SPECIFIC AIMS: Approx. 31%-64% of patients with stroke experience moderate to severe impairment of the upper limb, despite intensive rehabilitation. Upper-limb function may be improved by delivering rehabilitation in conjunction with a promising experimental approach known as brain stimulation, believed to affect excitability of cortical areas that contribute to plastic mechanisms in recovery. However, improvements observed in moderately/severely-affected patients remain limited. *This is because stimulation is delivered using a generic approach, based on a concept about plasticity that is pertinent only to the recovery of mildly-affected patients* [1, 2]. Stimulation is delivered to always facilitate the excitability of the ipsilesional primary motor cortex (iM1) and suppress the excitability of the undamaged, contralesional motor cortices ("conventional approach"), based on the concept that the iM1 makes the most important contributions towards recovery, while the contralesional motor cortices exert excessive inter-hemispheric inhibition (IHI) and limit paretic-limb movement. But ipsilesional corticospinal pathways are extensively damaged in moderately/severely-affected patients (58%-83% of patients in many studies). Therefore, these patients cannot experience facilitation of iM1 for return of paretic-limb function, evidence based on our AHA studies [3-5].

In this Transformational Project Award (TPA), we take our exploratory AHA findings to the 2nd stage and test whether facilitating the intact, contralesional motor cortices would yield the maximum improvement in paretic-limb function in moderately/severely impaired patients, based on plastic mechanisms most pertinent to patients' recovery *(scientific premise)* (Fig. 1). Our in-progress AHA study and other studies have revealed that intact, contralesional motor cortices make functionally significant contributions to paretic-limb movement when there is extensive ipsilesional damage. Contralesional motor cortices reduce IHI and excite uncrossed output to support movements of the proximal and distal paretic-limb, including reaching and grasp/grip. Therefore, in our recent AHA study, facilitation of the contralesional motor cortices, particularly the contralesional dorsal premotor cortex (cPMd), given just for a single session, leads to 20% more improvement in paretic-limb reaching speed than the conventional approach facilitating iM1 in moderately/severely affected patients [3]. Here, we will test whether the promise and mechanisms of facilitating cPMd elicited within a single session in our recent AHA study can be consolidated to generate clinically meaningful improvements in function in moderately/severely-affected patients by applying multiple sessions in rehabilitation.

In a pilot, randomized controlled study, 24 patients will receive facilitation of cPMd or iM1 (conventional approach) in conjunction with rehabilitation given for 2 days a week for 6 weeks. Moderately/severely-impaired patients with complete loss of ipsilesional corticospinal pathways will be selected, because these patients have been shown to have the best therapeutic response to cPMd facilitation in our in-progress AHA study [3, 6]. Primary outcome will be upper limb impairment, and secondary outcomes will be tests of functional abilities, proximal reaching performance and patient-reported disability. Associated neural mechanisms will also be studied using neurophysiological and functional connectivity MRI techniques. Damage to ipsilesional corticospinal pathways will be indexed with diffusion tensor imaging (DTI).

AIM 1: Determine the effect of facilitating cPMd on upper-limb impairment, functional abilities, proximal control and patient-reported disability. *Hyp 1: Facilitation of cPMd will lead to greater reduction in impairment and disability and to superior improvements in functional ability and proximal reaching control than facilitation of iM1.*

AIM 2: Investigate the effects of facilitating cPMd on inter-hemispheric connectivity. *Hyp 2: Facilitation of cPMd will lead to greater reduction of IHI imposed upon iM1 and a larger increase in cPMd-to-iM1 functional connectivity compared with facilitation of iM1.*

AIM 3: Investigate the effects of facilitating cPMd on uncrossed output. *Hyp 3: Facilitation of cPMd will lead to greater excitation of uncrossed output to the paretic upper limb compared with facilitation of iM1.*

AIM 4: Explore how ipsilesional corticospinal damage influences the response to facilitation of cPMd. *Hyp 4: Improvements elicited with facilitation of cPMd vs. iM1 will vary as a function of the degree of damage to ipsilesional corticospinal pathways.*

IMPACT: In line with the mission of the AHA to build healthier lives for all, the proposed project will offer the most disadvantaged patients, those who typically cannot improve with conventional therapies, a unique opportunity to benefit from a novel brain stimulation approach tailored to their mechanism of plasticity. As such, the project will spearhead the development of targeted therapies to supplant generic approaches. In a broader sense, the project will revolutionize the understanding of stroke recovery in the fields of rehabilitation and neurology that generally have disparaged the potential of uninjured contralesional motor areas- neural resources consistently viable to support paretic-limb function in the most-affected patients.

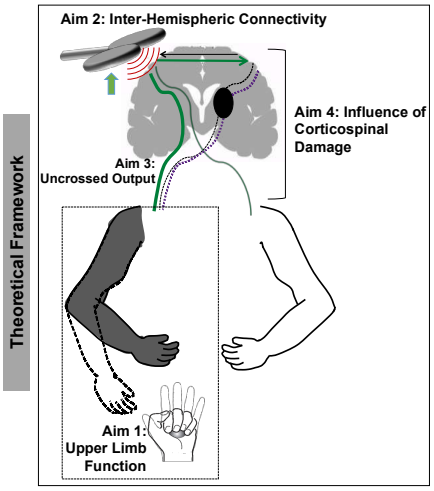

Figure 1: *Scientific Premise:* Stimulation delivered to facilitate the excitability of the uninjured (contralesional) motor cortices will lead to improvement in proximal (e.g., reaching) and distal (e.g., grasp/grip) paretic-limb function in patients with extensive damage to ipsilesional pathways (Aim 1). Mechanisms will involve strengthening of inter-hemispheric connectivity (Aim 2) and excitation of uncrossed pathways (Aim 3). Improvements will vary as a function of the degree of ipsilesional damage (Aim 4).

SIGNIFICANCE

Helping the most affected patients achieve the maximum improvement in function. Of the 7 million stroke survivors living in the US, nearly three-fourths experience residual paresis of the upper limb [7]. Of them, approximately 31%-64% experience moderate to severe paresis, which limits participation in daily activities and self-care tasks, and increases reliance on caregivers for meeting every personal need. Patients with moderate/severe paresis generally do not benefit sufficiently from conventional or promising rehabilitation therapies, unlike the mildly-affected patients [6, 8-18]. *Here, we aim to specifically help promote rehabilitation outcomes in moderately/severely-impaired patients to address an unmet clinical need and give these patients the same opportunities for recovery as those enjoyed by mildly-affected patients.*

Discarding *one-type-suits-all* approaches and adopting targeted therapies. Though several techniques have been developed to promote rehabilitation outcomes, such as peripheral electrical stimulation and robotics, the one technique that has gained widespread attention owing to its potential to *directly* tap into the plasticity of the recovering brain is brain stimulation [1, 19-30]. Originally developed for use as a surgically implanted technique, brain stimulation became widely popular when noninvasive alternatives were introduced [20]. Commonly known as "transcranial" techniques, these alternatives deliver currents from atop the scalp/skull without requiring surgery. A typical example is transcranial magnetic stimulation (TMS), which delivers currents based on the principle of electromagnetic induction. TMS pulses applied in repeated

succession, known as repetitive TMS (rTMS), have the potential to modulate cortical excitability, thereby function, for long periods of time [1, 19-23, 25, 27, 31-35].
But improvements witnessed in moderately/severely-impaired patients remain limited [15, 25, 28, 36-38]. We have explained based on AHA and NIH studies (Grant-in-Aid and Beginning Grant-in-Aid, K01) that *stimulation is delivered using a generic approach, based on a concept about plasticity that is pertinent only to the recovery of mildly-affected patients* [1, 2]. Stimulation is always delivered to facilitate iM1 and suppress contralesional motor cortices, based on the view that iM1 makes the most important contributions to recovery, while contralesional motor cortices exert excessive IHI and limit paretic-limb movement. But ipsilesional corticospinal pathways are damaged extensively in moderately/severely-affected patients (58%-83% of patients in many studies). Therefore, these patients cannot experience facilitation of iM1 for restoration of function of the paretic-limb [1, 6, 15, 27, 31]. *Rather than perpetuate a one-type-suits-all approach that is relevant only to the recovery of select few with minimal damage, here we offer a novel targeted approach meant to facilitate areas consistently viable to support recovery in the majority of patients with extensive damage.*

Targeting the long-disparaged contralesional motor areas - neural resources consistently viable to support recovery in patients with extensive damage. We premise that the uninjured, contralesional motor cortices would support maximum recovery of paretic-limb function in moderately/severely-impaired patients, based on plastic mechanisms most pertinent to patients' recovery (Fig. 1). Evidence presented by our group and other groups has indicated that contralesional motor cortices make functionally relevant contributions to paretic-limb movement in patients with extensive ipsilesional damage [27, 39]. Functional MRI (fMRI) evidence shows that uninjured, contralesional motor cortices are more active than ipsilesional regions during paretic-limb movement in seriously affected patients [4, 5, 40-48]. Contralesional over-activation is essential to paretic-limb movement, because TMS-induced suppression of this activity, especially that of the contralesional dorsal premotor cortex (cPMd), leads to slowing of ongoing paretic-limb movement [3, 37, 49]. This means that cPMd is functionally significant to paretic-limb movement in the more-affected patients [3, 37, 49]. *Therefore, we recommend facilitating the cPMd instead of the conventional target- iM1- for generating the maximum improvement in paretic-limb function in moderately/severely-impaired patients* (*Aim 1*). *Our recommendation aligns with the contemporary view that contralesional not ipsilesional areas are functionally significant in the presence of extensive ipsilesional damage, but it contrasts with the conventional concept that a single area (iM1) is responsible for recovery. As such, our recommendation provides the impetus to supplant generic with targeted therapies for achievement of maximum recovery in every patient.*

Characterizing mechanisms by which contralesional motor cortices can contribute to recovery of the paretic-limb. We believe there are two key mechanisms by which uninjured contralesional motor cortices can contribute to paretic-limb recovery (*Aims 2 and 3*) (Fig. 1).

(a) Strengthening of inter-hemispheric connectivity: Inter-hemispheric (callossal) connections offer a rich resource for information flow between hemispheres. It is thus conceivable that as iM1 is rendered less capable of controlling paretic-limb movement on account of extensive damage, intact contralesional motor cortices enhance their cooperation with weak iM1 to collectively control paretic-limb movement. Bestmann et al. [5] have tested this idea using a combination of TMS and fMRI. TMS was delivered to cPMd while fMRI was collected during the performance of paretic-limb movement. Targeting of cPMd led to an increase in fMRI activation of remote ipsilesional sensorimotor regions, which otherwise were inactive during

paretic-limb movement in moderately/severely-impaired patients. *Therefore, we anticipate that rTMS-based targeting of cPMd delivered in conjunction with paretic-limb rehabilitation would lead to strengthening of inter-hemispheric connectivity with weak ipsilesional regions, amplifying the gain of residual ipsilesional signals conveyed to the paretic limb in patients with extensive damage (Aim 2) [5].*

(b) *Unmasking of uncrossed (ipsilateral) pathways:* Contralesional motor cortices can also support paretic-limb movement via evolutionarily conserved uncrossed pathways [50-55]. Morphologic evidence from animal studies has shown that in the presence of extensive ipsilesional corticospinal injury, sparse, but intact, uncrossed corticospinal and brainstem-mediated reticulospinal pathways provide robust outgrowth to the affected spinal cord [52, 56-59]. *Facilitating cPMd could further excite these uncrossed pathways to promote paretic-limb function in patients with extensive damage to ipsilesional pathways (Aim 3).*

INNOVATION

Tapping into promising improvements elicited with a novel approach of brain stimulation. Based on an ongoing AHA award, we have conducted *the first-in-human study* to facilitate the undamaged, contralesional motor cortices [3]. In a crossover design, patients received facilitatiion of cPMd and iM1 (conventional approach) for a single session each. Facilitation of cPMd led to robust improvements in paretic-limb reaching spped in moderately/severely-affected patients who failed to improve with the conventional approach involving the facilitation of iM1 (Aim 1) (Fig. 2A). Underlying mechanism involved strengthening of inter-hemispheric and uncrossed connectivity (Aims 2 and 3) (Fig. 2B) [3]. Here, we will test whether the promise and mechanisms of facilitating cPMd elicited within a single session can be consolidated to generate clinically meaningful improvements in function by applying multiple sessions in rehabilitation. This would make the proposed study the *first-in-human* study to deliver long-term facilitation to the undamaged, contralesional motor cortices.

Unique opportunity to characterize neural mechanisms otherwise evidenced only in animal studies. Animal studies have demonstrated that intact contralesional motor cortices offer uncrossed pathways to support paretic-forelimb recovery when there is extensive damage to ipsilesional pathways (Fig. 1) [53-55]. There is anecdotal evidence to suggest a similar phenomenon occurs in humans. In patients with severe stroke, TMS applied to the contralesional motor cortex elicits muscle-evoked potentials (MEPs) in the paretic-limb. These MEPs, known as ipsilateral (same-side) MEPs (not to be confused with contralateral MEPs elicited with TMS delivered to the opposite motor cortex), represent unmasked uncrossed output [4, 52, 57, 58, 60-73]. No study to date, however, has characterized the plasticity of this uncrossed output in humans. *The proposed study will demonstrate for the first time recovery-associated gain in size of ipsilateral MEPs with facilitation of parent cPMd (Aim 3). This finding would offer concrete evidence of the existence of direct contribution from the intact hemisphere and its plasticity in support of paretic-limb recovery, a novel translational achievement.*

PRELIMINARY APPROACH

Published and preliminary data acquired in our ongoing and recent AHA studies (Grant-in-Aid and Beginning Grant-in-Aid) and an NIH K01 study has provided support for our scientific premise. Data was acquired as part of short-term and long-term experiments.

SHORT-TERM EXPERIMENT: Moderately/severely-impaired patients with extensive damage who fail to improve with the conventional approach show robust improvements in paretic-limb movement with novel approach involving facilitation of cPMd [3]: Fifteen

patients with mild to severe impairment after chronic stroke (≥6 months) received single sessions of facilitation of cPMd, facilitation of iM1 (conventional approach), and facilitation of a control region, contralesional M1 (cM1), in a randomized, sham-controlled, crossover study. Facilitation was delivered using rTMS. Sessions were separated by ≥1 week to allow for washout of effects. At baseline, impairment (Upper Extremity Fugl-Meyer, UEFM) and corticospinal damage (indexed using DTI as Fractional Anisotropy, FA) were measured. Outcomes included paretic-limb reaching speed and IHI exerted from the contralesional upon the ipsilesional motor cortices (studied using TMS) [3].

In line with findings of other studies, we observed that moderately/severely-impaired patients with extensive ipsilesional damage failed to achieve any improvement in paretic-limb reaching with facilitation of iM1 [15, 25, 28, 36-38]. But a unique finding was that these same patients achieved significant improvement with facilitation of cPMd (t_{13} =2.57; p =0.012; Fig. 2A). Effect of facilitating cPMd was related to a reduction in IHI; patients who became faster at paretic-limb reaching with cPMd facilitation experienced greater reduction in IHI from contralesional upon ipsilesional cortices, i.e., better inter-hemispheric connectivity (r=0.75, p <0.001, Fig. 2B).

Effect of facilitating cPMd was more remarkable than effect of facilitating cM1. Facilitation of cPMd led to faster paretic-limb reaching (t_4=3.479, p=0.025) and greatly reduced IHI compared to facilitation of iM1 (z=1.83, p=0.06) (Fig. 2D)[3]. This result aligns with findings of other studies, where transient suppression of cPMd leads to greater slowing of paretic-limb reaching than transient suppression of cM1 (Fig. 2C)[4, 5, 74]. Collectively, evidence from our work and previous work indicates that cPMd is more indispensible for paretic-limb movement than other contralesional areas. Bilateral organization and robust uncrossed connectivity likely affords cPMd the flexibility to control ipsilateral besides contralateral movements [5, 52, 64-67, 74-80].

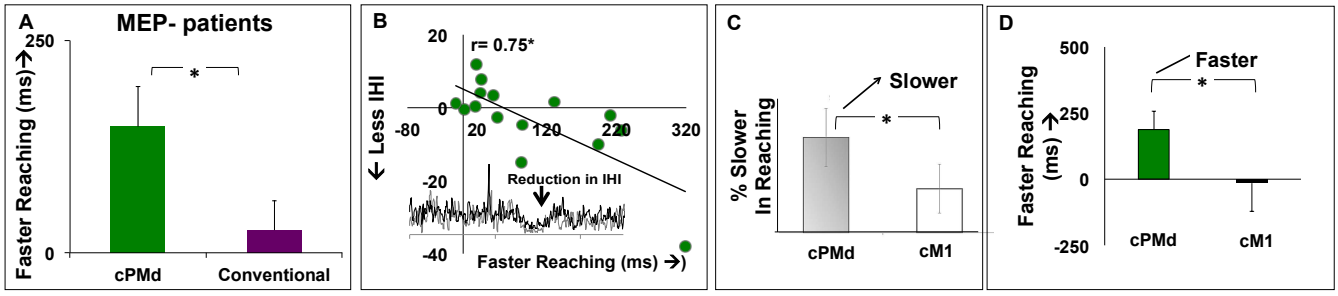

Figure 2 (A) and (B). Adapted from our recent short-term study (Sanakarasubramanian, Plow et al. *Clin Neurophysiol* 2017). (A) Effect of our new approach of cPMd facilitation upon paretic-limb reaching speed is compared to the effect of the conventional approach of iM1 facilitation in patients with extensive damage (MEP-). (B) Improvement in paretic-limb reaching-speed was related to reduction in IHI following cPMd (not iM1) facilitation. (C) Adaptation from Harris-Love et al. 2016, 2017 comparing the effects of transiently suppressing the activity of cPMd and cM1 upon ongoing paretic-limb reaching. (D) Adaptation from our work comparing the effects of transiently facilitating the activity of cPMd and cM1 upon ongoing paretic-limb reaching (Sanakarasubramanian, Plow et al. 2017).

Overall, our short-term data has revealed that cPMd is a more promising target than iM1 or other contralesional regions for promoting paretic-limb function in the most-disadvantaged patients (Aim 1). cPMd contributes to paretic-limb movement by reducing IHI, i.e., strengthening inter-hemispheric connectivity (Aim 2). Our short-term data has also helped stratify patients mostly likely to respond to cPMd facilitation. Using machine learning, co-I Dr. Wang [3, 34, 45, 81, 82] has identified that moderately/severely-impaired patients (UEFM ≤ 42 out of 66) with extensive damage to ipsilesional pathways [inability to elicit MEPs in paretic-muscle with TMS delivered to iM1 (MEP-) and FA values < 50% of normal white-matter integrity] show the best response to cPMd facilitation; mildly-affected patients show the poorest response [3]. Therefore, we will only

enroll the most-affected patients who fit criteria identified in our short-term study. *Enrolling a homogeneous sample with high likelihood of response would contribute to scientific rigor and statistical power and improve the chances of success.*

LONG-TERM EXPERIMENT: Moderately/severely-impaired patients with extensive damage achieve dramatic improvements in paretic-limb function with multiple sessions of cPMd facilitation: In line with the design of the proposed study, we conducted a pilot randomized controlled study. Three patients with moderate/severe-impairment and extensive damage to ipsilesional pathways, meeting criteria specified in our short-term study (UEFM ≤42, MEP-), were randomly assigned to receive facilitation of cPMd (n=2) or iM1 (conventional approach) (n=1) in conjunction with rehabilitation given for 3 days/wk for 5 wks. Facilitation was delivered using rTMS [3]. Outcomes included impairment (UEFM) and functional ability to perform paretic-limb tasks (Wolf Motor Function Test, WMFT) [83]. Neural metrics were also studied with TMS, including IHI and output of uncrossed pathways (ipsilateral MEPs).

Our findings revealed that patients receiving cPMd facilitation achieved dramatic improvements upon UEFM (9-point gain from 30 ± 8.4 to 39.0 ± 9.90) that exceeded the minimal-clinically important difference (5.2-point gain [84]). This improvement also exceeded the gain witnessed in patients receiving iM1 facilitation by two-fold (4.3-point gain on UEFM from 31.4 ± 11.07 to 35.7 ± 10.34) (Fig. 3A) [85, 86]. Improvements achieved upon UEFM translated to recovery of functional abilities. Patients receiving cPMd facilitation became 75% faster on WMFT (12.15±3.32 to 20.81±14.24 movements per min), while the patient receiving iM1 facilitation became slower (17.20 to 13.30 movements per min).

In association with recovery, patients receiving cPMd facilitation experienced a reduction in IHI from the contralesional motor cortices. IHI was studied here as suppression of ongoing voluntary paretic-muscle activity elicited with TMS given to the contralesional motor cortex (referred to as ipsilateral silent period or iSP) (Fig. 3B). Patients receiving cPMd facilitation showed considerable shortening of iSP (19.5±16.46ms to 11.75 ±3.89ms) compared to the patient receiving iM1 facilitation (12ms to 25.5ms), implying reduction in IHI and strengthening of inter-hemispheric cooperation during paretic-muscle activity. Reduction in IHI offered iM1 a reprieve; a patient originally lacking MEPs (MEP-) showed restoration of MEPs in the paretic-muscle (MEP+) after receiving cPMd facilitation, indicating amplification (dis-inhibition) of residual signals to the paretic limb (Fig. 3C). MEPs were not restored after iM1 facilitation.

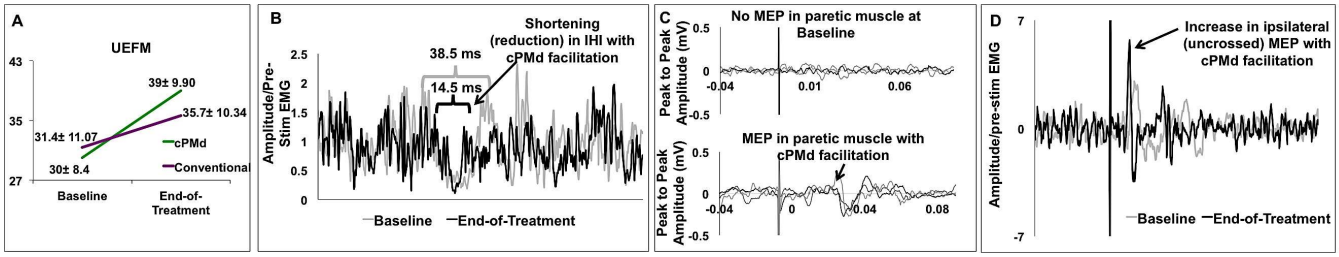

Figure 3 (A) UEFM improvement; (B) IHI reduction: shortening of iSP duration; (C) restoration of MEPs in paretic muscle in a patient who could not elicit MEPs at baseline. (D) Increase in uncrossed or ipsilateral MEPs after cPMd facilitation.

Patients receiving cPMd facilitation also showed larger ipsilateral MEPs after treatment than the patient receiving iM1 facilitation (705.38μV and 622.12μV vs. 481.56 μV) (Fig. 3D). Ipsilateral MEPs were already present in our sample though contralateral MEPs were lacking (MEP-). This means that intact motor cortices were already contributing to paretic-limb function via uncrossed

pathways in the absence of ample ipsilesional pathways. Facilitation of cPMd further strengthened this uncrossed contribution to favor paretic-limb recovery [53-55].

Overall, our long-term data has revealed that cPMd facilitation can help generate clinically meaningful gains in function in moderately/severely-impaired patients who otherwise show limited improvement with conventional iM1 facilitation (Aim 1). cPMd facilitation strengthens inter-hemispheric and uncrossed connectivity, amplifying any descending signals to the paretic-limb (Aims 2 and 3). In this study, we will also explore how response to cPMd facilitation varies as a function of ipsilesional damage (DTI) for responder stratification (Aim 4).

APPROACH

Study Design and Criteria: In a pilot, randomized-controlled, single-blind study, a target of 24 patients will be assigned to either receive facilitation of cPMd or facilitation of iM1 (conventional approach), delivered daily in conjunction with rehabilitation for 2 days/wk for 6 wks. They will be assigned to treatment groups using a stratified randomization scheme to minimize group imbalances on 4 key patient characteristics: (1) time post-stroke (<2 yrs vs. ≥2 yrs), (2) cortical vs. subcortical stroke, (3) presence of active wrist extension vs. no wrist extension, and (4) paretic side (dominant vs. non-dominant). Assessments will be completed at baseline and at the end of treatment after 6 wks, except assessments for Aim 1 that will also be completed at screening and at 3-month follow-up visit (Table 1). Ten age matched healthy controls, fifteen age matched mild, and up to 5 moderately impaired participants (who will undergo rTMS and CCFES based-therapy) will also be enrolled to record comparative neural indices. The goal will be to establish age-based norms for healthy, mild, moderate, and severe neurophysiologic metrics related to EDC, FDI, Biceps, and Triceps muscles.

Table 1: Schedule of Assessments

		Screening & Eligibility	Baseline (0 weeks)	End-of-Treatment (6 weeks)	Follow-up (3 months)
	History, Physical & Neurological Examination	X			
	Eligibility testing: Inability to elicit MEPs (TMS), i.e., MEP-	X			
Aim 1	Impairment (UEFM)		X	X	X
Aim 1	Functional Ability (WMFT)		X	X	X
Aim 1	Distal movement (Grasp/Grip Strength		X	X	X
Aim 1	Patient-perceived Disability (SIS-16)		X	X	X
Aim 2	IHI imposed on iM1 (TMS)		X	X	
Aim 2	Inter-hemispheric connectivity (resting state fMRI)		X	X	
Aim 3	Uncrossed pathways or Ipsilateral MEPs (TMS)		X	X	
Aim 4	Ipsilesional corticospinal damage (DTI)		X		

Patients ***included*** will be (1) between the ages of 18 and 90 yrs; 2) in chronic phase (≥6 months) after index ischemic/hemorrhagic stroke; 3); moderate or severely impaired with extensive damage to ipsilesional pathways (MEP -) [note: patients meeting these criteria typically make up 40%-83% of the sample in our studies and in other studies] or have <10° active wrist extension or <10° active thumb abduction/extension or <10° active extension in at least two additional digits (i.e., will not meet minimum CIMT criteria) [3, 6, 27, 69]; and 4) medically stable. Patients will be ***excluded*** if they have 1) brainstem stroke; 2) cerebellar stroke 3) bilateral strokes; 4) severe cognitive impairment; 5) substantially elevated tone/spasticity in wrist/hand (Modified Ashworth Scale >3); 6) severe contracture; 7) participation in OT or Botox therapy within 2 months; 8) exclusion criteria for TMS and MRI (metal implant in head, H/O seizures, alcohol or substance abuse, intake of medications contraindicated with TMS [89], cardiac pacemaker or programmable implant). For healthy control and mild participants, the exclusionary criteria will be the same as mentioned above. Healthy control inclusion criteria is age between 18-90 years old, without any diagnosis of neurological disease. Mild inclusion criteria includes age between 18-90 years old and UEFM score of 47 or above. For moderate participants, the exclusion criteria will be the same as mentioned above. Moderate inclusion criteria include having >10° active wrist extension and >10° active thumb abduction/extension and >10° active extension in at least two additional digits (i.e., will meet minimum CIMT criteria) and adequate active movement of

shoulder and elbow to position the paretic hand on one’s lap for performance of functional task practice and CCFES-assisted hand opening exercises.

Participants with multiple and/or bilateral strokes that meet the following criteria will be considered for eligibility based on study neurologists review of previous MRI/CT scans:

1. The non-target infarct is not affecting sensorimotor structures and pathways
2. The non-target infarct is not affecting both UE and does not impair study participation and assessment
3. All strokes occurred over 6 months ago (chronic)

Subject Recruitment: Cleveland Clinic logs >3200 annual visits for stroke, based on which >7975 patients have been included in an ongoing database created by the PI. Approx. 282 patients from this database have been screened, and 80 have been enrolled in the past 5 years (~21% screen-in rate). This database will serve as the primary source for recruitment. In case more subjects are needed, referrals from stroke physicians (see Dr. Machado’s letter) and assistance from NINDS’ Regional Stroke Clinical Trials network will be sought. For this study we will contact subjects who previously completed the optional pilot testing protocol in the 16-128 study, “Novel Brain Stimulation Therapies in Stroke Guided by Expressions of Plasticity”. The optional pilot testing these subjects completed was the exact protocol that we are performing in this current study protocol. We will ask them to allow us to use their data from the visits they completed in the 16-128 study, “Novel Brain Stimulation Therapies in Stroke Guided by Expressions of Plasticity”, in this current study.

Once a potential subject is identified, an email or EPIC Messaging/MYCHART will be sent to their physician at the Cleveland Clinic, seeking permission to contact the subject. If permission is received, a letter or EPIC Messaging/MYCHART will be sent to the subject. The letter will briefly outline the procedures of the study and ask the subject to call if they are interested in participating. If the subject expresses interest, then a preliminary eligibility screening will be completed over the phone. If subjects do not call back within 2 weeks of the original date of mailing, then the study staff will call the subject to determine if they are interested in participating. Candidates who meet eligibility requirements over the phone call will be scheduled to come in for informed consent visit, interview and physician screening/examination.

History, Physical and Neurologic Examination, and Screening/Eligibility Testing: Stroke physicians at Cleveland Clinic will screen patients at the beginning of the study to determine eligibility, either on-site or through a video screen for subjects who cannot reasonably make it to one of the sites. Therapists will also conduct a screening to assess upper limb functionality before subjects are enrolled. This is typically done on-site before or after the physician screening, unless participants are not within a reasonable distance to the Cleveland Clinic and a virtual visit is more appropriate. The therapists will assess active/passive range of motion, and determine the participant’s ability to move their upper limbs in a functional space. For interested candidates that would like to perform a video screen for eligibility they will provide a separate informed consent for the video screen. Given that the screening consent is meant to preclude the need for the patient to come for an on site visit, it will be completed online. Through secure Cleveland Clinic RedCap data management server, the participant receive an electronic mail (e-mail) providing links the informed consent form that will also contain space for providing e-signature. The participant will be given few days to review the screening consent form and provide consent to undergo

eligibility assessments over video. The screening consent form would remind participants that they are not giving consent to undergo study procedures, but to be interviewed over video. After screening consent is obtained, research team, therapist and/or physician will perform video screening with the participant. The video screen will be conducted on CCF encrypted devices (ex: CCF computer, CCF phone) using CCF Skype for Business or ExpressCare.

Stimulation: Stimulation will be delivered using rTMS, based on the expertise of the PI [3, 25, 32, 45, 47, 81, 82, 90-93]. Facilitation will be achieved using 5Hz rTMS, capable of facilitating the excitability of both higher motor (PMC and adjoining SMA) and primary motor cortices (M1). In the cHMC facilitation group, a region 2 cm anterior and 1 cm medial to the contralesional motor hotspot will be targeted, corresponding to the location of premotor and adjoining SMA complex.Forty two 10-sec trains of 50 pulses each will be delivered over a period of 21.21 min (2100 pulses total).. Patients in the iM1 facilitation group will receive stimulation to the ipsilesional motor hotspot, unless the hotspot cannot be identified, in which case the mirror location of the contralesional hotspot will be targeted. rTMS will be delivered at an intensity of 90% Active Motor Threshold (AMT) based on the wrist extensor (extensor digitorum communis (EDC)) muscle (details later). Choice of EDC is driven by the clinical need for restoration of wrist-extension, a key predictor of recovery [69, 87, 88].

Rehabilitation: Immediately after rTMS, patients will receive 1-hr of task- or goal-oriented training, optimized for use in moderately/severely-impaired patients by co-I Dr. Wolf's group and other groups [45, 105-109]. rTMS and training will be delivered for 2 days/wk for 6 wks, a dose found to be sufficient for eliciting clinically-meaningful gains in function in our work [45].

AIM 1: Determine the effect of facilitating cPMd on upper-limb impairment, functional abilities, proximal control and patient-reported disability. At baseline, end-of-treatment and 3-month follow-up, we will collect the following indices. *Impairment* will be measured using UEFM, one of the most widely used assessments in stroke [110]. UEFM will serve as our *primary outcome* because it is sensitive to discerning the effects of rTMS/rehabilitation [14, 45, 111-114], and has excellent reliability (ICC= 0.97), consistency (Cronbach's α= 0.84) and validity [115-120]. *Functional ability* to use the paretic upper limb in a variety of tasks will be assessed using WMFT (developed by co-I, Dr. Wolf). Time to complete each task will be noted and converted to rate (60/Performance Time (sec)), optimized for measurement in moderately/severely-impaired patients [83]. WMFT rate shows high validity and reliability in this population [83]. Grip strength will also be recorded with WMFT. *Proximal motor control* will be assessed using an upper extremity task. The task will characterize motor control in moderately/severely-impaired patients who typically lack adequate distal movements. *Patient's perceived disability* related to physical function will be indexed using the Stroke Impact Scale (SIS-16), a reliable (ICC= 0.94) and valid index [127, 128].

Expected outcomes and interpretations: Based on the findings of our AHA study, we expect that facilitation of cPMd will lead to greater improvement on UEFM, WMFT rate, grip strength, and SIS-16 than facilitation of iM1 (Fig. 3A). This finding would mean that facilitation of the intact hemisphere promotes paretic upper-limb recovery in patients who cannot rely on injured cortices due to extensive ipsilesional damage.

AIM 2: Investigate the effects of facilitating cPMd upon inter-hemispheric connectivity. Inter-hemispheric connectivity will be characterized using IHI collected with TMS and functional connectivity collected with resting-state fMRI (rsfMRI). IHI will serve as the *primary outcome*

because it is sensitive to capturing the effects of rTMS [3, 45, 47, 125, 129-131]. Functional connectivity will complement IHI measurement as a secondary outcome because while IHI records neurophysiologic interactions between a contralesional and a weak ipsilesional region, functional connectivity defines “global” interactions across multiple regions.

Before describing the measurement of IHI, it is important provide details about TMS procedures. Single-pulse TMS will be delivered using a figure-of-eight coil with stereotactic guidance from patient’s MRI. Surface EMG electrodes affixed to paretic and non-paretic EDC will measure TMS-evoked MEPs and “silence” of ongoing muscle-activity. At the screening visit, TMS will be delivered to iM1 to confirm the absence of ipsilesional MEPs in paretic EDC (MEP-) [69, 87, 88]. Patients showing ≥50μV MEPs in consistent trials (≥6 of 10) in resting paretic EDC (10%-20% contraction) will be excluded. Eligible participants will undergo repeat testing of TMS targeting iM1 at baseline and at end-of-treatment to identify restoration of ipsilesional MEPs, as seen in our pilot study (Fig. 3C). TMS will also be delivered to cM1. Motor hotspot will be identified as the site eliciting ≥100μV MEPs in consistent trials (≥6 of 10) in slightly contracted non-paretic EDC (10%-20% contraction). The lowest intensity required to elicit these criterion-level MEPs will be termed as AMT. TMS will be delivered at 100% MSO to cM1 and cPMd during voluntary paretic muscle-activity (50% contraction) for measurement of IHI. Silence elicited in muscle-activity, called iSP, will be recorded (Fig. 3B) [45, 47, 132]. % EMG suppression during iSP (relative to pre-stimulus EMG) is labeled IHI.

rsfMRI will denote temporal correlation between low-frequency Blood Oxygenation Level-Dependent (BOLD) fluctuations occurring across different regions as intrinsic functional connectivity [133-136]. rsfMRI obviates the need for performance of a movement, offering an advantage over motor task-based fMRI for testing of moderately/severely impaired patients [133-136]. Methods and analysis will follow steps outlined in our work with Dr. Sakaie [133, 134, 136-143]. Based on this work, we have found that moderately/severely-impaired patients demonstrate an increase in functional connectivity between cPMd and iM1 in association with recovery (n=9) [142]. Here, we will examine whether this intrinsic connectivity strengthens with facilitation of cPMd. Temporal correlation between reference time series of cPMd, iM1 and different areas will be computed and converted to t- and z-score maps (Fig. 4A) [142, 143].

Expected outcomes and interpretations: Based on our AHA studies, we expect that facilitation of cPMd will lead to a greater reduction of IHI and a larger increase in cPMd-to-iM1 functional connectivity than facilitation of iM1 (conventional approach) (Fig. 3B, 4A). This finding would mean that facilitation of the intact hemisphere helps strengthen inter-hemispheric connectivity with weak iM1 to promote paretic-limb recovery in patients with extensive ipsilesional damage.

AIM 3: Evaluate the effects of facilitating cPMd upon uncrossed output to the paretic-limb. Output of uncrossed pathways will be studied as ipsilateral MEPs elicited in the paretic-muscle with TMS (Fig. 3D) [144]. During tonic contraction of the paretic-muscle (100% contraction), high-intensity TMS (100% of maximum device output) will be delivered to cM1 and cPMd (30 trials each) [144]. Ipsilateral MEPs will be identified as potentials exceeding pre-stimulus EMG by >1SD at a latency ~6-15ms longer than the latency of contralateral MEPs elicited in the corresponding non-paretic muscle. Uncrossed pathways mainly supply spinal motor neurons of proximal and distal flexors, so we will record ipsilateral MEPs from flexor carpi radialis muscle as well as EDC and biceps [82, 93, 144]. Ipsilateral MEP area will be calculated as 100*area of rectified EMG in ipsilateral MEP/(avg pre-stimulus EMG* ipsilateral MEP). We will also use a clinical peripheral electrical stimulation technique called H-Reflex to study spinal

pathway excitability. H-reflex will be collected using a clinical grade neurostimulator used to collect H-reflex in the clinical setting along with sticker electrodes to record the stimulation readings in a muscle of the forearm.

Expected outcomes and interpretations: Based on our AHA study, we expect that facilitation of cPMd will lead to larger gains in ipsilateral MEP area than facilitation of iM1 (Fig. 3D). This finding would mean facilitating the intact hemisphere strengthens its uncrossed contributions to favor paretic-limb recovery in patients who otherwise lack adequate ipsilesional contributions.

AIM 4: Explore how ipsilesional corticospinal damage influences response to cPMd facilitation. At baseline, damage to ipsilesional corticospinal pathways will be indexed using DTI. DTI enables the investigation of structural integrity and orientation of pathways *in vivo* through the estimation of magnitude and directionality of water diffusion [69, 145-149]. DTI metrics can help quantitate damage even when patients show no response to TMS due to extensive damage (MEP-) (Fig. 4B) [3, 47, 69]. High angular resolution diffusion weighted images will be acquired and analyzed using steps outlined in our work with Dr. Sakaie [34, 47, 91, 150-154]. Ipsilesional and contralesional corticospinal tracts will be reconstructed using probabilistic tractography [47, 91, 153, 155]. FA, a unit-less measure of white matter integrity, will be calculated [156, 157]. $FA_{Asymmetry}$ given by $FA_{Contralesional} - FA_{Ipsilesional}/FA_{Contralesional} + FA_{Ipsilesional}$, will be used to express integrity of ipsilesional vs. contralesional tracts. Higher values of $FA_{Asymmetry}$ indicate severe damage. Stroke neurologist, Dr. Conforto, will identify lesion location (posterior limb of internal capsule (PLIC) or non-PLIC) and volume (cm^3) [158].

Expected outcomes and interpretations: Based on our AHA study, we expect that improvements associated with facilitation of cPMd will vary as a function of baseline corticospinal damage [3]. This would allow identification of a threshold level of damage, beyond which patients fail to show criterion-level improvement (5.2-point gain [84]) on UEFM, necessary for responder stratification for this new approach involving facilitation of intact areas.

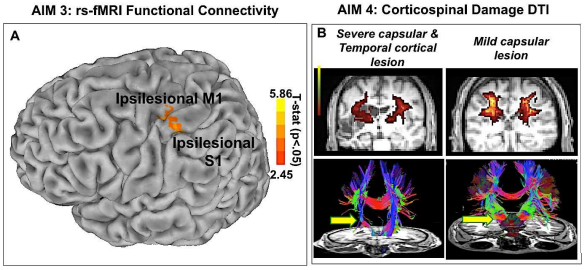

Figure 4. (A) Group rsFMRI data from moderately/severely-impaired patients (n=9) reveals areas in ipsilesional M1 and sensory cortices (S1) (MNI: X: 49 Y: 29 Z: 48) that show an increase in functional connectivity with cPMd (MNI: 26, -6, 53) (peak t-value= 3.25) following rehabilitation. (B) Examples from our work demonstrating the feasibility of successfully generating FA maps (*top*) and reconstructing corticospinal tracts (*bottom*) in patients with severe (*left panel*) and mild damage (*right panel*).

STATISITICAL ANALYSIS: For analysis of aims 1, 2 and 3, linear mixed effects models will be used to compare change in UEFM (primary endpoint), WMFT rate, functional ability, grip strength, SIS, IHI, functional connectivity, and ipsilateral MEP area from baseline to end-of-treatment (and 3-month follow-up) between groups. Models will account for spasticity, baseline wrist extension (none; ≤10°; >10°), lesion size/location, time post-stroke, side of paresis, biologic variables (e.g., sex) and handedness. Bivariate (Pearson's) correlation will be used to explore relationships between change in function and change in IHI, functional connectivity and ipsilateral MEP area. Chi-square or Fisher's Exact test will help compare the frequency of responders (those achieving ≥5.2-point UEFM gain [84]) and patients showing restoration of ipsilesional MEPs (MEP+) between groups. For aim 4, regression models will capture the influence of baseline $FA_{Asymmetry}$ upon improvements associated with facilitation of cPMd vs. iM1l, and separately the influence of baseline UEFM and wrist extension.

Additional data analysis will be conducted using quantum machine learning (QML) to develop a classification model for assessing the functional capacity of stroke patients to use the affected upper extremity. We will utilize behavioral outcome measures signifying the functional capacity collected during this study. The ultimate goal of this analysis is to discern variations in functional capacity among individuals affected by stroke for tailoring rehabilitation interventions to each patient's specific needs.

Potential Pitfalls and Alternative Solutions: *If not all patients can elicit ipsilateral MEPs in the paretic muscle,* we will compare groups upon the frequency of evidence of these MEPs after treatment (Chi-square/Fisher's Exact) [4, 52, 57, 58, 60-73]. *If effects of cPMd facilitation are weak,* we will perform sub-group analyses based on baseline wrist extension to determine which category of patients shows the best response. We will also determine what level of baseline $FA_{Asymmetry}$, connectivity, impairment (UEFM) predicts response vs. non-response (based on attainment of 5.2-point UEFM gain [84]). *Anticipating that cPMd facilitation may have effects on bilateral control,* we will adopt bimanual test used in our recent study [159].

Sample size Estimation and Power Analysis: Table 2 shows sample size estimations based on two-sample t conducted across difference scores between groups. We expect to enroll 22 subjects but in accounting for ~10% attrition, a total of 24 subjects will be enrolled.

Table 2: Sample Size Estimation

	Metric	cPMd vs. iM1	Alpha	80%	85%	90%	95%
Aim 1	UEFM	9±1.41 vs. 4.3±3.56	0.05	14	16	18	22
Aim 2	IHI	-9.25±5.89 vs.6±14.05	0.05	20	22	26	30
Aim 3	Ipsilateral MEP	311.63±29.96 vs. 255.75±93.29	0.05	22	24	38	46
Aim 4	DTI α UEFM	15% diff. in slopes	0.05	18	20	23	28

IMPACT: While greater damage produces greater impairment following stroke, it also generates a widespread plastic response involving the intact cortices in the contralesional hemisphere. Although this response may not be sufficient to support complete recovery, it is likely to support more recovery than what is otherwise possible to achieve [4]. Demonstrating that facilitating these intact areas can lead to restoration of paretic-limb function in patients who fail to benefit from any therapies on account of extensive damage will carry tremendous clinical impact, provide the impetus to develop targeted therapies and depart from conventional beliefs that have always disparaged the potential offered by the intact hemisphere.

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