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Original Research

Methods for an Investigation of Neurophysiological and Kinematic Predictors of Response to Upper Extremity Repetitive Task Practice in Chronic Stroke

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List of abbreviations: ARAT, Action Research Arm Test; AD, anterior deltoid; AUROC, area under the receiver operating characteristic curve; BDNF, brain-derived neurotrophic factor; COMT, catechol-O-methyltransferase; ECR, extensor carpi radialis; FMA, Fugl-Meyer Assessment; LASSO, least absolute shrinkage and selection operator; MEP, motor-evoked potential; MRI, magnetic resonance imaging; RMT, resting motor threshold; TMS, transcranial magnetic stimulation; WMFT, Wolf Motor Function Test.

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KEYWORDS
Magnetic resonance imaging;
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Abstract *Objective:* To demonstrate the feasibility of algorithmic prediction using a model of baseline arm movement, genetic factors, demographic characteristics, and multimodal assessment of the structure and function of motor pathways. To identify prognostic factors and the biological substrate for reductions in arm impairment in response to repetitive task practice.
Design: This prospective single-group interventional study seeks to predict response to a repetitive task practice program using an intent-to-treat paradigm. Response is measured as a change of ≥5 points on the Upper Extremity Fugl-Meyer from baseline to final evaluation (at the end of training).
Setting: General community.
Participants: Anticipated enrollment of community-dwelling adults with chronic stroke (N=96; onset≥6mo) and moderate to severe residual hemiparesis of the upper limb as defined by a score of 10-45 points on the Upper Extremity Fugl-Meyer.
Intervention: The intervention is a form of repetitive task practice using a combination of robot-assisted therapy coupled with functional arm use in real-world tasks administered over 12 weeks.
Main Outcome Measures: Upper Extremity Fugl-Meyer Assessment (primary outcome), Wolf Motor Function Test, Action Research Arm Test, Stroke Impact Scale, questionnaires on pain and expectancy, magnetic resonance imaging, transcranial magnetic stimulation, arm kinematics, accelerometry, and a saliva sample for genetic testing.
Results: Methods for this trial are outlined, and an illustration of interindividual variability is provided by example of 2 participants who present similarly at baseline but achieve markedly different outcomes.
Conclusion: This article presents the design, methodology, and rationale of an ongoing study to develop a predictive model of response to a standardized therapy for stroke survivors with chronic hemiparesis. Applying concepts from precision medicine to neurorehabilitation is practicable and needed to establish realistic rehabilitation goals and to effectively allocate resources.

Stroke is a leading cause of long-term disability[1] with total annual direct and indirect costs in the United States projected to increase from $105.2 billion in 2008 to over $240 billion by 2030.[2] Recent global trends toward stroke onset earlier in the lifespan[3,4] and increased survival result in more individuals living longer with chronic stroke-related disability,[5] highlighting the need for effective long-term rehabilitation strategies. Although decision trees have been developed and validated to predict spontaneous recovery during the acute phase,[6] prediction of therapy-induced changes during the chronic phase is a poorly developed area and is complicated by factors related to deconditioning, compensatory movements, and rehabilitation intensity.[7,8] Chronic stage improvements are generally reliant on intense task repetition as seen in large multisite trials of constraint-induced movement therapy (EXCITE)[9] and robot-assisted training (VA ROBOTICS),[10] and differences in outcomes may not be associated with baseline scores[11] because they are in the acute phase. Understanding the potential for rehabilitation and prediction of recovery beyond the subacute period, particularly in response to specific therapeutic interventions, is critical to maximizing care use and delivering personalized therapy.

Systematic reviews suggest that high-dose repetitive task practice, such as robot-assisted therapy, is beneficial for arm function[12] as well as associated activity-dependent neuroplasticity after stroke.[13] However, several repetitive task trials have demonstrated modest and/or equivocal results,[10,13-16] indicating that response in chronic stroke may be highly variable. In our prior work, rather than a universally modest effect across participants, we see a group with little to no change and another group with a significant response, even when accounting for apparent baseline differences.[14] Differentiating between these groups by identifying biomarkers that predict response to a well-regimented therapy method could allow for more targeted, effective neurorehabilitation.

The examination of surrogate indicators of the post-stroke state provide a window into recovery potential,[15] and use of predictive variables for recovery or treatment response is growing.[17] Recent advances in neuroimaging and neurophysiology provide new methods for examining brain structure and connectivity for possible biomarkers. Prior work has correlated changes in resting state connectivity on functional magnetic resonance imaging with motor recovery during robot-assisted therapy,[18] and diffusion

tensor imaging has been used to demonstrate a relationship between degree of damage in the corticospinal tract and impairment.[19] Transcranial magnetic stimulation (TMS) has been used to investigate the structural integrity of corticospinal pathways, with better upper limb recovery prognosis when motor-evoked potentials (MEPs) are elicited within days after stroke.[20-22] In the chronic phase, MEP presence is not as reliable a predictor but has been associated with better response to an intervention as measured by the Fugl-Meyer Assessment (FMA) and Wolf Motor Function Test (WMFT).[23]

In concert with neurophysiology, genetic factors are likely to influence central nervous system responses to motor experience[24] and have been suggested to affect stroke recovery.[25] Among the potential candidate genes is brain-derived neurotrophic factor (BDNF),[26] which has a common polymorphism known to affect motor function and plasticity.[24,27] Recently, BDNF genotype was shown to be associated with motor outcomes for the arm and was a predictor for patients with severe baseline motor deficits in the subacute phase of recovery.[28] Other polymorphisms that affect function of biogenic amines, including catechol-O-methyltransferase (COMT) and dopamine transporter,[29] are known to influence mediation of dopaminergic systems. Dopamine activity levels in the brain are documented both to be affected by stroke and to influence poststroke motor recovery.[30] *Klotho*, a gene with a polymorphism related to lifespan, has been associated with cognition and neuroplasticity.[31] We are interested in assessing the beneficial or deleterious role of each of these genetic factors in predicting motor neurorehabilitation and treatment response.

While severity of motor deficits has long been used as a primary predictor of functional outcome, new tools and applications provide fresh potential and nuance. Robot-derived kinematic evaluation allows for more precise measurement and characterization of motor deficits and has been modeled as a predictor of early stroke recovery.[32] Pain is an underrecognized consequence of stroke,[33] and pain behaviors may limit participation in rehabilitative therapies, suggesting pain's potential predictive role in outcome and participation. The expectancy theory of motivation to predict outcomes in stroke rehabilitation is an additional area of increasing interest.[34]

The purpose of this study is to identify baseline prognostic factors in chronic stroke that influence motor recovery in response to repetitive task practice and to develop a predictive model of response to a standardized intervention for the upper limb. In this manner, we propose to contribute to understanding the mechanisms of recovery and develop an algorithm to better match patients in the chronic phase to effective therapy based on their individual behavioral, neurophysiological, and genetic composition.

Methods

Study design

Basis

The present single-group predictive study is based on a previous 12-week randomized controlled trial comparing 2 robot-assisted therapy paradigms in stroke survivors with chronic hemiparesis.[14] In that prior study, behavioral,demographic, and electrophysiological baseline variables correlated with changes in FMA and WMFT. Those correlations along with larger trends toward precision medicine in other practice areas contributed to the conceptualization of our predictive model of response. To be included participants must be 18 years or older with stroke onset $\geq$6 months, have mild or moderate to severe arm impairment (FMA score, 10-45), be free of serious medical complications, and be free of upper extremity botulinum toxin for $\geq$4 months prior to enrollment. All participants provided written informed consent, and the study was approved by the local institutional review board.

Treatment regimen

All eligible participants are assigned to the same repetitive task practice regimen consisting of 1-hour sessions with 45 minutes of robot-assisted therapy followed by 15 minutes of transition-to-task functional arm use activities (fig 1). This intervention is performed approximately 3 times per week for 12-18 weeks for a target maximum of 36 sessions. The training progression is sequential with the first 12 sessions focused on distal movements, followed by 12 sessions of proximal movements, and concluding with 12 sessions alternating between the 2. This progression is achieved using either a combination of the InMotion2 wrist robot and InMotion2 shoulder/elbow robot[a] or appropriate games on the ArmeoPower robot.[b]

One quarter of each intervention session is composed of transition-to-task training, which involves repetitive functional arm use in domains such as homemaking, hygiene, feeding, and dressing. This sequence is consistent with Brokaw et al who demonstrated distinct robot-mediated improvements and greater gains when robotic therapy preceded conventional.[35] These seated tabletop activities are selected by a therapist and performed under supervision to discourage compensatory movements and maximize use of available motor control.

Intent to treat and retention

Following an intent-to-treat paradigm, participants are encouraged to attend all evaluations even if they do not complete the full 36 intervention sessions in the allotted time. Number of sessions completed and reasons for withdrawal are documented.

Tests and procedures

Overview

Participants are evaluated at 5 time points during the study (fig 2): baseline, post 1 (after 12 sessions), post 2 (after 24 sessions), final (after 36 sessions or 18wk), and follow-up (3mo after final). Assessments can be grouped into 3 domains: basic and self-report, motor, and neurophysiological. Participants' baseline measures serve as potential inputs for prediction of the primary outcome: change in FMA score from baseline to final assessment.

Basic and self-report

At the outset of study participation, demographic data are collected, stroke history is confirmed via medical records,

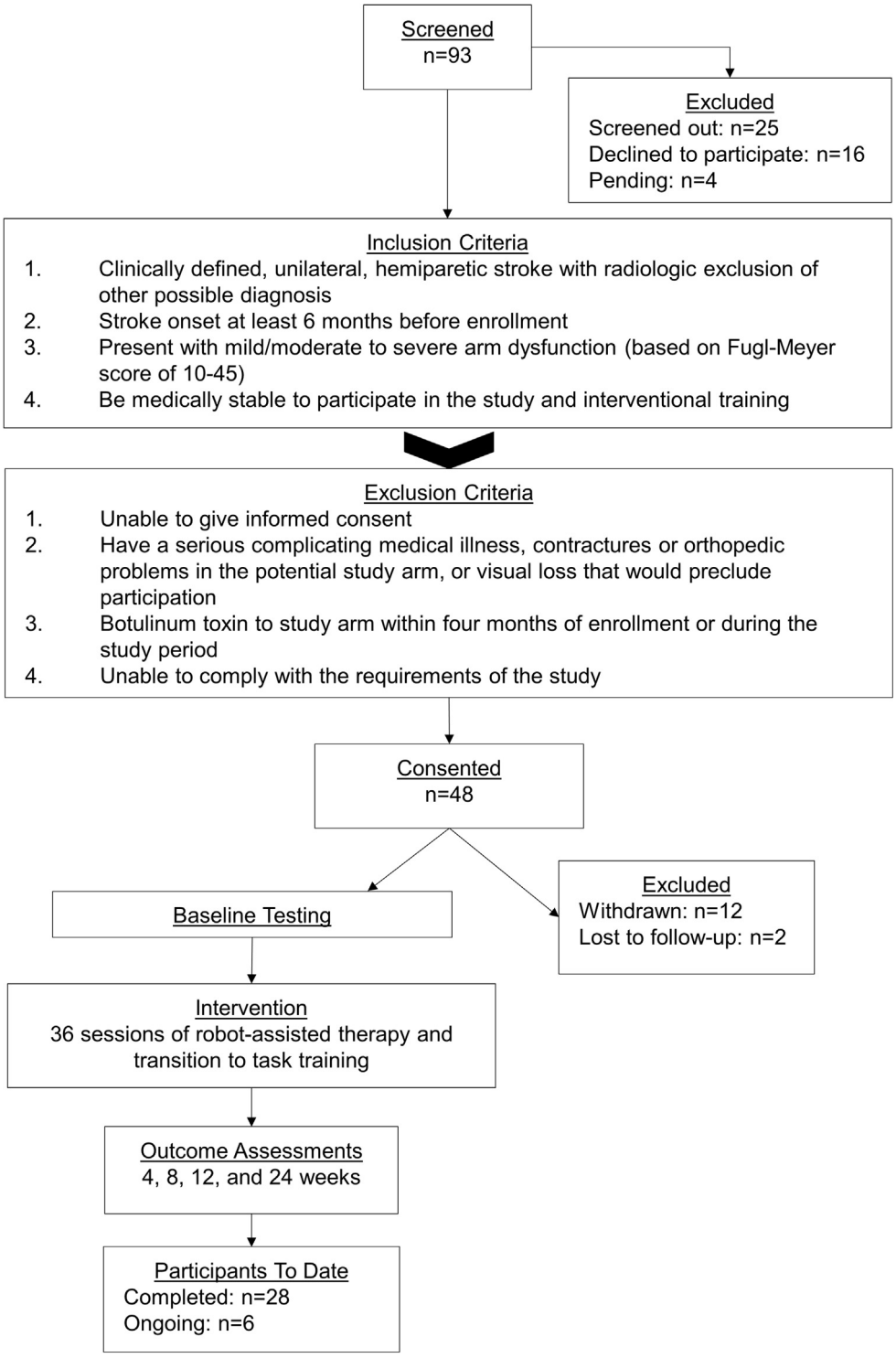

Fig 1 Study flow (Consolidated Standards of Reporting Trials diagram).

and a medical evaluation is completed by a neurologist. Self-reported questionnaires are administered during baseline testing. Specifically, the Stroke Impact Scale is a structured interview designed to assess physical, cognitive, and emotional changes contributing to poststroke quality of life. Higher scores indicate greater function and life satisfaction.[36] The Brief Pain Inventory[37] is collected to measure both pain severity and interference in activities. We measure expectancy using the brief 3-item Adapted Credibility/Expectancy Questionnaire.[38]

Motor

The upper extremity portion of the FMA[39] is a stroke-specific measure of impairment and is the primary

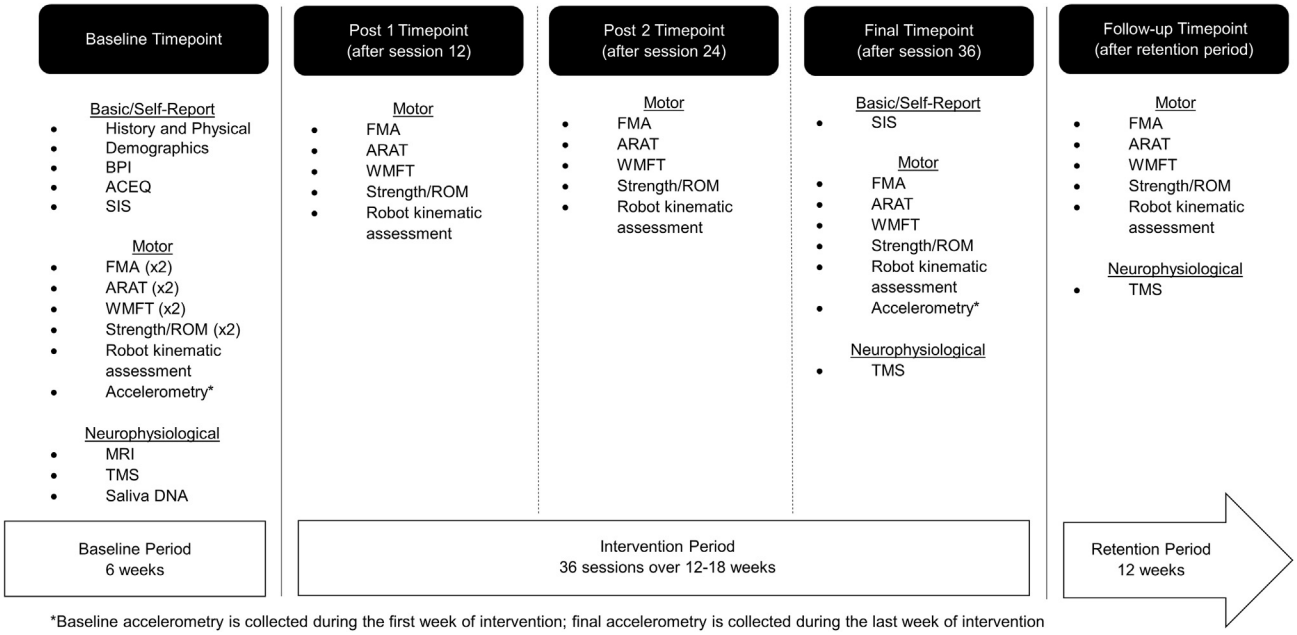

Fig 2 Tests and procedures. Abbreviations: ACEQ, Adapted Credibility/Expectancy Questionnaire; BPI, Brief Pain Inventory; ROM, range of motion; SIS, Stroke Impact Scale.

outcome variable for the planned predictive model. The assessment has demonstrated high interrater and test-retest reliability and construct validity.[40] It was chosen because of its responsiveness to change in moderately to severely impaired stroke survivors[40] and because its widespread use allows for comparison with other rehabilitation studies.

The Action Research Arm Test (ARAT)[41] evaluates grasp, grip, pinch, and gross movement of the upper extremity by observation during a set of graded functional or quasi-functional tasks. The 6-item WFMT was chosen for comparability with other rehabilitation studies and good sensitivity in the population with chronic stroke.[42] Additional upper extremity measures include active and passive range of motion measurements, manual muscle tests of shoulder abduction and finger extension,[6] and grip strength dynamometry.

Kinematic assessments are completed using the InMotion2 robot evaluation, described in the literature,[43] and involve unassisted reaching for a series of point-to-point targets, reaching against resistance, response to perturbation, and circle drawing. Variables assessed include initiation time, distance from target, movement time, peak velocity, mean velocity, number of targets hit, and path ratio. These assessments provide a quantitative characterization of motor function[44] and track with clinical arm assessments.[45]

Accelerometers are used to quantify duration and intensity of daily arm activity in stroke survivors and to measure the ratio of use of the affected vs unaffected arm.[46,47] At the beginning and end of the intervention period, participants wear 3-axis accelerometers[c] on both wrists with a nonremovable wrist band to record 3 full days of data.[48]

Neurophysiological

Magnetic resonance imaging (MRI) was obtained using a 3T Siemens Tim-Trio[d] scanner for the initial 13 participants and then upgraded to a 3T Siemens Prisma[d] for subsequent participants. The MRI protocol consists of the following: high-resolution anatomic imaging (ie, MPRAGE, FLAIR, T2) to identify regions affected by stroke and determine regions of brain activation in functional imaging protocols, arterial spin labeling scans (pseudocontinuous sequence) to account for vascularization differences across participants, resting state functional magnetic resonance imaging (two 10-min scans) to assess functional connectivity, and finally, diffusion tensor imaging to assess integrity of white matter tracts using fractional anisotropy analysis. These measures of structural integrity, functional connectivity, and neurophysiology will serve as potential variables in the predictive model.

TMS is performed using a MagStim 200 magnetic stimulator[e] to assess neurophysiological corticospinal integrity. Surface electromyography[f] is used to record muscle activity from 3 muscles (first dorsal interosseous, extensor carpi radialis [ECR], and anterior deltoid [AD]) for both paretic and nonparetic arms. Signal[g] scripts are used to drive single-pulse TMS and collect simultaneous electromyography data through a Power 1401 (CED) system. Neuronavigation software (Brainsight)[h] records 3-dimensional coordinates of each TMS stimulation site, measured using an optical digitizing device and matched to the individual's MRI, ensuring reproducible locations.

TMS at 100% maximum stimulator output is used to identify the hotspot for each muscle from a 3×3 grid centered on the hand knob for both paretic and nonparetic sides. At the identified hotspot for each muscle, if the mean MEP$>$0.05 mV, the resting motor threshold (RMT) is

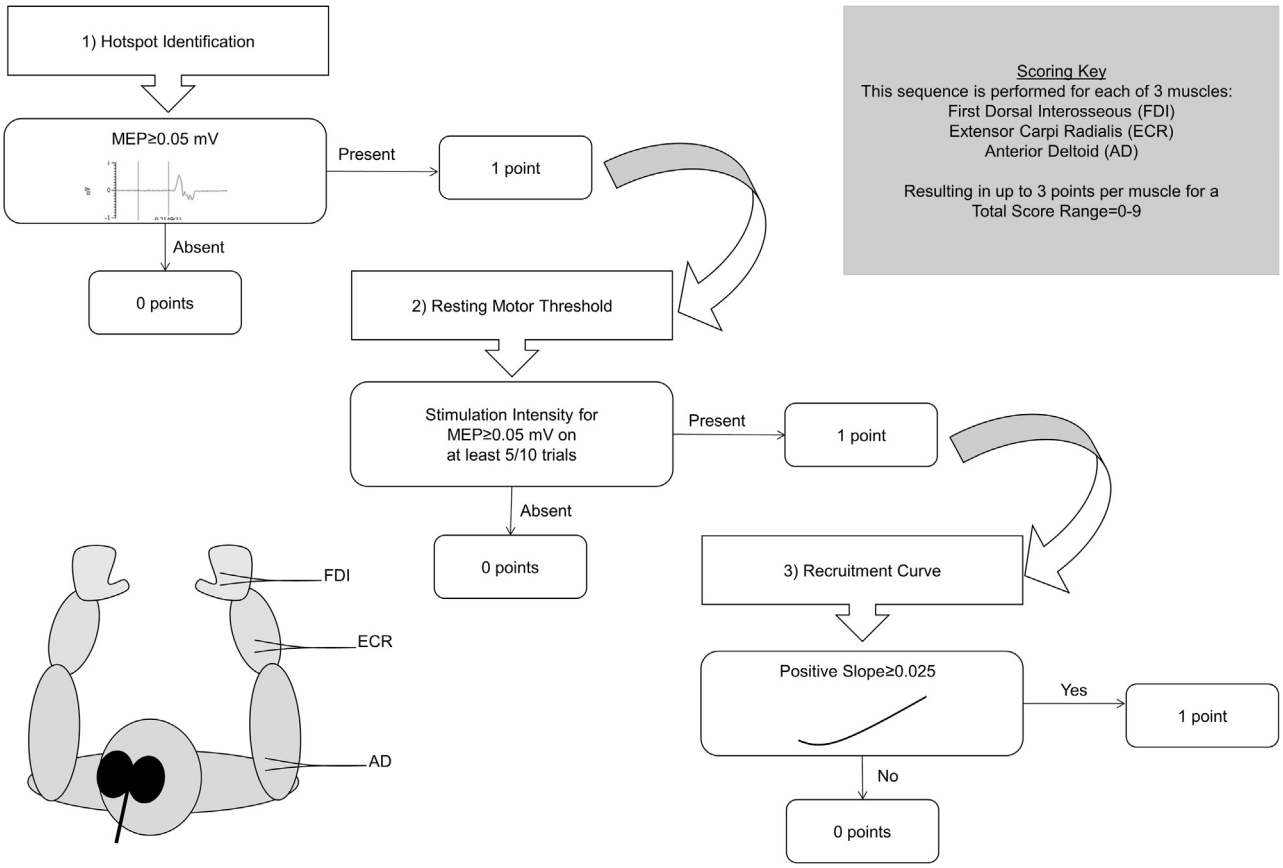

Fig 3 Neurophysiological corticospinal integrity score.

determined. The RMT is defined as the minimal amount of stimulation needed to evoke MEPs≥0.05 mV on at least 5 of 10 trials.[49] If an RMT could be identified, then a recruitment curve of corticospinal excitability is established[50]; the range of stimulation intensities is anatomically defined from the RMT of the muscle of interest to the RMT of the nearest muscle (ie, ECR for first dorsal interosseous, AD for ECR, ECR for AD). A recruitment curve is then collected from 3 trials at each of 8 stimulation intensities within this range. For each muscle, a score is calculated assigning 1 point each for presence of MEPs, establishment of an RMT, and presence of a recruitment curve with positive slope≥0.025. The slope value is derived based on the 95th percentile in a sample of healthy adults (M.A. Dimyan, unpublished data, 2019). Thus, scores for each muscle can range from 0-3, and total neurophysiological corticospinal integrity scores on each side can range from 0-9 (fig 3).

Genetic polymorphisms in 4 genes related to brain plasticity are analyzed by polymerase chain reaction and targeted sequencing for each participant. They are BDNF, COMT, dopamine transporter, and Klotho, which are related to growth, dopamine (COMT and dopamine transporter), and aging, respectively. A saliva collection kit (Oragene OGR-500)[i] is being used during baseline evaluations. An alternative pediatric collection kit (Oragene OC-175)[i] with sponge tips is used for participants who have difficulty providing a sample.

Data management

All data are collected according to written instructions for each study procedure. Evaluations are conducted by examiners trained and assessed for reliability. To establish interrater reliability, 3 examiners viewed videotapes of FMA, WMFT, and ARAT administration. All discrepancies were discussed and the written instructions clarified until agreement reached 100%. Completed assessment forms are stored under a study identifier, entered into our research database by a study staff member, and then verified with the source document by a second staff member to ensure accuracy.

Analytical plans

Prediction model

Logistic regression models will be developed on the primary binary outcome of increase in FMA score>4 points at final evaluation, which is considered the minimal clinically important difference.[51] A variety of techniques for model development are available based on final sample size and number of predictors selected. One traditional technique for variable selection is stepwise regression, which does not impose any penalty for including too many variables. Alternatively, ridge regression, least absolute shrinkage and selection operator (LASSO), and elastic net fall into a class

Table 1 Current enrollment demographics

Characteristic	(N=28)
Age, mean (range) (y)	62 (38-87)
Sex, n female (%)	9 (32.1)
Race, n (%)	
African American/black	16 (57.1)
White	12 (42.9)
Oxfordshire classification, n (%)	
Not applicable, primary hemorrhage	4 (14.3)
Lacunar	11 (39.3)
Partial anterior circulation	8 (28.6)
Total anterior circulation	2 (7.1)
Posterior circulation	3 (10.7)
Time since stroke, mean (range) (mo)	63.7 (9-264.3)
Handedness-affected upper extremity, n (%)	
Right-right	11 (39.3)
Right-left	12 (42.9)
Left-left	4 (14.3)
Ambidextrous-right	1 (3.6)
Baseline Outcome Measures, mean ± SD	
Fugl-Meyer Upper Extremity Score	20.1±10.0
Wolf Motor Function Test (s)	84.7±40.8
Action Research Arm Test	15.4±15
Stroke Impact Scale-Hand Subscale	22.9±30.3

of regularization methods developed to improve variable selection with a penalty imposed for overfitting. Ridge regression imposes a penalty on the absolute size of the regression coefficients. LASSO regularization in logistic regression penalizes the absolute size of the regression coefficients such that some are shrunk to 0.[52] Elastic net regularization, which penalizes both the absolute size and the squared regression coefficients, incorporates both ridge regression and LASSO. Elastic nets work well even for highly correlated predictors.[53,54] We will develop several prediction models: (1) demographic variables only, (2) 1 plus measures of motor ability, (3) 2 plus neurophysiological data, and (4) 3 plus genomics data. The summary statistics of the area under the receiver operating characteristic curve (AUROC) will be used to measure prediction performance. Sensitivity and specificity, positive predictive value, and negative predictive value[55] will be calculated from the optimal threshold determined by Youden index.[55]

The prediction models will be cross-validated by training and testing methodology.[56] To investigate if additional data will improve prediction performance, comparison of AUROCs between prediction models will be tested by the DeLong method.[55] The significance of the comparison will indicate whether a prediction model with additional data adds value and improves predictive power.

Sample size and current enrollment

Projected sample size was calculated based on estimating the AUROC with adequate precision.[57] We anticipate enrollment of 96 individuals with 12% attrition resulting in a final sample of 85. At the time of writing, we have enrolled 48 participants, 28 of whom have completed the study through the final evaluation time point (table 1). While we are not undertaking a preliminary analysis of a predictive model, we present 2 participants (table 2) who illustrate the variability in response to repetitive task practice among individuals with similar arm impairment at baseline.

Discussion

In summary, we are undertaking a single-arm trial of robot-assisted repetitive task practice to reduce upper extremity motor impairment in patients with chronic stroke. The goal of the trial is to discover baseline factors that predict clinically meaningful improvement. Potential predictors include measures of motor impairment, demographics, pain, expectancy, and neurophysiology, including response to TMS, neuroimaging, and plasticity-related gene polymorphisms.

For survivors of stroke, particularly those with residual hemiparesis, there is beginning recognition of the importance of rehabilitation not simply for a discrete time period after the event but rather, as a lifelong practice. We now know that not only maintenance of function but actual motor recovery is possible long after the initial insult.[58] Yet, answering the questions of how much and for whom remains a challenge, particularly at the individual level. Participants A and B, presented in table 2, exemplify the difficulty clinicians face when setting expectations with patients. On clinical assessment, these participants appear nearly identical and have matched scores on the FMA and WMFT. Participant B is younger, his stroke is more recent, and he scores better on the Stroke Impact Scale Hand subscale; Participant A scores a few points higher on the ARAT, but he is a decade older and more than 20 years have passed since his stroke. We seek to better understand why participant A responds to repetitive task practice while participant B does not.

Study limitations

Pursuit of prognostic accuracy in neurorehabilitation is fraught with challenges: limited reproducibility of many

Table 2 Participant comparison

Participant	Participants			Baseline Measures*				Outcomes	
	Demographics	Stroke Type	Time Since	FMA	WMFT (time, score)	ARAR	SIS Hand	Final FMA	FMAΔ
A	78-y/o man	Lacunar	264 mo	19	103.7s, 1.17	12	40	30	11
B	66-y/o man	Lacunar	63 mo	18.5	103.98s, 1.17	5.5	80	18	−0.5

Abbreviations: SIS, Stroke Impact Scale; y/o, year-old.

* Range of possible scores: FMA (0-66), WMFT (up to 120s, 0-6), ARAT (0-57), SIS Hand (0-100); for all assessments higher score indicates improved limb use with the exception of WFMT time.

therapeutic interventions, how to measure improvement, and the necessary scale of this type of clinical trial. To meet the challenge of reproducibility, this study has used a form of repetitive task practice that can be recreated not only on multiple robotic systems but also via intensive nonrobotic training. The VA ROBOTICS study demonstrated no difference in average outcome between robotic rehabilitation and a closely matched nonrobotic system of practice,[10] and there is little reason to believe that predictive factors would vary widely depending on the specific methodology. In measuring improvement, each outcome tool imposes its own limitations. The widespread use of the FMA and its position along the continuum between precision of measurement and functional relevance made it the most reasonable starting point for prediction. Future directions may explore the use of alternative measures. Large-scale neurorehabilitation studies are exigent but achievable, as demonstrated by the successful completion of trials such as EXCITE and SCILT, but should not be undertaken without a firm conceptual basis.[59] Prior work in chronic-phase rehabilitation, neuroimaging and neurophysiology, motor recovery algorithms, and genetics of plasticity provided the necessary foundation to take this next step toward precision medicine in neurorehabilitation for chronic stroke. Future work should address some limitations discussed here as well as validation of the model developed, particularly novel components such as the scoring system for neurophysiological corticospinal integrity. In summary, the goal of this trial is to identify baseline biomarkers that predict clinically meaningful reduction in arm impairment in response to a standardized therapy and to demonstrate the feasibility of developing a subsequent predictive model.

Suppliers

a. InMotion2; Bionik Labs.
b. ArmeoPower; Hocoma AG.
c. Accelerometer; ActiGraph, LLC.
d. 3T Siemens Tim-Trio; 3T Siemens Prisma; Siemens Medical Solutions USA, Inc.
e. MagStim 200; MagStim Ltd.
f. Surface electromyograph; B&L Engineering.
g. Signal; Cambridge Electronic Design Ltd.
h. Brainsight; Rogue Research Inc.
i. Oragene OGR-500; Oragene OC-175; DNAGenotek.

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