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1-2015

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Recommended Citation

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Neural function, injury, and stroke subtype predict treatment gains after stroke

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Abstract

Objective—To better understand the high variability in response seen when treating human subjects with restorative therapies post-stroke. Preclinical studies suggest that neural function, neural injury, and clinical status each influence treatment gains, therefore the current study hypothesized that a multivariate approach incorporating these three measures would have the greatest predictive value.

Methods—Patients 3-6 months post-stroke underwent a battery of assessments before receiving 3-weeks of standardized upper extremity robotic therapy. Candidate predictors included measures of brain injury (including to gray and white matter), neural function (cortical function and cortical connectivity), and clinical status (demographics/medical history, cognitive/mood, and impairment).

Results—Among all 29 patients, predictors of treatment gains identified measures of brain injury (smaller corticospinal tract (CST) injury), cortical function (greater ipsilesional motor cortex (M1) activation), and cortical connectivity (greater inter-hemispheric M1-M1 connectivity). Multivariate modeling found that best prediction was achieved using both CST injury and M1-M1 connectivity (r^2=0.44, p=0.002), a result confirmed using Lasso regression. A threshold was defined whereby no subject with >63% CST injury achieved clinically significant gains. Results differed according to stroke subtype: gains in patients with lacunar stroke were exclusively predicted by a measure of intra-hemispheric connectivity.

Interpretation—Response to a restorative therapy after stroke is best predicted by a model that includes measures of both neural injury and function. Neuroimaging measures were the best predictors and may have an ascendant role in clinical decision-making for post-stroke

rehabilitation, which remains largely reliant on behavioral assessments. Results differed across stroke subtypes, suggesting utility of lesion-specific strategies.

Keywords

chronic stroke; restorative therapy; rehabilitation; neuroimaging; predictors

Introduction

Stroke is a very heterogeneous disease, with substantial variability between patients in response to treatment. This extends to clinical trials, where higher inter-subject variance means reduced study power and increased cost[1]. This issue has undergone considerable discussion in relation to acute stroke trials, where CT and MRI measures are under study to improve prediction of individual patient responses to reperfusion therapy[2, 3]. A similar challenge exists in the setting of restorative therapies, as the best approach to predicting treatment response remains undetermined[4].

Efforts to identify predictors of response to a restorative treatment in humans are informed by preclinical studies[5]. Behavioral gains in animals given a restorative therapy after experimental stroke has been linked to growth-related events in the brain that include axonal outgrowth, increased dendritic branching, and release of growth factors[6-8]. Predictors of these behavioral gains fall into three categories of measurement: (1) neural injury such as infarct topography[9, 10] and infarct volume[9-11]; (2) neural function such as motor cortex integrity[12, 13]; and (3) clinical status, such as baseline behavioral assessments[13], age[8, 14, 15] and vascular risk factors[8].

Results of human studies have been largely concordant, with predictors of response to a restorative therapy post-stroke generally grouped as measures of: (1) neural injury such as extent of injury to white matter or gray matter[16-20]; (2) neural function such as functional activation[21-24], functional connectivity[25, 26], and neurophysiological status[19, 22]; and (3) clinical measures such as demographics[27] and baseline behavioral status[16, 23, 28, 29]. Some data in humans suggest that genetic variation, particularly in the genes for brain-derived neurotrophic factor (BDNF) and apolipoprotein E (ApoE), might also be related to variance in response to a restorative therapy, as polymorphisms for each have been associated with poorer post-stroke outcome and reductions in some forms of cortical plasticity[30-32]. In addition, stroke subtype is important to many aspects of clinical decision-making for patients with cerebrovascular disease[33, 34] and has been suggested as important to recovery potential and improvements with restorative therapies in the chronic phase of stroke,[35] but this issue has received limited attention.

The number and diversity of these predictive measures reflects the complexity of neural repair after stroke. Optimal prediction of response to a restorative therapy may therefore likely require a multivariate approach that incorporates several types of measure[36, 37]. However, only a few human studies have taken this approach[16, 20, 22, 23, 38], and none has taken a multivariate approach that included measures of neural injury, functional activation, functional connectivity, genetics, and clinical/demographic measures in a heterogeneous stroke population.

The current study addressed these issues, with the primary hypothesis being that pre-therapy measures of neural injury, neural function, and clinical status together would best predict response to a restorative therapy, and would surpass the performance of any single measure. An additional hypothesis was that the best predictors of treatment gains differ according to stroke subtype, focusing on lacunar vs. non-lacunar stroke given substantial differences in their pathophysiology and outcomes[39-45].

Materials and methods

Patient enrollment

Forty-one patients with chronic stroke gave informed consent to be part of a longitudinal study of standardized robotic-assisted hand therapy (clinicaltrials.gov ID# NCT01244243) that was approved by the UC Irvine Institutional Review Board. Inclusion and exclusion criteria (Table 1) aimed to capture a population at a specific time point in stroke recovery (close to the time when spontaneous motor recovery is complete [46, 47]), with confirmed plateau in arm motor recovery, and within a wide but prescribed range of motor deficits. In one patient, baseline MRI revealed an incidental finding that met exclusion criteria, rendering the patient ineligible for the study. The forty eligible patients were studied as below.

Baseline assessments (Table 2) of candidate predictors were obtained, after which patients underwent a course of robotic therapy; all patients received robotic therapy, there was no comparison or placebo arm. These baseline assessments were organized into seven categories: 1) *demographics/medical history*; 2) *cognitive/mo*od; 3) *genetics*; 4) *impairment*; 5) *brain injury*; 6) *cortical function; and* 7) *cortical connectivity*.

Robotic therapy

Patients underwent twelve treatment sessions of robotic hand therapy over three weeks: 2 hours/day, 4 days/week for a total of 24 hours. All patients completed at least eleven of twelve robotic therapy sessions. Therapy consisted of repeated grasp-release ('close' and 'open') movements of the affected hand, with grasp coupled to wrist extension and release to wrist flexion, using a pneumatically-actuated robotic device described previously[48]. The average number of movement repetitions at each of the 12 sessions, recorded by the robot, was 954 for the fingers, 2,579 for the thumb, and 1,298 for the wrist; the thumb is greatest because some games required movement of four fingers and thumb only while other games required movement of wrist and thumb only.

Demographics/history

Medical history was obtained and acute stroke hospitalization records reviewed.

Cognitive/mood

included the Mini Mental State Exam and Geriatric Depression Scale.

Impairment

A single rater performed all behavioral assessments. Patients were assessed before, and one-month, after a three-week course of standardized robotic hand therapy. Baseline Fugl-Meyer (FM) and Action Research Arm Test (ARAT) assessments were performed twice before beginning therapy (once at baseline screening and again 1-3 weeks later) to ensure stability of motor status (e.g., the second FM score was required to be within 3 points of the first score), and averaged for each patient.

Genetics

A blood sample was obtained, and BDNF val[66]met polymorphism plus ApoE4 allele status were determined as described previously [31].

Brain injury

Image acquisition—Magnetic resonance imaging was performed at the second baseline visit and acquired using a 3.0T Philips Achieva system. Anatomical imaging consisted of a high-resolution T1-weighted image, T2-FLAIR, and diffusion tensor imaging (DTI). High-resolution T1-weighted images were acquired using a 3D MPRAGE sequence (repetition time (TR)=8.5 ms, echo time (TE)=3.9 ms, slices=150, voxel size=$1 \times 1 \times 1$ mm^3). T2-FLAIR (TR=11000 ms, TE=125 ms, slices=31 slices, voxel size=$.58 \times .58 \times 5$ mm^3) and intracranial MR angiogram (TR=23 ms, TE=3.45 ms, slices=100, voxels size=$.31 \times .31 \times .7$ mm^3) images were also acquired. One set of diffusion-weighted images was acquired (32 directions; b-value 1000 smm^{-2}; 60 slices; voxel size=$1.75 \times 1.75 \times 2$ mm^3).

Image analysis—Image analysis was performed blinded to clinical data. Three classes of brain injury metrics were extracted: (1) total brain injury (infarct volume); (2) gray matter injury (to primary motor cortex (M1), dorsal premotor cortex (PMd), plus total cortical injury); and (3) white matter injury (percent lesion overlap with corticospinal tract (CST), or CST integrity within ipsilesional cerebral peduncle using DTI fractional anisotropy (FA) values).

Infarct volume—Using MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron), each patient's infarct was outlined by hand on the T1-weighted MRI image, informed by the T2-FLAIR image as described previously[38].

Gray matter injury—To determine how injury to specific regions of gray matter is related to treatment-induced behavioral gains, the degree of overlap between cortical regions of interest (ROI) and each infarct was calculated. Using FSL, the whole-brain cortical ROI was generated via FAST segmentation of the 1mm^3 T1 template. Precentral gyrus (M1) and PMd gray matter ROIs were manually drawn on this template. These ROI masks and the stroke masks were then multiplied to generate an overlap image in MNI space. The number of infarct voxels overlapping with each of the three ROIs was counted and expressed as cc. Injury was recorded as both a continuous and a dichotomous variable.

White matter injury—White matter integrity within the CST was quantified using FSL to probe FA within the CST at the level of the cerebral peduncle (CP) as described previously[38].

Corticospinal tract injury was also evaluated as the amount of overlap in MNI stereotaxic space between the normal corticospinal tract descending from M1[18, 49], generated as described previously[38], and each patient's infarct. This method has been shown to perform comparably to calculating lesion overlap using tracts generated from patients' brains[50].

Cortical function

Image Acquisition—Three runs of blood oxygenation level-dependent fMRI images were acquired using a T2*-weighted gradient-echo echo planar imaging sequence, as described previously[38]. Subjects were visually guided to use the paretic distal upper extremity to execute the grasp-release movements that were at the center of robotic training, while wearing a splint that was a non-actuated plastic exoskeleton identical to the robotic interface. Prior to MRI data acquisition, patients were trained until each could independently perform this task. Throughout the fMRI scan, investigators visually monitored patient movements.

Image Analysis—Two measures of brain function were extracted from fMRI images: (1) activation beta (contrast) estimate and (2) activation volume, each measured in four ROIs, right and left M1 plus right and left PMd. Functional data were processed as described previously[38].

Cortical connectivity

Functional connectivity was assessed as the temporal correlation using an ROI-ROI approach. After the fMRI data were preprocessed in SPM8, intra- and inter-hemispheric functional connectivity metrics were calculated using the Conn toolbox[51]. Time courses were filtered between 0.008 and 0.13 to minimize low-frequency drift and high-frequency noise. Within-subject realignment parameters, outliers, and main session effects were included as first-level covariates. The three connections evaluated for functional connectivity were ipsilesional M1-ipsilesional PMd (iM1-iPMd), ipsilesional M1-contralesional M1 (iM1-cM1), and ipsilesional M1-contralesional PMd (iM1-cPMd). Fisher-transformed correlation coefficients were extracted for each connection in each patient.

Patient characteristics

Data from twenty-nine patients were available for analysis (Table 2). Of the forty patients enrolled, four could not complete MRI due to claustrophobia and seven patients were excluded due to excessive head motion during fMRI scanning. These twenty-nine patients did not differ significantly from the excluded eleven patients in age or baseline FM (p>0.1). The stroke was ischemic in 27 and hemorrhagic in two.

Demographics/medical history—Mean time post-stroke was 4.3 months and mean age was 56.5 years. All but two were right-handed.

Cognitive/mood—Overall, patients were neither cognitively impaired nor clinically depressed.

Genetics—The genotypic frequencies for the BDNF val[66]met polymorphism and the ApoE4 allele were in Hardy-Weinberg equilibrium, and these polymorphisms were present in 28% and 14% of patients, respectively.

Impairment—Overall, patients had mild global impairment and moderate-severe upper extremity motor impairment. Preserved voluntary movement (5 degrees of active range of motion) was present in the affected index finger metacarpophalangeal joint in 28/29, and in affected wrist in 25/29 patients.

Brain injury—Infarct volumes were moderate overall (average=33cc, range=0.6cc-178cc). The stroke affected left hemisphere in 55% of patients; dominant hemisphere, in 48%. Approximately one-third of patients had injury to PMd cortex and half had injury to M1 cortex; among these patients, extent of infarct overlap was greater with M1 than PMd. Extent of CST injury determined by lesion overlap showed substantial variability across patients ($55\pm33\%$, range 0-100%). Similar results were obtained when determining extent of CST injury using DTI, with mean FA in the affected cerebral peduncle being 0.38 ± 0.12, significantly (p<0.0001) lower than unaffected cerebral peduncle values (0.55 ± 0.1), indicating reduced integrity within the ipsilesional CST.

Cortical function—Patients varied in the quality of performance of the requested unilateral paretic hand grasp/release movement during the active blocks of fMRI scan acquisition, with full range of motion present in 38%, partial movement in 51%, and no visible movement (due to weakness) in 11%. In addition, 24% of patients had at least one associated movement[52] in the non-affected hand, the presence of which was associated with greater contralesional M1 activation (contrast estimate, p=0.009; activation volume, p=0.03) but not with differences in any other fMRI activation/connectivity measure, nor with a difference in treatment gains (p=0.99).

This task was associated with prominent bilateral activation within M1 and PMd. Activation contrast estimates within ipsilesional M1 were larger than within contralesional M1 (p=0.0002). Activation volumes were larger within ipsilesional M1 as compared to contralesional M1 (p=0.005), ipsilesional PMd (p=0.002), and contralesional PMd (p=0.03).

Magnetic resonance angiogram, available in twenty-three patients, disclosed significant ipsilesional internal carotid artery or middle cerebral artery disease in 26% of patients; none of the fMRI activation parameters differed significantly according to presence vs. absence of these cerebrovascular observations.

Cortical connectivity—During unilateral grasp/release of the paretic hand, functional connectivity was present in all three ipsilesional M1 connections (iM1-iPMd, iM1-cM1, iM1-cPMd). Functional connectivity was significantly greater in iM1-iPMd as compared to iM1-cM1 (p=0.04) and iM1-cPMd (p=0.003). There was no significant difference between iM1-cM1 and iM1-cPMd connectivity (p=0.60). Note that correlation coefficients were not

significantly related to any measure of *cortical function*, with the sole exception being iM1-cPMd functional connectivity and ipsilesional M1 activation volume (p=0.005), and correlation coefficients were not significantly different in relation to stroke subtype.

Statistical analyses

Predictors of treatment-induced behavioral gains - bivariate screening—

Bivariate screening was performed to identify the strongest predictors of treatment-induced behavioral gains. The primary outcome measure was change in arm motor status from baseline to one month post-therapy, defined by combining change measures in impairment (change in upper extremity FM) and in functional activity (change in ARAT) via principal component analysis (PCA)[53]; only the first component was used to define treatment-induced motor gains, as this accounted for 84% of variance in these two behavioral outcomes.

Bivariate screening determined the significance of the relationship between each baseline measure and the dependent measure (treatment-induced motor gains). Parametric statistical methods were used for measures for which the normality assumption was valid, using raw or transformed values; otherwise non-parametric methods were used. Continuous variables were evaluated using Pearson's correlation coefficient or Spearman's rank order, while categorical variables were evaluated using Student's t-test or the Wilcoxon signed-rank test. All analyses were two-tailed with alpha=0.05 and used JMP-8 software (SAS Institute, Inc., Cary, NC). For each of the seven categories, results of this bivariate screening determined whether any baseline measure survived as a predictor of treatment gains and would be advanced to multivariate modeling.

Predictors of treatment-induced behavioral gains - multivariate modeling—The

primary predictive model used a forward stepwise multivariate linear regression approach (0.1 to enter, 0.15 to leave the model), advancing the most significant predictors identified in bivariate screening. The strongest bivariate predictor within each of the seven categories was advanced as long as bivariate screening showed p<0.1. If a category had more than one variable with p<0.1 during bivariate screening, only the variable with the strongest correlation coefficient was advanced into the stepwise forward model. In order to understand whether results vary according to stroke subtype, the above analyses were repeated separately for the 8 patients with a lacunar infarct (defined as an infarct that is subcortical and has infarct volume <4cc[54]) and for the 21 patients with a non-lacunar infarct.

Predictors of treatment-induced behavioral gains - group Lasso regression

method—To confirm findings from multivariate modeling, a secondary approach to predictive modeling used a penalized regression approach. Numerous variables have been reported to influence stroke outcomes[55-59]. The statistical question is therefore high-dimensional, suggesting the utility of a secondary approach that used a penalized regression, or regularization,[60] method for predictive modeling, which (a) makes conclusions based on joint consideration of all variables simultaneously, and (b) reduces overfitting, which can be associated with models that perform well on one dataset but do not generalize well to new datasets). Lasso (least absolute shrinkage and selection operator[61]) was chosen as the penalized regression model because it selects a subset of useful predictors from a total pool

of candidate predictors and, unlike linear regression, minimizes the influence of outliers. Specifically, a group Lasso model was used, which is similar to the standard Lasso regression but takes the grouping of variables (i.e., categories) into account[62]. The Lasso procedure requires a tuning parameter, lambda, which was chosen in a standard way through (five-fold) cross-validation. Numerical variables were standardized before running the Lasso model.

Results

Treatment-induced behavioral gains

Patients showed significant gains across the 3 weeks of robotic therapy, with improvements from baseline to 1 month post-therapy in both primary endpoints (FM: 3.7 points, p<0.0001; ARAT: 4.1 points, p=0.002).

Prediction of treatment-induced behavioral gains -- all patients

Bivariate screening—When each of the variables from the seven categories was examined in bivariate screening, four categories (*demographics*, *impairment*, *genetics*, and *cognitive/mood*) had no variables significantly predicting gains, while three categories (*brain injury*, *cortical function*, and *cortical connectivity*; Table 3) had at least one variable that significantly predicted treatment-induced behavioral gains. The most significant bivariate predictor of gains from each of these three, respectively, was percent CST injury determined by lesion overlap (Figure 1A: r=-0.49, p=0.007), ipsilesional M1 activation contrast estimate (r=0.37, p=0.045), and iM1-cM1 functional connectivity (Figure 1B: r=0.45, p=0.01). Excluding the two subjects with hemorrhagic stroke had no effect on results. Excluding patients with 50% damage to cortical ROIs[63] had no effect on connectivity findings.

For one of these three measures (*brain injury*: percent CST injury), a threshold was identified for achieving the minimal clinically important difference (MCID) for treatment-induced motor gains in the setting of chronic stroke (4.25 points on the FM scale[64]): 63% injury to the CST. None of the 12 patients with 63% CST injury achieved the MCID. Note that most (65%) subjects with <63% CST injury did achieve the MCID, and that no MCID threshold was found for *cortical function* or *cortical connectivity*.

Multivariate modeling—To generate a predictive model, the three variables that best correlated with change in behavior based on bivariate screening were entered into multivariate analyses. The resultant model predicted 44% of variance in treatment-induced behavioral gains (p=0.002; Table 4); a measure of *brain injury* (percent CST injury) and a measure of *cortical connectivity* (iM1-cM1 functional connectivity) remained significant in this model.

Lasso regression method—To independently verify the results from bivariate screening, Lasso regression was applied to the same 29 patients' data. This analysis identified the same two categories--*brain injury* and *cortical connectivity*--as having variables significantly predictive of treatment-induced behavioral gains. In the *brain injury*

category, the selected variables were percent injury to the CST and cortical injury (yes/no). In the *cortical connectivity* category, the selected variable was the iM1-cM1 functional connectivity correlation coefficient. Estimated Lasso coefficients appear in Figure 2.

Prediction of treatment-induced behavioral gains -- stroke subtype

In order to understand how differences in stroke pathophysiology influence prediction of treatment-induced behavioral gains, the above analyses were repeated examining only the subgroup of patients with a lacunar infarct (n=8). Baseline measures in this subgroup were overall similar to those found in the subgroup of 21 patients with a non-lacunar infarct (Table 2), except that patients with lacunar infarct had higher prevalence of hypercholesterolemia (p=0.03), less severe sensory deficits (p=0.001), and less severe injury by several measures such as percent CST injury by lesion overlap (p=0.04). Patients with a lacunar infarct had a greater treatment response compared to patients with a non-lacunar infarct (5.8±3.2 vs. 2.8±3.4 for FM, p=0.02; 8.8±7.0 vs. 2.3±5.1 for ARAT, p=0.02).

Bivariate screening in patients with a lacunar infarct found significant predictors of treatment-induced behavioral gains in only two categories: *cortical function* (ipsilesional M1 activation contrast estimate (r=0.79, p=0.02, Figure 3A) and ipsilesional M1 activation volume (r=0.76, p=0.03)) and *cortical connectivity* (iM1-iPMd correlation coefficient (r=0.81, p=0.02, Figure 3B)). Because of significant collinearity between the ipsilesional M1 contrast estimate and the iM1-iPMd correlation coefficient, a multivariate model was not pursued for the lacunar subgroup. These findings contrast with results of bivariate screening in the subgroup of 21 patients with a non-lacunar infarct, among whom the significant predictors of motor gains were the same as in the full cohort of 29 subjects: percent CST injury (r=-0.51, p=0.02) and iM1-cM1 functional connectivity (r=0.56, p=0.009).

Discussion

Stroke is a very heterogeneous disease, with patients showing wide differences in measures of injury, neural function, and response to therapy. These sources of variability complicate prescription of restorative therapies, as the best predictor(s) of response to a post-stroke restorative therapy remains uncertain. Concordant with preclinical studies, the results of the current study suggest that neural injury and neural function remain important in human subjects: multivariate modeling found that a measure of *brain injury* (smaller extent of CST injury) combined with a measure of *cortical connectivity* (greater iM1-cM1 functional connectivity) best predicted greater treatment-induced behavioral gains, a result independently confirmed by the group Lasso regression model. These variables outperformed traditional predictors of stroke outcome such as age or infarct volume. Different results emerged when examining only patients with a lacunar infarct. Overall, these findings emphasize the importance of a multivariate approach to patient selection and stratification for restorative therapies after stroke.

Prediction of treatment-induced behavioral gains -- all patients

The current study found that a combination of *brain injury* and *cortical connectivity* measures was best for predicting treatment gains. These findings broadly agree with a prior

study that also found combining measures of neural injury (CST FA) and neural function (motor evoked potential) to be optimal for predicting upper extremity treatment gains in patients with chronic stroke[16], and agree with preclinical studies that emphasize neural injury and neural function as key determinants of training-induced behavioral gains after stroke[13, 15]. This combined approach explained far more variance in outcome (44%, Table 4) than that provided by any single measure (up to 24%, Table 3). Clinical measures were also hypothesized to be significant predictors, but none reached significance (Tables 3, Figure 2). That neuroimaging measures were the best predictors takes on increased significance in light of the fact that triage and distribution of post-stroke rehabilitative care is still primarily based on behavioral assessments[65].

Among the measures of neural injury, extent of CST injury measured with the lesion overlap method best predicted treatment-induced motor gains, consistent with prior studies using the current method[18, 19] or using related methods[49, 66] for estimating CST injury. The current study also confirmed a prior report[18] that whenever a therapy targets a specific neural system (e.g., the motor system), an injury measure focused on that specific neural system (CST injury) is more precise than a global injury measure (e.g., infarct volume) for predicting treatment gains (Table 3). The presence of cortical injury was also an important predictor of treatment gains (Table 3) and furthermore was identified as significant by the Lasso regression method. This is consistent with previous studies that found significant differences in treatment response[67] and neurophysiological integrity[19] according to whether or not the stroke involved the cerebral cortex. Together, the results highlight the importance of measuring both white and gray matter injury, and of considering system-specific injury measures.

A novel finding was an injury threshold for achieving the minimal clinically important difference (MCID) in arm gains from robotic therapy. In 0 of the 12 patients with >63% injury did treatment gains reach the MCID (>4.25 points on the arm motor FM scale)[64]. This suggests that a certain amount of the CST must be intact for a patient to derive clinically significant benefit from upper extremity therapy, similar to what has been proposed for walking after CST injury[68] or for control of hand movements after cortical stroke[69]. This threshold echoes similar findings by Stinear et al[70], who found that meaningful gains from a motor intervention were not possible with CST FA asymmetry >0.25. Identification of such threshold values may be useful for stratifying individuals to an intervention in a clinical trial setting[71].

Among the measures of neural function, iM1-cM1 functional connectivity best predicted therapy-induced gains, a result also confirmed by the Lasso regression method. The current finding that greater baseline iM1-cM1 functional connectivity predicted larger treatment gains agrees with one[26] but not a second[25] prior study, perhaps due to differences in the population studied or the connectivity technique used. Overall this finding is concordant with cross-sectional studies that have found greater inter-hemispheric connectivity to be correlated with smaller motor deficits after stroke in humans[72, 73] and an animal stroke model[74]. The exact manner by which iM1-cM1 functional connectivity is related to treatment gains in the current cohort is uncertain and could reflect changes in motor cortex activity[53, 75, 76], contralesional hemisphere excitability[77], ipsilesional hemisphere

excitability[78-80], or inter-hemispheric inhibition[81-83]. The results underscore the potential value of connectivity measures for understanding behavioral state after stroke[84], and support prior reports[85-87] that connectivity may have advantages over regional assessments of brain function for some questions.

Prediction of treatment-induced behavioral gains -- stroke subtype

Results supported the secondary hypothesis that the best measures for predicting treatment-induced behavioral gains vary according to stroke subtype (lacunar vs. non-lacunar). Patients with a lacunar stroke tend to differ in multiple ways from patients with a non-lacunar stroke, including risk factor profile[39, 88], lesion volume[54], and clinical prognosis[89, 90 39-45]. The current results extend this list, suggesting that patients with lacunar stroke might also differ in terms of measures predicting response to a restorative therapy. The strongest predictors of treatment-induced behavioral gains among patients in the lacunar subgroup were measures of *cortical function* and intra-hemispheric *cortical connectivity*, specifically greater M1 activation and greater iM1-iPMd functional connectivity. This contrasts with findings among patients in the non-lacunar subgroup, where measures of *brain injury* and inter-hemispheric *cortical connectivity* best predicted treatment gains. The importance of *cortical function* to treatment gains after lacunar infarct is consistent with prior results[91, 92]. The basis for the observed difference between stroke subtypes is uncertain but may be related to cortical excitability, as affected arm movements increase motor cortex excitability after subcortical but not cortical stroke [93], or to lesion-specific differences in patterns of post-stroke brain plasticity[91, 93].

Study considerations and limitations

Strengths of the current study include examination of multiple classes of candidate predictor variables in parallel, attention to stroke subtype, and confirmation of results using independent statistical methods. The heterogeneity of the current cohort is both a strength and a limitation. There is a balance between studying a narrowly defined population of stroke survivors, where statistical power is high due to low variance but results do not generalize, versus a broadly defined population, among whom heterogeneity limits statistical power but results are more likely to generalize. Enrollment in the current study (Table 1) prioritized time post-stroke (had to be early after the time when spontaneous arm motor recovery reaches a plateau after stroke[46, 47]) and severity of stroke (a wide range of motor deficits was allowed albeit minor nor devastating). Studies that enroll in relation to different priorities or that focus on different therapies might reach different findings regarding predictors of treatment gains.

Weaknesses of the study include the possibility that results of genetic analyses may suffer from Type II error. Although studies with comparable sample sizes have found significant predictive value for these genotypes with respect to motor learning[94-97], the current study may have been insufficiently powered to detect an association between genotype and treatment-induced behavioral gains in the setting of stroke. The multivariate predictive model explained only 44% of the variance in treatment-induced behavioral gains; the predictive value of this model in other study populations would likely vary depending on the degree of homogeneity of such cohorts. What might account for the remaining variance? A

number of candidate measures might be considered, across a range of biopsychosocial factors important to stroke outcomes, including socioeconomic factors[98], stress level[99], other genes[100], caregiver status[101], neurophysiological status[37], and other cognitive/psychological tests[102].

The current findings indicate that across all patients a multivariate approach combining measures of neural injury and neural function best predicts behavioral gains from a standardized course of therapy in patients who have recently reached a plateau in spontaneous recovery. The approach to predicting treatment-induced behavioral gains varies in relation to stroke subtype. The findings also emphasize that neuroimaging methods may have a role in clinical decision-making for rehabilitation therapy after stroke is currently driven by clinical assessments[65].

Acknowledgments

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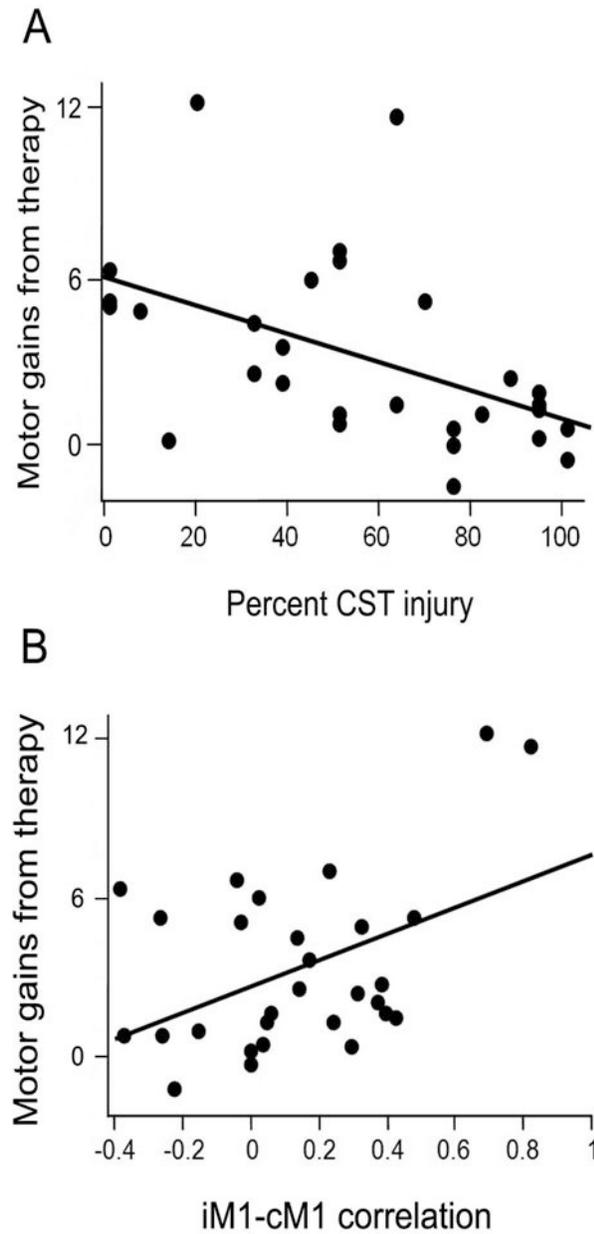
Figure 1.
Across all subjects, (A) Smaller percent injury to M1 corticospinal tract (r=-0.49, p=0.007) and (B) greater ipsilesional M1-contralesional M1 functional connectivity (r=0.45, p=0.01) each significantly predicted larger treatment-induced behavioral gains. Behavioral gains were assessed as the principal component of the change in FM and ARAT scores from baseline to one-month post-therapy. To aid interpretation, the change in FM score is included on the Y-axis.
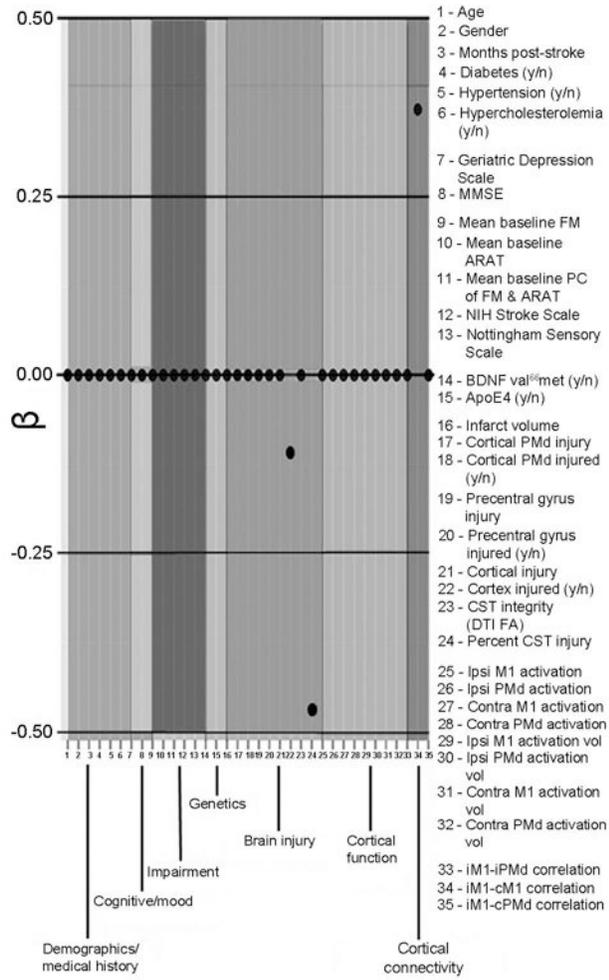
Figure 2.
Regression coefficients determined using the group Lasso regression method. Variables identified as important for treatment-induced behavioral gains came from the cortical connectivity, cortical function, and brain injury categories.
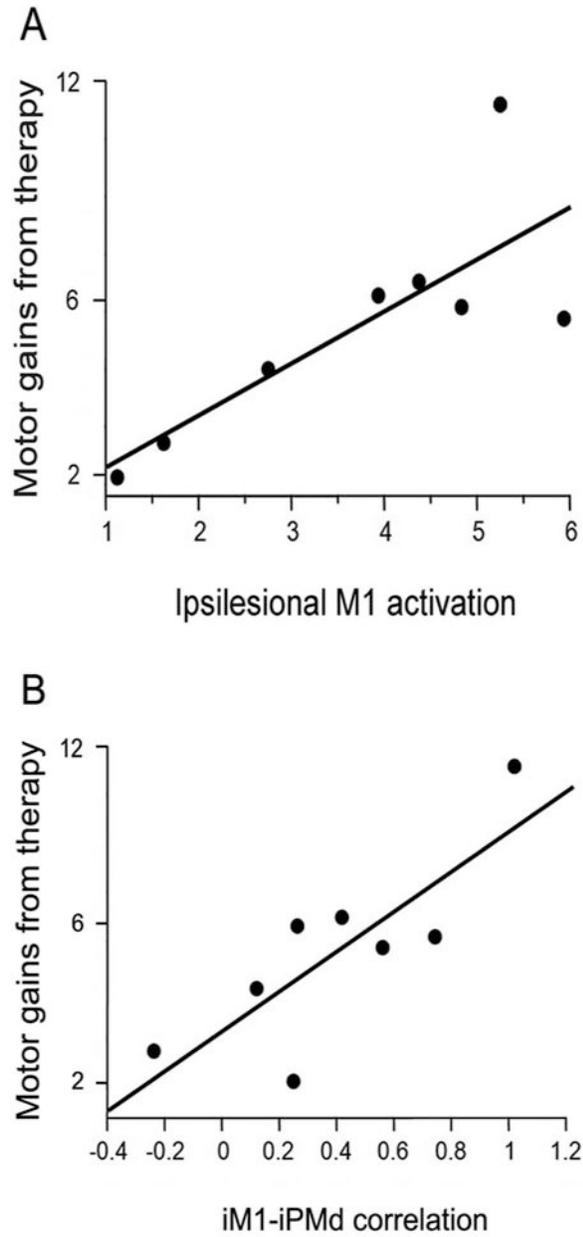
Figure 3.
In the subgroup of patients with a lacunar infarct, greater (A) ipsilesional M1 activation (r=0.79, p=0.02) and (B) ipsilesional M1-ipsilesional PMd functional connectivity (r=0.81, p=0.02) each significantly predicted larger treatment-induced behavioral gains. Behavioral gains were assessed as the principal component of the change in FM and ARAT scores from baseline to one-month post-therapy. To aid interpretation, the change in FM score is included on the Y-axis.

Table 1

Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Age 18 years	Contraindication to MRI
Stroke with onset 11-26 weeks prior	Severe cognitive impairment
Residual arm motor deficit (ARAT<52 or 9-hole peg test score > 25% longer than with unaffected hand	Concurrent diagnosis affecting arm/hand function
	Arm motor status not at stable plateau
Preserved voluntary movements in distal upper extremity (5 degrees of active range of motion in affected wrist or index finger metacarpophalangeal joint	

Table 2

Baseline measures.

	All patients	Non-lacunar	Lacunar
Number	29	21	8
Demographics/medical history			
Age (years)	56.5 (13.9)	55.3 (13.9)	55.3 (5.4)
Time post-stroke (months)	4.3 (1.0)	4.2 (1.0)	4.5 (0.9)
Gender	8 F/ 21 M	7 F/ 14 M	1 F/ 7 M
Diabetes mellitus	8 Y/ 21 N	6 Y/ 15 N	2 Y/ 6 N
Hypertension	14 Y/ 15 N	8 Y/ 13 N	6 Y/ 2 N
Hypercholesterolemia	12 Y/ 17 N	6 Y/ 15 N	6 Y/ 2 N
Cognitive/mood			
Mini Mental State Exam (normal = 30)	27.5 [25-30]	28 [25-30]	27 [25.25-29.75]
Geriatric Depression Scale (normal = 0)	3.0 [1.5-4.5]	2 [0.5-4]	3 [2-6.75]
Impairment			
NIH Stroke Scale (normal = 0)	4.2 (1.8)	4.4 (1.7)	3.5 (1.9)
Fugl-Meyer Scale (normal = 66)	36.3 (14.8)	35.7 (16.1)	37.7 (11.7)
Action Research Arm Test (normal = 57)	26.2 (18.8)	25.7 (20.2)	27.5 (15.9)
Nottingham Sensory Assessment (normal = 17)	13.5 (4.3)	12.2 (4.4)	16.9 (0.4)
Genetics			
BDNF val[66]met polymorphism present	8 Y/ 21 N	5 Y/ 16 N	3 Y/ 5 N
ApoE4 allele present	4 Y/ 25 N	2 Y/ 19N	2 Y/ 6 N
Brain injury			
Infarct volume (cc)	32.6 (48.4)	44.6 (52.3)	1.2 (0.6)
Precentral gyrus injury?	14 Y/ 15 N	14 Y/ 7 N	0 Y/ 8 N
Precentral gyrus injury (cc)	0.61 (1.1)	0.85 (1.2)	0
Cortical PMd injury?	10 Y/ 19 N	10 Y/ 11 N	0 Y/ 8 N
Cortical PMd injury (cc)	0.25 (0.52)	0.34 (0.58)	0
Cortical injury?	21 Y/ 8 N	21 Y/ 0 N	0 Y/ 8 N
Total cortical injury (cc)	19.8 (33.6)	27.3 (69.9)	0
Corticospinal tract integrity (DTI FA)	0.39 (0.12)	0.39 (0.13)	0.36 (0.08)
Percent injury to CST	54.5 (32.6)	61.2 (34.2)	35.2 (18.0)
Cortical function			
Ipsilesional M1 activation - contrast estimate	2.9 (1.9)	2.6 (1.9)	3.7 (1.7)
Ipsilesional PMd activation - contrast estimate	2.0 (1.3)	1.8 (1.5)	2.3 (1.0)
Contralesional M1 activation - contrast estimate	1.7 (1.3)	1.6 (1.3)	1.9 (1.2)
Contralesional PMd activation - contrast estimate	2.2 (1.7)	2.2 (1.7)	2.3 (1.7)
Ipsilesional M1 activation volume (voxels)	67 (42)	64 (44)	72 (38)
Ipsilesional PMd activation volume (voxels)	43 (46)	40 (46)	49 (47)
Contralesional M1 activation volume (voxels)	39 (41)	38 (42)	42 (42)
Contralesional PMd activation volume (voxels)	49 (42)	45 (44)	45 (41)
Cortical connectivity			

	All patients	Non-lacunar	Lacunar
iM1-iPMd correlation coefficient	0.31 (0.32)	0.28 (0.30)	0.38 (0.38)
iM1-cM1 correlation coefficient	0.13 (0.30)	0.14 (0.30)	0.13 (0.31)
iM1-cPMd correlation coefficient	0.10 (0.21)	0.11 (0.19)	0.07 (0.26)

Table 3

Bivariate correlations between baseline measures and arm motor gains with therapy--all patients.

Baseline variable	Correlation with treatment-induced motor gains	
	r	p
Demographics/medical history		
Age	0.07	0.72
Time post-stroke	0.06	0.76
Gender (M/F)	0.03	0.80
Diabetes mellitus (y/n)	-0.04	0.71
Hypertension (y/n)	0.04	0.86
Hypercholesterolemia (y/n)	0.09	0.60
Cognitive/mood		
Mini Mental State Exam	-0.13	0.50
Geriatric Depression Scale	0.11	0.58
Impairment		
NIH Stroke Scale	-0.26	0.17
Mean baseline Fugl-Meyer	-0.05	0.79
Mean baseline Action Research Arm Test	0.04	0.82
Nottingham Sensory Assessment	0.25	0.20
Genetics		
BDNF val[66]met polymorphism present (y/n)	0.19	0.35
ApoE4 allele present (y/n)	0.19	0.43
Brain injury		
Infarct volume (cc)	-0.42	**0.02**[*]
Precentral gyrus injury (y/n)	-0.15	0.54
Precentral gyrus injury (cc)	-0.18	0.36
Cortical PMd injury (y/n)	-0.28	0.07
Cortical PMd injury (cc)	-0.36	0.06
Cortical injury (y/n)	-0.46	**0.008**[*]
Total cortical injury (cc)	-0.41	**0.03**[*]
Corticospinal tract integrity (DTI FA)	0.18	0.34
Percent injury to CST	-0.49	**0.007**[**]
Cortical function		
Ipsilesional M1 activation - contrast estimate	0.37	**0.045**[*]
Ipsilesional PMd activation - contrast estimate	0.36	0.05
Contralesional M1 activation - contrast estimate	0.28	0.14
Contralesional PMd activation - contrast estimate	-0.01	0.95
Ipsilesional M1 activation volume	0.16	0.40
Ipsilesional PMd activation volume	0.02	0.92

Baseline variable	Correlation with treatment-induced motor gains	
	r	p
Contralesional M1 activation volume	-0.01	0.94
Contralesional PMd activation volume	-0.10	0.60
Cortical connectivity		
Ipsilesional M1-Ipsilesional PMd connectivity	0.11	0.58
Ipsilesional M1-Contralesional M1 connectivity	0.45	**0.01**[*]
Ipsilesional M1-Contralesional PMd connectivity	0.13	0.50

[*] For normally distributed variables, r is the Pearson correlation coefficient. For variables that are not normally distributed, r is Spearman's rho. For dichotomous variables, X^2 is presented. The change in motor behavior was assessed as the principal component of change in FM and ARAT scores from baseline to one-month post-therapy.

Table 4

Multivariate predictor model--all patients.

Variable	Estimate	Standard Error	95% CI	P
Intercept	0.269	0.890	--	0.765
Ipsilesional M1 activation - contrast estimate	0.276	0.161	-0.05 to 0.61	0.10
iM1-cM1 connectivity	2.57	1.005	0.49 to 4.64	0.017*
Percent injury to CST	-0.020	0.010	-0.40 to -0.0001	0.049*