiting phone call and performa analsyses using computers running software for statistical and

graphical analysis of data (MATLAB, SPSS, others). All computerized data will be password protected and stored only on the network share drive. This project also has access to an Imaging Analysis Workstation at MRRI, dedicated to image processing and analysis. This workstation, housed in a dedicated, climate-controlled room, consists four rack-mounted servers (file service and compute servers, a 16 terabyte storage system, and a tape backup system. The cluster is Linux-based and also supports Windows through virtualization. It is equipped with software for image analysis (e.g., MRIcro/MRIcron, SPM, ANTS, VoxBo), MATLAB to support the use of SPM, and SPSS for descriptive and exploratory statistical analysis.

h. If applicable, describe the availability of medical or psychological resources that subjects might need as a result of the anticipated consequences of this research: N/A

## 6) Study Design

### a. Recruitment Methods:

i. Describe when, where, and how potential subjects will be recruited (***Describe the source of subjects. Describe the methods that will be used to identify potential subjects. Describe materials, such as advertisements, that will be used to recruit subjects (include these with submission materials. If study is a chart review, describe which records will be accessed to collect data and how you will access them*** **:**
Participants will primarily be recruited by searching the MRRI Research Registry, then making an initial phone call to introduce the study and invite participation, and then meeting in person to explain the study and complete the informed consent process. Participants will also be recruited using a flyer distributed by therapists in the clinical programs at MossRehab involving older stroke patients. The flyer will contain a brief summary of the project, and will provide telephone contact information for the research assistant on the study, who will provide all information about the study. Study team members will distribute the flyers to the therapists, and instruct the therapist to limit their discussion of the project to only the information on the flyer. Flyers will also be distributed by the research staff to participants in stroke support groups in the Philadelphia metropolitan area. As part of the consent process, we explain to potential participants that if they meet the inclusion criteria, we may find they are eligible to have a new brain scan (MRI or CT), free of charge, through our collaborators at the University of Pennsylvania Hospital, and that they are free to choose whether or not they want to hear more about this. Brain scanning (both MRIs and CTs) will be completed under a separate IRB protocol at the University of Pennsylvania with Dr. Coslett as the site PI.

ii. Will payments to subjects be provided?

☒ Yes, amount and timing: $15 per hour for sessions completed at MRRI. For travel costs in excess of $5, we also contribute to the costs up to a maximum of $50 per session. Payment is made in cash at each session attended. For each 30 minute treatment session a participant completes at at home, they will receive $5. Payment will be made in cash at the weekly laboratory sessions. In order to receive this payment, the experimenter must be able to verify that the participant completed the session using the video recordings he/she will make. If the participant does not bring these recordings with him/her to a weekly laboratory session, he/she will have the opportunity to be paid at the next weekly laboratory session that he/she brings the recordings to. In the event of a camera mulfuntion or other event that would prevent viewing of the video recordings, the

researcher will take the participant's word and pay him/her for each session he/she says were completed. At the end of the 4 weeks of treatment the participant will receive a bonus of $50 if he/she completes at least 36 of the 40 treatment sessions.

☐ No
☐ N/A

**b. Inclusion and Exclusion Criteria:**

i. Describe how you will screen for eligibility (**e.g. review charts, perform specific screening tests, etc.**): After recruitment, the first session will be devoted to inclusion criteria and exclusion testing.

ii. Describe the criteria that define who will be included or excluded in your final study sample:
All participants will be between 21 and 85 years of age, will have suffered a stroke at least 6 months prior to study participation, be no longer participating in upper-extremity physical or occupational therapy, and have a caregiver willing and able to assist with therapy delivery. The primary motor inclusion criteria will be a score of 10 to 50 on the upper-extremity portion of the Fugl-Meyer, a scale which ranges from 0 to 66. The Fugl-Meyer is a standard clinical measure of upper-extremity impairment that has been frequently used in treatment studies of hemiparesis. The particular range of Fugl-Meyer scores was chosen to exclude patients with almost no movement of the limb as well as those whose functioning is sufficiently high to not significantly affect daily life. Aphasia comprehension will be assessed with the 20 item comprehension subscale of the Western Aphasia Battery [75]. Participants with comprehension scores below 8 will be excluded from further testing, as will patients with significant perceptual deficits (such as a hemianopia that prevents vision of both limbs in the mirror). Any patient will be excluded if they report previous head trauma, psychiatric illness or chronic exposure to medications that might be expected to have lasting consequences for the central nervous system (e.g., haloperidol, dopaminergics). Subjects with a history or neuropsychological findings suggestive of dementia will also be excluded. This initial screening should take approximately 90 minutes.

**c. Study Timelines:**

i. Duration of an individual subject's participation in the study: All participants will complete the initial screening session to determine whether they meet inclusion and exclusion criteria. If they meet the criteria, they will complete 2 additional 90 minute pre-treatment testing sessions which will include other study endpoint assessments as well as the measures of individual differences (see 6.e.iii). They will also be asked to complete a 60 minute MRI or CT scan (if unable or unwilling to undergo MRI scanning because of claustrophobia or medical contraindications, e.g., pacemaker, aneurysm clips, other metallic implants) at the University of Pennsylvania. MRIs and CTs will be completed under a separate IRB protocol at the University of Pennsylvania with Dr. Coslett as the site PI. Then therapy will begin, which will include 2 daily 30 minute therapy sessions, 5 days per week over a 4 week period, which will be done in the participant's home. At the end of each week of therapy, the participant will come into the lab for a 60 minute mid-treatement assessment. Once the therapy is completed, participants will complete two 60 minute post-treatment assessments (1 day and 3 months after final treatment session).

ii. Time period anticipated to enroll all study subjects or to complete chart review: 4.5 years

iii. Estimated overall study duration (***i.e. from initiation to completion of primary analyses***): 6 years

**d. Study Endpoints:**

i. Describe the primary and secondary study endpoints (***i.e. the outcome(s) that the study is designed to evaluate***): Overall, the study will examine motor functioning of the impaired arm as well as sensation in the limb as well as hemispatial neglect (participants with right hemisphere lesions only). The primary outcome measures will be the (1) upper extremity portion of the Fugl-Meyer test, a standard clinical measure of arm motor impairment, (2), Action Research Arm Test (ARAT), a valid and reliable measure of arm function in simulated ADLs, (3) the Rivermead Assessment of Somatosensory Performance (RASP), which tests proprioception, two-point discrimination, surface pressure touch, surface localization, and tactile extinction [121], and (4) in right hemisphere patients only, a virtual-reality assessment of navigation (VRLAT) developed by Dr. Buxbaum [77], which is more sensitive to mild forms of hemispatial neglect than paper-and-pencil tests. Secondary outcome measures will be (1) the Stroke Impact Scale, a self-report measure of use of limb in activities of daily living (2) timed finger tapping, (3) maximum grip and pinch force, as assessed using a dynamometer, and (4) the Wolf Motor Function Test [78] to assess function limitations and allow comparison with the results of CIMT (used as a secondary measure because patients with lower Fugl-Meyer score will not be able to complete many items on this test).

ii. Describe any primary or secondary safety endpoints (***e.g. any disease or symptom that would result in the withdrawal of that subject from the study***): N/A

## e. Human Research Methods:

i. Describe and explain the study design ***(e.g. randomized, double-blind, placebo-controlled clinical trial or retrospective chart review)***: randomized, placebo-controlled clinical trial

ii. Describe all research activities involved in this protocol, including a study visit timeline if appropriate: C.5. PRE-TREATMENT ASSESSMENT: Should the patient meet the inclusion criteria, an additional battery of pre-treatment assessment tests will be completed as the first measure of the primary and secondary outcome measures. The primary outcome measures will be the (1) Fugl-Meyer test, described above, (2), Action Research Arm Test (ARAT), a valid and reliable measure of arm function in simulated ADLs, (3) the Rivermead Assessment of Somatosensory Performance (RASP), which tests proprioception, two-point discrimination, surface pressure touch, surface localization, and tactile extinction [121], and (4) in right hemisphere patients only, a virtual-reality assessment of navigation (VRLAT) developed by Dr. Buxbaum [77], which is more sensitive to mild forms of hemispatial neglect than paper-and-pencil tests. Secondary outcome measures will be (1) Stroke Impact Scale [76], (2) timed finger tapping, (3) maximum grip and pinch force, as assessed using a dynamometer, and (4) the Wolf Motor Function Test [78] to assess function limitations and allow comparison with the results of CIMT (used as a secondary measure because patients with lower Fugl-Meyer score will not be able to complete many items on this test). Finally, the confirmatory behavior tests listed in Table 1 will be included in the pre-treatment assessment (see B.4 for details). We anticipate that the full pre-treatment screening can be completed in 2 90-minute sessions. De-identified data from both the inclusion screening and pre-treatment assessment will be discussed with the PI before brain scanning is undertaken (C.6) and the patient is assigned to a therapy group

(C.7.a) to ensure that the patient meets inclusion criteria and that no unusual combination of scores might suggest errors in data collection or scoring.

C.6. LESION IDENTIFICATION: Neuroimaging data will be analyzed to examine the relationship between treatment outcomes and lesion location & volume. Existing neuroimaging data may be used if the scan is an acceptable resolution. Scan data and processed (mapped) images may be obtained from the MRRI Cognition and Action or Language and Aphasia laboratories if available. Scan records from other facilities may be requested if necessary. However, for the majority of patients, a high-resolution MRI scan will be performed including a T1-weighted spoiled gradient-recalled-echo transverse images with 1-mm slice thickness, no gap, 1mm in-plane resolution with a 192 X 256 matrix. Images will be obtained on a 1.5T scanner at a single site (Hospital of the University of Pennsylvania). Based on past experience, 30% of the patients who consent to scanning will be unable or unwilling to undergo MRI scanning because of claustrophobia or medical contraindications (e.g., pacemaker, aneurysm clips, other metallic implants). These patients will have a CAT scan of the brain without contrast. CAT scans will be obtained on a 64-slice Siemens scanner at the University of Pennsylvania with 1.5 mm gap throughout. For analysis of brain-behavior relationships in brain lesion subjects, imaging data will transformed to a common template ("Colin27" from MNI) using procedures outlined in [79]. Briefly, for MRI scans, lesions will be delineated in the subject's native space (that is, on the subject's MRI) by Dr. Coslett, an experienced neurologist and co-investigator. The structural scans and lesion maps will be registered to a common template using a symmetric diffeomorphic registration algorithm [80]. A single mapping from this intermediate template to the MNI-space "Colin27" volume will be used to complete the mapping from subject space to MNI space. For CAT scans, the Colin27 brain in MRICro will first be re-pitched to match the angle of acquisition of the subject's scan. The lesion contour identified in the patient's scan will then be manually drawn onto the template on a slice-by-slice basis by Dr. Coslett, taking into consideration the distance from the lesion margin and identifiable landmarks such as gyri, ventricles and subcortical structures. We have previously demonstrated excellent intra- and inter-rater reliability with this method [79]. Dr. Coslett will be blind to the behavioral data when tracing lesions.

C.7. THERAPY REGIMEN

a. Group assignment: A research assistant (RA), who will not be involved in any assessments, will assign patients to the MT or placebo therapy (identical therapy with an opaque divider rather than a mirror) using stratified randomization based on the patient's Fugl-Meyer score. Before starting the trial an assignment order will be developed based on whether a patient's pre-treatment Fugl-Meyer score was low (between 10 and 30) or moderate (between 30 and 50). A previous MT RCT using a similarly chronic patient population and an identical placebo therapy showed little benefit of the placebo therapy . Thus, we must consider a balance between the scientific requirements of an appropriate control group and the ethical considerations of using patients' time to complete a therapy that is known to be ineffective. To balance these considerations, we will assign patients to the MT and placebo treatment groups in a 2:1 ratio, respectively. This inequality in sample size will only reduce statistical power by approximately 3% [81]. In addition, patients assigned to placebo treatment will be given the option of being crossed over to receive MT after the three month assessment. Patients will not be aware of which therapy is the placebo because both therapies will be described as studying the role of visual feedback rather than a test of "mirror therapy." Both treatments will include 2 daily 30 minute

therapy sessions, 5 days per week over a 4 week period.
b. Training therapies: Therapy instructions for both treatment groups will be presented using the same DVD shown using a portable DVD player. The 30 minute video will consist of 2 repetitions of a set of 15 movements including flexion and extension of the thumb, index, and middle fingers, opening and closing the hand, pinch grip with the thumb and index fingers, sequences of finger movements, wrist movement (pronation/supination, flexion/extension, radial/ulnar deviation), and flexion and extension at the elbow. Each trained movement will first be shown to the patient 3 times, after which the screen will go blank to allow the patient to focus on viewing their movements rather than the video monitor. A metronome sound will be presented on the video at 30 bmp and patients will be instructed to move in time with it. The metronome will run for 1 minute and 45 seconds followed by a 15 second rest break, after which the next movement will be presented. Instructions on the video will remind participants to make the same movement with both limbs "as well as possible" [19].
c. Compliance assurance: Several steps will insure that the treatment procedure is followed. First, at the start of each patient's therapy the device will be delivered to the patient's home by the RA, who will instruct the patient and caregiver on use of the system. The RA will lead the first session and then observe the second session. To further ensure compliance, and control for the timing of the mid-treatment assessments relative to the previous treatment session (see C.8), after every fifth therapy session (before day 6, 11, and 16) will be completed in the lab in the presence of the RA (and in a different room from the assessor) immediately prior to the mid-treatment assessment. Compliance outside of the RA's oversight will be assessed by including a simple, detachable, flash-memory video recorder on the mirror/divider apparatus. The video recorder will be selected for its ease of use (e.g., recording is done by pressing a single red button). Pilot testing with 7 patients indicated that patients had little trouble completing therapy outside of researcher supervision, and our use of video recording resulted in 100% compliance without any reports of difficulty using the video system. The RA will also deliver a pre-made therapy packet including a step-by-step checklist for each of the 20 therapy days, including a reminder to start the video recorder and questions to be completed before treatment (pain level) and after treatment (pain level, discomfort level, effort exerted during therapy, free-form question about any adverse effects). Before each mid-treatment assessment (see C.8), the RA will call and remind the patient and caregiver to bring the packet and recorder with them. The RA (who will know the therapy assignment) will download the video while the assessor completes the mid-treatment assessment. The RA will then view the video and confirm compliance with instructions regarding timing and production of movements. If non-compliance is discovered, the RA will discuss the issue with the patient. The RA will raise (without revealing the patient's group assignment) any compliance concerns with the PI.
C.8. MID-TREATMENT ASSESSMENTS: Three mid-treatment assessments will be performed, one immediately before every 5th day of therapy (before start of day 6, 11, and 16; see C.7.c), and will include only the primary outcome measures. The assessors will be unaware of group assignment, and before each session the assessor will remind patients to avoid mentioning any details of their therapy. The assessor will be given a questionnaire at the end of each assessment concerning the treatment to which they believe the patient has been assigned.
C.9. POST-TREATMENT ASSESSMENTS: The two post-treatment assessments (1 day and 3

months after final treatment session) will test both primary and secondary outcome measures. Procedures will be identical to mid-treatment assessments. To maximize retention at 3 months, the research assistant will make monthly calls to participants to maintain contact with the patient and be aware of any upcoming scheduling issues that might prevent timely follow-up.

iii. Identify which tests/procedures are being administered solely for research purposes and which are being conducted as part of standard of care (i.e. procedures that would be done even if the participant were not involved in research): All tests are solely for research purposes. As a summary these tests are the screening tests (Fugl-Meyer, Western Aphasia Battery comprehension test, clinical hemianopia test, spatial action recognition test, Parson's test of hand laterality decisions, imagined grasping of objects) and assessment tests (Fugl-Meyer, Action Research Arm Task, Rivermead Assessment of Somatosensory Performance (RASP), virtual reality laterized attention task, Stroke Impact Scale, timed finger tapping, maximum grip and pinch force, Wolf motor function task) and brain scans (MRI or CT). Brain scanning (both MRIs and CTs)will be completed under a separate IRB protocol at the University of Pennsylvania with Dr. Coslett as the site PI.

iv. Describe steps taken to lessen the probability or magnitude of risks associated with tests/procedures being done for research purposes only (***e.g. only appropriately trained personnel involved in procedures, extra tests being done for safety purposes***): Risks to subjects from the behavioral tests are minimal. No adverse effects of mirror therapy have been reported. To protect against fatigue, subjects will be permitted to rest or discontinue testing at any time. Should subjects appear to be made anxious by the tasks, testing will be terminated. Subjects will be told that they are free to withdraw from the study at any time. A second potential risk comes from brain imaging. CVA subjects will undergo high resolution, anatomic MRI imaging using standard pulse sequences (e.g., T1-weighted, T-2 weighted, FLAIR and MPRAGE) or a CT scan of the brain. Brain scanning (both MRIs and CTs) will be completed under a separate IRB protocol at the University of Pennsylvania with Dr. Coslett as the site PI. Neither gadolinium or iodine containing contrast will be administered. The major risk from MRI is that the strong magnetic field will dislodge a metallic object inside the subject's body (e.g., aneurysm clip) or interfere with an implanted device (e.g., cardiac pacemaker). Standard protocols have been developed at the University of Pennsylvania to ensure that subjects at risk do not undergo an MRI scan. This protocol includes an extensive checklist that is completed by the subject or family member; additionally, the MRI technician interviews patients prior to entering the MRI suite. A second potential concern comes from loose metallic objects in the MRI suite that can serve as missiles if they are drawn to a powerful magnet. Metallic objects that are not secured to the floor or wall are not permitted in the MRI suite. We note that these procedures have been employed in the clinical and research settings at the University of Pennsylvania for many years; no adverse effects from MRI scanning have been experienced to date. Subjects who are or think they might be pregnant will be excluded because the safety of MRI in pregnancy has not been established. The major risk from CT scan is a small dose of ionizing radiation. This procedure will be approved by the Penn IRB and subjects will be asked to sign a consent form in which the potential risks are discussed.

v. Describe alternative treatments that are available to subjects if they choose not to participate in research: Participants will be notified in the consent form that they may choose traditional physical or occupational therapy if they do not wish to participate in the study.

vi. Describe the source records that will be used to collect data: MRRI Research Registry records, clinical MRI / CT scans; neuroimaging data from MMRI Labs [Perceptual-Motor Control Lab; the Cognition and Action Lab, and/or the Language and Aphasia Lab]

vii. Describe what data (variables) will be collected for this research: Times and accuracy at performing a number of movement tasks, sensory abilities, and general cognitive functioning; brain lesion information as determined by neuroimaging.

viii. Describe any plans to conduct audio or video recording of research participants during the conduct of the research. Specify whether recording is optional or not and how information on how recordings will be used and how long they will be retained is being shared with subject: All participants will be video-recorded during the behavioral experiments. Participants are informed of this during the informed consent process, and they will sign a separate permission to videotape document which will detail how long the videos will be retained.

**f. Specimen Management:**

i. Will any type of specimen (e.g. blood or tissue) be collected for this study?
☐ Yes
☒ No , skip to section on Data Management

ii. What information will be associated with the specimens collected for this study?

iii. If specimens will be banked for future use, describe where and how the specimens will be stored:

iv. Specify how long specimens will be stored locally:

v. Specify who will have access to the specimens locally:

vi. Will specimens be sent out or received: ☐ No ☐ Yes

a. Who is responsible for receipt or transmission of the specimens?

b. How will specimens be transported?

c. Describe the procedures to release specimens, including: the process to request a release, approvals required for release, who can obtain specimens, and the data to be provided with specimens:

**g. Data Management**

i. Describe steps that will be taken to secure the data (e.g. training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality and separation of identifiers and data) during storage, use and transmission: All computerized data will be password and stored only on the network share drive.

ii. Describe the data analysis plan, including any statistical procedures and method for determining the sample size for the study: C.11. Testing Specific Aim 1 (benefit of home-based MT)

Tests for improvement in the primary and secondary outcome measures (see C.4) administered during the pre-treatment assessment and the two post-treatment assessments will be separately compared using ANCOVA analyses with post-treatment values as DVs, therapy type (MT, placebo) as the IV, and pre-treatment assessment score as the covariate [74]. Confirmation of MT's benefit will be tested in the main effect of therapy type.

C.12. Testing Specific Aim 2 (optimal treatment dosing)

Optimal treatment dosing will be examined by expressing each primary outcome measure's average value at the three mid-treatment assessments and the three-month post-treatment assessment as a percentage between pre-treatment (0%) and immediate post-treatment (100%) assessments. This information could then be used in clinical decision-making when determining whether the magnitude of change expected in a given time period would be "worth" the additional treatment time or whether that addition time would be better spent trying another therapy. Inferential tests will not be used because of the problem of being unable to detect "non-significant" differences between two time points as well as the possibility that the large sample size will be able to detect statistically-significant differences across adjacent time points even though the clinical significance of the differences' magnitudes are questionable.

C.13. Testing Specific Aim 3 (predicting individual differences in therapeutic benefit)

All tests of Specific Aim 3 will focus on data from the MT group only.

a. Testing predicted relationships between processes underlying MT and MT benefit using lesion location: We will examine the relationship between the change in primary and secondary outcome measures and lesion location using whole-brain voxel-based lesion-symptom mapping (VLSM) analyses [83]. VLSM measures whether a behavioral score systematically differs between participants with and without damage to each voxel under investigation. Tests of this difference use a t-statistic to describe the difference in means between the damaged-group and non-damaged-group while taking into account the variances within each group. The t-statistic is thus used as a convenient measure of group differences, without the intention of comparing it to the parametric t distribution. Instead, statistical significance will be determined by non-parametric permutation tests [84], in which the distribution used for inferential statistic calculations are created by sampling from the observed data rather than assuming an a priori distribution. Thresholds for significance will be calculated from the 95th percentile of this distribution, to ensure a family-wise false positive rate of 0.05 [84]. The total number of comparisons will also be reduced by only performing analyses on those voxels that are damaged in at least 10% of participants (to avoid undue influence of a small number of participants).

As in the previous measures, we will use an ANCOVA-like procedure to determine whether post-treatment scores (the DV) are affected by damage status to each individual voxel under consideration (the IV) after controlling for pre-treatment score and total lesion volume (covariates). Separate VLSM analyses will be done for each primary and secondary outcome

measure. The voxels identified as being predictive of MT benefit using the VLSM analysis should be consistent with the a priori ROI predictions (Table 1). VLSM will also allow us to test whether voxels outside of these ROIs predict MT benefit.

b. Testing predicted relationships between processes underlying MT and MT benefit using behavioral scores: In addition to using VLSM to test how the proposed neural substrates of the four sensorimotor processes are able to predict MT's benefit, we will also use the confirmatory behavioral measures (our proxy for the integrity of the processes) to predict MT's benefit. We will use linear stepwise regression to predict post-treatment scores (the DV) using each behavioral measure (the second level predictor/ IV) after controlling for pre-treatment score (the first level predictor/ IV). Note that this analysis is identical to the ANCOVAs used above except that a continuous IV is used, thus requiring regression rather than ANOVA. Analyses will be done separately for each of the four processes and each primary and secondary outcome measure. Testing our predictions about the processes will involve examining the sign and significance of second level predictor's regression weight. For example, if poor proprioception leads to reduced benefit of MT(see B.2), the regression weight for RASP (where high score corresponds to better proprioception) will be significantly positive. Alternatively, if poor proprioception lead to increased benefit of MT, the regression weight will be significantly negative. Finally, if proprioception does not affect MT benefit, the regression weight will not significantly differ from zero. Determining the influence of action observation, visual-proprioception integration, and motor imagery will use the same logic.

c. Testing predicted relationships between lesion areas and confirmatory behavioral measures
As summarized in Table 1, we predict that damage to particular ROIs will cause deficits in particular sensorimotor processes, which we will assess using the confirmatory behavioral tests. We will test these predictions in two ways. First, we will use t-tests to determine whether the pre-treatment confirmatory behavioral tests (the only time the tests are administered) will differ as a function of damage status to a particular ROI (using a 20% of volume criteria). Second, we will use linear stepwise regression to predict behavioral measure scores using percent damage to each predicted ROI after first controlling for total lesion volume. We have previously used both approaches successfully in a study of action observation [68].

iii. Describe where and how data will be stored locally: All computerized data will be password protected and stored only on the network share drive. Paper copies of data will be kept in locked filing cabinets in research staff members' offices.

iv. Specify how long data will be stored locally: 6 years

v. Specify who will have access to the data locally: Only research personnel listed on the Application for Human Research.

vi. Describe process that will be followed to ensure accuracy of collected data: Collected data that is entered into computer databases/spreadsheets will regularly be checked by research staff for data entry errors. Any errors will be discussed, reconciled, and the data re-entered on the spreadsheet.

vii. Will data be sent out or received: ☐ No ☒ Yes

a. Who is responsible for receipt or transmission of the data? The research assistant (RA).

b. How will the data be transported? Brain scan data (MRI or CT) on a DVD will be transferred from the University of Pennsylvania to the Medical Arts Building of the Elkins Park Campus by the RA. Password protected files transported will also be transported via Groupwise Email.

**h. Provisions to monitor the data for the safety of subjects (Required only when Human Research involves more than minimal risk):**

i. Describe plans to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe. Include what data will be reviewed, who will review the data and when the data will be reviewed: N/A

**i. Withdrawal of Subjects:**

i. Describe the anticipated circumstances under which subjects will be withdrawn from the research without their consent: Participants will be withdrawn without their consent only if it is determined, after consent, that they no longer meet study criteria, or if it becomes apparent that the study is causing the participant undue fatigue or frustration.

ii. Describe the procedures that will be followed when subjects withdraw from the research (or request that their data be withdrawn), including partial withdrawal from procedures with continued data collection: Following a participant's withdrawal or request for data withdrawal, no new information about that participant is collected. Data already gathered are retained and, if appropriate, used in the group analysis. Participants are informed of this in the consent form.

## 7) Risks to Subjects:

a) List the reasonably foreseeable risks, discomforts, hazards or inconveniences to the subjects. For each indicate the probability, magnitude, and duration when possible (consider physical, psychological, social, legal and economic risks as well as risks related to confidentiality): Anticipated risks include fatigue or frustration during the behavioral experiments. Probability of fatigue or frustration is more than would be expected among healthy control participants, but not more than is experienced by this population in everyday life. Participants who seem fatigued or frustrated are invited to take breaks, as needed, during the sessions and are informed of their right to withdraw from the study if they so choose. This should decrease the magnitude and duration of the fatigue and frustration.

b) If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable: None.

c) If applicable, indicate which procedures may have risks to an embryo or fetus should the subject or the subject's partner be or become pregnant: N/A

d) Describe, if applicable, the process that will be followed if a subject or the subjects' partner becomes pregnant while participating in the study: N/A

e) If applicable, describe risks to others who are not subjects: N/A

## 8) Potential Benefits to Subjects

a) Describe the benefits that individual subjects may experience (include when possible the probability, magnitude and duration of the potential benefits) or indicate if there is no direct benefit: Based on pilot studies and previous published reports, mirror therapy has the potential to modestly improve arm functioning, arm sensory ability, and neglect. The duration of these benefits are unknown.

## 9) Medical care and compensation for injury (Required for Greater than Minimal Risk Studies Only):

a) Describe any provisions for medical care and available compensation in the event of a research related injury: N/A

b) Provide the contract language, if any, relevant to compensation for research-related injury: N/A

## 10) Cost to participants:

a) Describe any actual or potential cost that subjects may incur through participation: Participants may incur transportation costs in order to get to/from the research facility. Under certain circumstances, we help cover these costs; see item 6b of this document.

## 11) Provisions to Protect the Privacy Interests of Subjects:

a) Describe the steps that will be taken to protect the subjects' privacy interests and make them feel at ease. In this case, "privacy interest" refers to a person's desire to control access of others to themselves (*e.g. has consideration been made to having same gender interviewers, the disclosing of cameras, conducting physical exams in private rooms, discussing study health concerns of subjects in private rooms instead of public waiting areas, etc.*): All sessions are conducted in a private room with the research staff member and the participant.

## 12) Subject Authorization

Are you planning to obtain written HIPAA authorization from study subjects?

☒ Yes
☐ No (if checked, written approval for waiver from Privacy Officer is required)

**13) Consent process:**

a) Indicate the type of informed consent you propose to utilize in this research project:

☐ Requesting Waiver of Consent Process

Provide justification for why it would not be practicable (feasible) to conduct this research without a waiver:

Explain whether or not subjects will be provided with additional pertinent information after their participation and if yes, describe what information will be provided and how it will be communicated (*e.g. a summary of study results will be provided to subjects in a newsletter*):

SKIP TO SECTION 14

☐ Requesting an Alteration to the Consent Process (i.e. no documentation in writing)

Provide details on alteration requested (***e.g. only verbal consent will be obtained, required information will not be disclosed or the research involves deception***) and why it is necessary:

☒ Consent process with Documentation in Writing

b) Describe when and where the consent discussion will take place: During the first session; at MRRI (MAB, 3rd floor)

c) Describe the role of the individual(s) involved in obtaining consent from study subjects **(e.g. investigator, study coordinator, recruiter, etc.)**: Study investigators and research assistant.

d) Specify the time that will be devoted to the consent discussion: As much time as needed to thoroughly explain the study procedures, risks, benefits, confidentiality, and data collection/storage, as well as provide time for the participant to ask questions and have them adequately answered. Approximately 30 minutes. In addition, the consent form will be mailed to the participant 1 week before the screening session so that he/she will be able to read over the consent before coming in for the session that includes the consent completion.

e) Will subjects be given the opportunity to think about the information provided as part of the consent discussion, ask questions, and discuss the research with family or friends if desired?

☒ Yes
☐ No

f) Describe the steps that will be taken to minimize the possibility of coercion or undue influence:
Participants will be invited to participate or decline participation both on the phone, when initially invited to come in for research and in person, after the consent form is reviewed.

g) From whom will consent or permission for research participation be sought (i.e. subject, parent, legally authorized representative): Only participants (no LARs) will be approached for consent.

h) Describe process to ensure subject/parent/LAR's understanding: By slowly going over the consent form and prompting participants to ask questions during and after the consent process.

i) Do you plan to consent subjects or their legally authorized representatives when the subject does not speak English?

☒ Yes
☐ No

If yes, select one of the two options below that best describes your study:

☐ The research targets a specific population that is non-English speaking OR a significant proportion of subjects are anticipated to be non-English speaking (*if this is true, translations of the standard (i.e. IRB-approved, full-description) informed consent documents must be reviewed and approved by the IRB prior to enrollment of any non-English speaking subjects*).

☒ The research does not target a non-English speaking population, AND only a small proportion of subjects are anticipated to be non-English speaking (*if this is true and a translated study consent form is not available, the short form consent process must be used. For more information, see the Investigator Manual*.)

Describe your plan for conducting study visits and long-term follow-up with these subjects:
Interpreters from the EHN pool may be used during the informed consent process and assessment of mental functions. However, participants (with or without the aid of a friend / family member) must possess sufficient English language skills to follow directions related to assessment of upper extremity functioning and the completion of the home-based exercise regimen.

j) Does the study allow for and do you plan to enroll adult participants with diminished decision making capacity?

☐ Yes
☒ No

If yes, select one of the two statements in each group below that is most appropriate for your study (if neither statement applies in one or both groups, your study does not meet the regulatory criteria for enrollment of these subjects):

Criterion 1(*must select one box below if you plan to enroll adults who are unable to consent for themselves*):

☐ The aims of the research cannot be accomplished if the subjects were limited to adults capable of consent.

☐ The research is intended to be beneficial to the subjects in a manner that is not available outside the research context.

Criterion 2 (*must select one box below if you plan to enroll adults who are unable to consent for themselves*):

☐ The research involves no more than minimal risk to subjects. Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life of normal persons or during the performance of routine physical or psychological examinations or tests in normal persons [45 CFR 46.102(i)].

☐ The research involves more than minimal risk to subjects, but the research holds out the prospect of direct benefit to the individual subjects.

Describe your plan for assessing a potential subject's ability to provide informed consent (e.g. clinical interview, standardized psychological or neuropsychological test, specially developed capacity assessment instrument, etc.):

**14) Vulnerable populations:**

a) Indicate if any individuals who are potentially vulnerable to coercion or undue influence will be included in the study:

- ☐ Children (if checked, must complete Appendix C. Children on Application for Human Research)
- ☐ Pregnant Women
- ☐ Neonates of Uncertain Viability or Non-viable Neonates
- ☐ Prisoners
- ☐ Adults with Diminished Decision Making Capacity
- ☐ Students/ Employees

***You may not include members of the above populations as subjects in your research unless it is indicated in the inclusion criteria of the protocol and approved by the IRB.**

b) If vulnerable populations will be participating in the study, describe the rationale for including this population and the additional safeguards to protect their rights and welfare:

c) If research involves children, describe the following:

i. Will parental permission be obtained from either both parents or just one parent:

ii. Will assent be obtained from all, some, or none of the children? If assent will be obtained from some children, indicate which children will be required to assent:

iii. When assent of children is obtained, describe whether and how it will be documented:

**15) Is this Community-Based Participatory Research (***i.e. research conducted in communities in which community members, persons affected by condition or issue under study and other key stakeholders in the community's health have the opportunity to be full participants in each phase of the work including conception, design, conduct, analysis, interpretation, conclusions, and communication of results***):**

- ☐ Yes
- ☒ No, go to section 16)

Describe involvement of the community in the design and conduct of the research:

**16) Sharing of results with participants:**

a) Describe any plans for sharing results with participants: If participants request it, they can have access to 1) a personalized report of the behavioral tests they completed and their strengths and weaknesses related to those tests; and/or 2) participants may be told (in person or writing) about the overall results of the experiment.

b)

c)

d) References

e)

f) 1. Kwakkel, G., B. Kollen, and E. Lindeman, Understanding the pattern of functional recovery after stroke: Facts and theories. Restorative Neurology & Neuroscience, 2004. 22(3-5): p. 281-299.

g) 2. Bohannon, R.W., Andrews, A.W., Smith, M.B., Rehabilitation goals of patients with hemiplegia. International Journal of Rehabilitation Research, 1988. 11: p. 181-183.

h) 3. Balliet, R., B. Levy, and K.M. Blood, Upper extremity sensory feedback therapy in chronic cerebrovascular accident patients with impaired excessive aphasia and auditory comprehension. Archives of Physical Medicine and Rehabilitation, 1986. 67: p. 304-310.

i) 4. Rosamond, W., et al., Heart disease and stroke statistics--2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation, 2007. 115(5): p. e69.

j) 5. Colebatch, J.G. and S.C. Gandevia, The distribution of muscular weakness in upper motor neuron lesions affecting the arm. Brain, 1989. 112(3): p. 749-763.

k) 6. Shelton, F. and M.J. Reding, Effect of lesion location on upper limb motor recovery after stroke. Stroke, 2001. 32(1): p. 107.

l) 7. Stinear, C.M., Barber, P.A., Smale, P.R., Coxon, J.P., Fleming, M.K., Byblow, W.D., Functional potential in chronic stroke patients depends on corticospinal tract integrity. Brain, 2007. 130: p. 170-180.

m) 8. Smania, N. and S. Aglioti, Sensory and spatial components of somaesthetic deficits following right brain damage. Neurology, 1995. 45: p. 1725-1730.

n) 9. Winstein, C.J., et al., A randomized controlled comparison of upper-extremity rehabilitation strategies in acute stroke: a pilot study of immediate and long-term outcomes. Archives of Physical Medicine and Rehabilitation, 2004. 85(4): p. 620-628.

o) 10. Burgess, J.K., Bareither, R., Patton, J.L., Single limb performance following contralateral bimanual limb training. IEEE Transactions on Neural Systems and Rehabilitation Engineering, 2007. 15(3): p. 347-355.

p) 11. Powell, J., et al., Electrical stimulation of wrist extensors in poststroke hemiplegia. Stroke, 1999. 30: p. 1384-1389.

q) 12. Wolf, S.L., Winstein, C.J., Miller, J.P., Taub, E., Uswatte, G., Morris, D., Giuliani, C., Light, K.E., Nichols-Larsen, D., Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: The EXCITE randomized clinical trial. JAMA, 2006. 296(17): p. 2095-2104..

r) 13. Lo, A.C., et al., Robot-assisted therapy for long-term upper-limb impairment after stroke. New England Journal of Medicine, 2010.

s) 14. Ramachandran, V.S. and E.L. Altschuler, The use of visual feedback, in particular mirror visual feedback, in restoring brain function. Brain, 2009.

t) 15. Dohle, C., Pullen, J, Nakaten, A., Kust, J., Rietz, C., Karbe, H., Mirror therapy promotes recovery from severe hemiparesis: A randomized controlled trial. Neurorehabilitation and Neural Repair, 2009. 23: p. 209-217.

u) 16. Holmes, N.P. and C. Spence, Visual bias of unseen hand position with a mirror: Spatial and temporal factors. Experimental Brain Research, 2005. 166(3): p. 489-497.

v) 17. Sathian, K., Greenspan, A.I., Wolf, S.L., Doing it with mirrors: A case study of a novel approach to neurorehabilitation. Neurorehabilitation and Neural Repair, 2000. 14: p. 73-76.

w) 18. Stevens, J.A. and M.E. Stoykov, Using motor imagery in the rehabilitation of hemiparesis. Arch Phys Med Rehabil, 2003. 84(7): p. 1090-1092.

x) 19. Altschuler, E.L., Wisdom, S.B., Stone, L., Foster, C., Galasko, D., Liewellyn, M.E., Ramachandran, V.S., Rehabilitation of hemiparesis after stroke with a mirror. The Lancet., 1999. 353: p. 2035-2036.

y) 20. Yavuzer, G., Selles, R., Sezer, N., Sutbeyaz, S., Bussmann, J.B., Koseoglu, F., Atay, M.B., Stam, H.J., Mirror therapy improves hand function in subacute stroke: A randomized controlled trial. Arch Phys Med Rehabil, 2008. 89: p. 393-398.

z) 21. Michielsen, M.E., et al., Motor recovery and cortical reorganization after mirror therapy in chronic stroke patients: A phase II randomized controlled trial. Neurorehabilitation and Neural Repair, In press.

aa) 22. Wu, C., et al., Effects of modified constraint-induced movement therapy on movement kinematics and daily function in patients with stroke: a kinematic study of motor control mechanisms. Neurorehabilitation and Neural Repair, 2007.

bb) 23. Barzel, A., et al., Comparison of two types of Constrain-Induced Movement Therapy in chronic stroke patients: A pilot study. Restorative Neurology & Neuroscience, 2009. 27: p. 673 - 682.

cc) 24. Buxbaum, L.J., On the right (and left) track: Twenty years of progress in studying hemispatial neglect. Cognitive Neuropsychology, 2006. 23(1): p. 184-201.

dd) 25. Buxbaum, L.J. and H.B. Coslett, Neglect of chimeric figures: Two halves are better than a whole. Neuropsychologia, 1994. 32: p. 275-288.

ee) 26. Buxbaum, L.J., et al., Hemispatial neglect: Subtypes, neuroanatomy, and disability. Neurology, 2004. 62: p. 749-756.

ff) 27. Buxbaum, L.J., et al., Amantadine Treatment of Hemispatial Neglect. American Journal of Physical Medicine and Rehabilitation, 2007. 86(7): p. 527-537.

gg) 28. Coslett, H. and L.J. Buxbaum, Treatment of neglect, in Neurological therapeutics: Principles and practice., J. Noseworthy, Editor. 2002, Martin Dunitz: London.

hh) 29. Coslett, H., et al., Cognitive rehabilitation interventions for neglect and related disorders: moving from bench to bedside in stroke patients.

ii) . Journal of Cognitive Neuroscience, In Press.

jj) 30. Platz, T., Winter, T., Muller, N., Pinkowski, C., Eickhof, C., Mauritz, K.H., Arm ability training for stroke and traumatic brain injury patients with mild arm paresis: A Single-blind, randomized, controlled trial. Arch Phys Med Rehabil, 2001. 82: p. 961-968.

kk) 31. Krebs, H.I., Mernoff, S., Fasoli, S.E., Hughes, R., Stein, J., Hogan, N., A comparison of functional and impairment-based robotic training in severe to moderate chronic stroke: A pilot study. NeuroRehabilitation, 2008. 23: p. 81-87.

ll) 32. Wolpert, D.M. and J.R. Flanagan, Motor prediction. Current Biology, 2001. 11(18): p. R729-R732.

mm) 33. Wolpert, D.M., Z. Ghahramani, and J. Flanagan, Perspectives and problems in motor learning. Trends Cogn Sci,, 2001. 5(11): p. 487-94.

nn) 34. Rizzolatti, G., et al., Premotor cortex and the recognition of motor actions. Cognitive Brain Research, 1996. 3: p. 131-141.

oo) 35. Rizzolatti, G. and G. Luppino, The cortical motor system. Neuron, 2001. 31: p. 889-901.

pp) 36. Rizzolatti, G., L. Fogassi, and V. Gallese, Parietal cortex: from sight to action. Current Opinion in Neurobiology, 1997. 7: p. 562-567.

qq) 37. Kwakkel, G., B. Kollen, and E. Lindeman, Understanding the pattern of functional recovery after stroke: Facts and theories. Restorative Neurology & Neuroscience, 2004. 22(3-5): p. p. 281-299.

rr) 38. Jones, K.E., J. Wessberg, and A. Vallbo, Proprioceptive feedback is reduced during adaptation to a visuomotor transformation: Preliminary findings. NeuroReport, 2001. 12: p. 4029-4033.

ss) 39. Glover, S., et al., The effects of visual illusions on motor performance and motor imagery. Experimental Brain Research, In press.

tt) 40. Contreras-Vidal, J.L. and D.R. Gold, Dynamic estimation of hand position is abnormal in Parkinson's disease. Parkinsonism & Related Disorders, 2004. 10(8): p. 501-506.

uu) 41. Gordon, J., M.F. Ghilardi, and C. Ghez, Impairments of reaching movements in patients without proprioception. I. Spatial errors. Journal of Neurophysiology, 1995. 73(1): p. 347-360.

vv) 42. Ladavas, E., et al., Seeing or not seeing where your hands are. Experimental Brain Research, 2000. 131(4): p. 458-67.

ww) 43. Sainburg, R.L., H. Poizner, and C. Ghez, Loss of proprioception produces deficits in interjoint coordination. Journal of Neurophysiology, 1993. 70(5): p. 2136-47.

xx) 44. Balslev, D., Cole, J., Miall, R.C., Proprioception contributes to the sense of agency during visual observation of hand movements: Evidence from temporal judgments of action. Journal of Cognitive Neuroscience, 2007. 19(9): p. 1535-1541.

yy) 45. Buccino, G., et al., Action observation activates premotor and parietal areas in a somatotopic manner: An fMRI study. European Journal of Neuroscience, 2001. 13: p. 400-404.

zz) 46. Decety, J., et al., Brain activity during observation of action. Influence of action content and subject's strategy. Brain, 1997. 120: p. 1763-1777.

aaa) 47. Flanagan, J.R. and R.S. Johansson, Action plans used in action observation. Nature, 2003. 424(6950): p. 769.

bbb) 48. Fadiga, L., et al., Motor facilitation during action observation: A magnetic stimulation study. Journal of Neurophysiology, 1995. 73(6): p. 2608-2611.

ccc) 49. Grafton, S.T., et al., Premotor cortex activation during observation and naming of familiar tools. Neuroimage, 1997. 6: p. 231-236.

ddd) 50. Johnson-Frey, S.H., et al., Actions or hand-object interactions? human inferior frontal cortex and action observation. Neuron, 2003. 39(6): p. 1053-1058.

eee) 51. Buccino, G., F. Binkofski, and L. Riggio, The mirror neuron system and action recognition. Brain and Language, 2004. 89: p. 370-376.

fff) 52. Miall, R.C., Connecting mirror neurons and forward models. NeuroReport, 2003. 14(16): p. 1-3.

ggg) 53. Tai, Y.F., et al., The human premotor cortex is 'mirror' only for biological actions. Current Biology, 2004. 14(2): p. 117-20.

hhh) 54. Shenton, J.T., J. Schwoebel, and H.B. Coslett, Mental motor imagery and the body schema: evidence for proprioceptive dominance. Neuroscience Letters, 2004. 370(1): p. 19-24.

iii) 55. Coslett, H.B., Evidence for a disturbance of the body schema in neglect. Brain and Cognition, 1998. 37(3): p. 527-544.

jjj) 56. Fink, G.R., Marshall, J.C., Halligan, P.W., Frith, C.D., Driver, J., Frackowiak, R.S., Dolan, R.J., The neural consequences of conflict between intention and the senses. Brain, 1999. 122: p. 497-512.

kkk) 57. Lotze, M. and U. Halsband, Motor imagery. Journal of Physiology-Paris, 2006. 99(4-6): p. 386-395.

lll) 58. Buxbaum, L.J., S.H. Johnson-Frey, and M. Bartlett-Williams, Deficient internal models for planning hand-object interactions in apraxia. Neuropsychologia, 2005. 43(6): p. 917-929.

mmm) 59. Crammond, D., Motor imagery: never in your wildest dream. Trends Neuroscence, 1997. 20(2): p. 54-7.

nnn) 60. Farah, M.J., D. Levine, and R. Calvanio, A case study of mental imagery deficit. Brain and Cognition, 1988. 8: p. 147-164.

ooo) 61. Grush, R., The emulation theory of representation: Motor control, imagery, and perception. Behavioral and Brain Sciences., 2004. 27: p. 377-442.

ppp) 62. Jeannerod, M., The representing brain: Neural correlates of motor intention and imagery. Behavioral and Brain Sciences, 1994. 17: p. 187-245.

qqq) 63. Johnson, S., Thinking ahead: The case for motor imagery in prospective judgements of prehension. Cognition, 2000. 74: p. 33-70.

rrr) 64. Johnson, S.H., Cerebral organization of motor imagery: contralateral control of grip selection in mentally represented prehension. Psychological Science, 1998. 9: p. 219-222.

sss) 65. Johnson, S.H., P.M. Corballis, and M.S. Gazzaniga, Within grasp but out of reach: evidence for a double dissociation between imagined hand and arm movements in the left cerebral hemisphere. Neuropsychologia, 2001. 39(1): p. 36-50.

ttt) 66. Johnson-Frey, S.H., Stimulation through simulation? Motor imagery and functional reorganization in hemiplegic stroke patients. Brain and Cognition, in press.

uuu) 67. Sirigu, A. and J.-R. Duhamel, Motor and visual imagery as two complementary but neurally dissociable mental processes. Journal of Cognitive Neuroscience, 2001. 13: p. 910-919.

vvv) 68. Buxbaum, L.J. and S. Kalenine, Action knowledge, visuomotor activation, and embodiment in the two action systems. Ann N Y Acad Sci, 2010. 1191(1): p. 201-18.

www) 69. Wilson, B.A., Cockburn, J., & Braddeley, A.D., The Rivermead Behavioural Memory Test. 1985, Bury St. Edmunds: Thames Valley Test Company.

xxx) 70. Parsons, L.M., Temporal and kinematic properties of motor behavior reflected in mentally simulated action. Journal of Experimental Psychology: Human Perception and Performance, 1994. 20(4): p. 709-730.

yyy) 71. Rosenbaum, D., et al., Plans for object manipulation, in Attention and Performance XIV, D.E.M.S. Kornblum, Editor. 1993, MIT Press: Cambridge.

zzz) 72. Cohen, J., Statistical power analysis for the behavioral sciences, 2nd. ed. 1988, Hillsdale, NJ: Lawrence Erlbaum Assoc.

aaaa) 73. Kimberg, D.Y., H.B. Coslett, and M.F. Schwartz, Power in voxel-based lesion-symptom mapping. Journal of cognitive neuroscience, 2007. 19(7): p. 1067-1080.

bbbb) 74. Vickers, A.J. and D.G. Altman, Statistics notes: analysing controlled trials with baseline and follow up measurements. British Medical Journal, 2001. 323(7321): p. 1123.

cccc) 75. Kertesz, A., Western aphasia battery. 1982, New York: Grune & Stratton.

dddd) 76. FIM, Guide for uniform data set for medical rehabilitation. 1996, State University of New York at Buffalo: Buffalo, NY.

eeee) 77. Buxbaum, L., et al., Assessment of spatial attention and neglect with a virtual wheelchair navigation task. Journal of Clinical and Experimental Neuropsychology, 2008. 30(6): p. 650-660.

ffff) 78. Wolf, S.L., McJunkin, J.P., Swanson, M.L., Weiss, P.S., Pilot normative database for the Wolf Motor Function Test. Arch Phys Med Rehabil, 2006. 87: p. 443-445.

gggg) 79. Schwartz, M.F., et al., Anterior temporal involvement in semantic word retrieval: voxel-based lesion-symptom mapping evidence from aphasia. Brain, 2009. 132: p. 3411-3427.

hhhh) 80. Avants, B., P.T. Schoenemann, and J. Gee, Lagrangian frame diffeomorphic image registration: morphometric comparison of human and chimpanzee cortex. . Medical Image Analysis, 2006(10): p. 3.

iiii) 81. Pocock, S.J., Allocation of patients to treatment in clinical trials. Biometrics, 1979. 35(1): p. 183-197.

jjjj) 82. Geller, N.L. and S.J. Pocock, Interim analyses in randomized clinical trials: ramifications and guidelines for practitioners. Biometrics, 1987. 43(1): p. 213-223.

kkkk) 83. Bates, E., et al., Voxel-based lesion-symptom mapping. Nature Neuroscience, 2003. 6(5): p. 448-50.

llll) 84. Nichols, T.E. and A.P. Holmes, Nonparametric permutation tests for functional neuroimaging: a primer with examples. Human Brain Mapping, 2001. 15(1): p. 1-25.

mmmm) 85. Buxbaum, L.J., et al., Left inferior parietal representations for skilled hand-object interactions: Evidence from stroke and corticobasal degeneration. Cortex, 2007

nnnn) 43(3): p. 411-423.

oooo) 86. Buxbaum, L.J., Complex object-related action: Structure, meaning, and context. Journal of the International Neuropsychological Society, 2007. 13(6): p. 993-996.

pppp) 87. Jax, S.A., et al., More than (where the target) meets the eyes: Disrupted visuomotor transformations in optic ataxia. . Neuropsychologia, 2009. 47(1): p. 230-238.

qqqq) 88. Schwoebel, J., L.J. Buxbaum, and H.B. Coslett, Representations of the human body in the production and imitation of complex movements. Cognitive Neuropsychology, 2004. 21(2-4): p. 285-298.

rrrr) 89. Medina, J., S.A. Jax, and H.B. Coslett, Two-component models of reaching: evidence from deafferentation in a Fitts' law task. Neurosci Lett, 2009. 451(3): p. 222-6.

ssss) 90. Jax, S.A., L.J. Buxbaum, and A.D. Moll, Deficits in Movement Planning and Intrinsic Coordinate Control in Ideomotor Apraxia. Journal of Cognitive Neuroscience, 2006. 18(12): p. 2063-2076.

tttt) 91. Buxbaum, L.J., K.M. Kyle, and R. Menon, On beyond mirror neurons: Internal representations subserving imitation and recognition of skilled object-related actions in humans. Cognitive Brain Research, 2005. 25(1): p. 226-239.

uuuu) 92. Richards, L.G., Stweart, K.C., Woodbury, M.L., Senesac, C., Cauraugh, J.H., Movement-dependent stroke recovery: A systematic review and meta-analysis of TMS and fMRI evidence. Neuropsychologia, 2008. 46: p. 3-11.

vvvv) 93. Webster, B.R., P.A. Celnik, and L.G. Cohen, Noninvasive Brain Stimulation in Stroke Rehabilitation. Neurotherapeutics, 2006. 3(4): p. 474-481.94. Celnik, P., et al., Effects of combined peripheral nerve stimulation and brain polarization on performance of a motor sequence task after chronic stroke. Stroke, 2009. 40(5): p. 1764-1771.

**If separate protocol is not included, please attach list of references for background section etc. to this form.**