Neuroimaging Identifies Patients Most Likely to Respond to a Restorative Stroke Therapy

Jessica M. Cassidy, DPT, PhD; George Tran, BS; Erin B. Quinlan, PhD; Steven C. Cramer, MD

Background and Purpose—Patient heterogeneity reduces statistical power in clinical trials of restorative therapies. Valid predictors of treatment responsiveness are needed, and several have been studied with a focus on corticospinal tract (CST) injury. We studied performance of 4 such measures for predicting behavioral gains in response to motor training therapy.

Methods—Patients with subacute-chronic hemiparetic stroke (n=47) received standardized arm motor therapy, and change in arm Fugl-Meyer score was calculated from baseline to 1 month post-therapy. Injury measures calculated from baseline magnetic resonance imaging included (1) percent CST overlap with stroke, (2) CST-related atrophy (cerebral peduncle area), (3) CST integrity (fractional anisotropy) in the cerebral peduncle, and (4) CST integrity in the posterior limb of internal capsule.

Results—Percent CST overlap with stroke, CST-related atrophy, and CST integrity did not correlate with one another, indicating that these 3 measures captured independent features of CST injury. Percent injury to CST significantly predicted treatment-related behavioral gains (r=–0.41; P=0.004). The other CST injury measures did not, neither did total infarct volume nor baseline behavioral deficits. When directly comparing patients with mild versus severe injury using the percent CST injury measure, the odds ratio was 15.0 (95% confidence interval, 1.54–147; P<0.005) for deriving clinically important treatment-related gains.

Conclusions—Percent CST injury is useful for predicting motor gains in response to therapy in the setting of subacute-chronic stroke. This measure can be used as an entry criterion or a stratifying variable in restorative stroke trials to increase statistical power, reduce sample size, and reduce the cost of such trials. **(*Stroke*. 2018;49:433-438. DOI: 10.1161/STROKEAHA.117.018844.)**

Key Words: clinical trial ■ humans ■ pyramidal tracts ■ rehabilitation ■ stroke

Acute perfusion therapies introduced in the initial hours poststroke can improve patient outcomes, but there is substantial variability in patient response. Recent endovascular therapy trials addressed this by using imaging to exclude patients with large ischemic cores.[1] Currently, a limited fraction of patients arrives at the hospital in time to receive such interventions, largely because of the narrow time window. Restorative therapies may be able to improve clinical outcomes after stroke with a wider time window, measured in days–months. However, variability in patient responses is also a confounding factor in postacute stroke trials that evaluate restorative therapies. Therefore, studies have examined biomarkers of stroke-related injury in an attempt to improve patient selection for trials of restorative therapies.

Many restorative therapy trials have targeted motor deficits, which are among the most common after stroke[2] and which contribute substantially to poststroke disability. The neuroanatomy of the human motor system has characteristics favorable for biomarker development because its main white matter efferent—the corticospinal tract (CST)—runs in a single bundle relatively accessible to injury assessment.[3] Biomarkers have the potential to inform restorative trials in several ways, such as patient selection or stratification,[4,5] beyond what is provided by clinical measures.[6]

Several biomarkers of CST injury after stroke have been described. The current study compared 4 of these (1) cerebral peduncle area, which reflects Wallerian degeneration[7,8]; (2) percent CST overlap with stroke, which reflects the quantity of CST injured[9–13]; (3) cerebral peduncle[14,15]; and (4) posterior limb of internal capsule (PLIC)[16–18] fractional anisotropy (FA)—a diffusion tensor imaging measure that reflects the integrity or quality of CST white matter. The primary objective was to compare these CST injury measurements in patients with subacute-chronic stroke for their ability to predict response to a restorative therapy.

Methods

This study examined data from patients with hemispheric subacute-chronic stroke who participated in 1 of 2 clinical trials involving 3 to 4 weeks of a standardized therapy targeting arm movements. Details of the therapy are provided elsewhere.[11,19] Entry criteria included

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From the Department of Neurology (J.M.C., S.C.C.), Department of Anatomy and Neurobiology (G.T., E.B.Q., S.C.C.), and Department of Physical Medicine and Rehabilitation (S.C.C.), University of California, Irvine.

Correspondence to Jessica M. Cassidy, DPT, PhD, Department of Neurology, University of California, Irvine, Room 1331, Hewitt Hall, 843 Health Sciences Rd, Irvine, CA 92697. E-mail jcassid1@uci.edu

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radiologically confirmed stroke (ischemic or intracerebral hemorrhage), 2 to 24 months poststroke, age ≥18 years, and residual arm motor deficit defined either as an Action Research Arm Test score <52 (of 57) or affected arm completion time on the 9-Hole Peg Test ≥25% longer than with the unaffected arm. Exclusion criteria included contraindication to magnetic resonance imaging, Mini-Mental State Examination <24 (of 30), and a nonstroke diagnosis affecting arm function. Patients also had to have stable arm impairment at baseline before therapy, such that serial testing on the arm motor Fugl-Meyer scale (FM)[20] spaced 1 to 3 weeks apart could not differ by >3 points. The University of California Irvine Institutional Review Board approved both studies. All patients provided written informed consent. The data that support the findings of this study are available from the corresponding author on reasonable request.

Behavioral Assessment

Patients completed an assessment battery before treatment that included the Geriatric Depression Scale and National Institutes of Health Stroke scale. Treatment-induced gains in motor impairment were defined as the change in arm FM score from the mean of the 2 baseline scores to 1 month post-treatment.

Magnetic Resonance Imaging Acquisition

Before therapy, patients underwent a magnetic resonance imaging scan involving high-resolution T1-weighted imaging, T2 fluid-attenuated inversion recovery imaging, and diffusion tensor imaging. Scans were performed on a 3-Tesla Philips Achieva system (Best, the Netherlands). Investigators used a 3-dimensional magnetization-prepared rapid gradient echo sequence (repetition time, 8.5 ms; echo time, 3.9 ms; 150 slices; voxel size, 1×1×1 mm^3) to acquire structural T1-weighted images. Parameters for the remaining neuroimaging sequences were as follows: T2 fluid-attenuated inversion recovery (repetition time, 11 000 ms; echo time, 125 ms; 31 slices; voxel size, 0.58×0.58×5 mm^3) and diffusion tensor imaging (32 directions; b=1000 sec/mm^2; 60 slices; voxel size, 1.75×1.75×2 mm^3).

Image Analysis

Analysis of neuroimaging data was performed blinded to all clinical data. Six injury measures were extracted:

Percent Injury to CST

A CST template was constructed from diffusion tensor tractography from 17 healthy, right-handed individuals as described previously.[10–12] Briefly, seeds were placed in the left or the right precentral gyrus and cerebral peduncle. Each binarized and Montreal Neurological Institute–transformed tract was partitioned into 16 descending subsections. The binarized infarct mask was overlaid onto the CST template. The CST subsections were classified as injured if at least 5%[10] of the section overlapped with the infarct. Rather than computing the volume of overlap between each lesion and the CST, frequently referenced in the literature as the CST lesion load, we computed a percent injury to CST value by summing the total number of injured sections, dividing this value by 16 and multiplying by 100. Percent injury to CST, as compared with CST lesion load, has a stronger correlation with behavioral state,[10] possibly because dividing the CST into longitudinal subsections more closely models the trajectory of axon bundles and their injury by stroke.

Cerebral Peduncle Area

For each patient's T1-weighted image transformed to Montreal Neurological Institute space, the axial slice depicting the greatest cerebral peduncle cross-sectional area was identified. Image roll and pitch were corrected using MRIcron[21] to ensure that the ipsilesional and contralesional cerebral peduncles were in the same axial plane. Cerebral peduncle masks were drawn on these T1-weighted images with masks remaining ventral to and avoiding the substantia nigra. The number of voxels contained in each mask was determined to generate area measurements. The cerebral peduncle area was defined as the ratio of ipsilesional to contralesional cerebral peduncle area, with values <1 indicating ipsilesional peduncle atrophy.

CST Integrity in PLIC and in Cerebral Peduncle

Diffusion tensor images were corrected for eddy currents and head motion with a 3-dimensional affine registration using the FMRIB Software Library.[22] A diffusion tensor model was fit at each voxel using FMRIB's DTIFIT module, and a map of FA values was generated. FA values range from 0 to 1, with higher values suggestive of a greater degree of directionality of water diffusion and structural integrity.[23] Ipsilesional and contralesional masks of the cerebral peduncle[24] and PLIC were drawn on the T1-weighted image coregistered to the FA image. PLIC masks were drawn on 3 contiguous slices located midway between the appearance and disappearance of the lenticular nucleus and thalamus. Borders of the PLIC masks were the following: anterior=genu of the internal capsule, posterior=line from posterior putamen to thalamus, medial=thalamus, and lateral=globus pallidus. Ipsilesional and contralesional PLIC masks were drawn on the same slices. In cases of stroke-related damage, the ipsilesional PLIC was drawn to mirror the location and size of contralesional PLIC. Mean FA values were computed from the voxels within the masks. CST integrity was defined as the ratio of ipsilesional to contralesional FA, separately for peduncle and PLIC. Among the 47 patients studied, none sustained injury to the cerebral peduncle, whereas 23 had injury to the PLIC.

Infarct Volume

To calculate infarct volume, MRIcron[21] was used to manually outline each patient's infarct on the T1-weighted magnetic resonance imaging image, informed by the T2–fluid-attenuated inversion recovery image, as described previously.[24] Infarct masks were binarized and spatially transformed into Montreal Neurological Institute standard stereotaxic space.

Primary Motor Cortex Injury

As described previously,[11] a mask of primary motor cortex gray matter (M1) was defined on a 1-mm^3 T1 template, using the FMRIB Software Library. The number of voxels overlapping between this M1 mask and each infarct in Montreal Neurological Institute space was calculated and used to measure stroke-related injury to M1.

Statistical Analysis

All statistical analyses were performed with JMP software (version 13.1; SAS, Cary, NC). Parametric statistical methods were used for measures that were normally distributed or could be transformed to a normal distribution; otherwise, nonparametric methods were used. Correlation coefficients were calculated to assess the relationship that cerebral peduncle area, CST integrity in cerebral peduncle, CST integrity in PLIC, and percent injury to CST had with baseline FM scores, and an adjusted α value of 0.0125 was used to define significance. This was repeated using treatment-related gains (change in FM score from baseline to 1 month post-therapy) as the dependent variable. The same procedures were used to evaluate specificity of these injury measures.

Results

Patients

A total of 47 patients were studied. Deficits were stable at baseline because serial FM scores differed by only 0.3 points (P>0.20). Clinical and neuroimaging characteristics appear in Table 1. Patients were at a mean of 5.5 months poststroke, had wide-ranging arm motor deficits that ranged from mild to severe, had mean infarct volume 30.5 cc, and averaged 50.8% injury to CST.

Characteristics of the 4 CST Injury Measures

CST overlap with stroke, CST atrophy, and CST integrity did not correlate with one another, indicating that these 3 measures captured independent features of CST injury. CST peduncle

Table 1. Patient Clinical and Neuroimaging Characteristics

Measurement	Value	Range
Age, y	57.4±14.6	21 to 86
Time poststroke, mo	5.5±2.5	2.5 to 18.4
NIHSS score (normal=0)	4.0 [3–5]	0 to 11
GDS (normal=0)	3 [2–4]	0 to 10
MMSE (normal=30)	28 [25–30]	21 to 30
Baseline FM (normal=66)*	35.8±14.1	13.5 to 60
FM change, baseline to 1 mo post-treatment	4.1±3.5	−1.5 to 12
Infarct volume, cc	30.5±44.8	0.4 to 178
Peduncle area	0.9±0.1	0.6 to 1.1
CST peduncle integrity	0.70±0.20	0.26 to 1.15
CST PLIC integrity	0.75±0.16	0.33 to 0.95
Percent injury to CST	50.8±34.2	0 to 100

Values presented as mean±SD or median [interquartile range]. The population had mild-to-severe deficits, with the lowest quartile of Fugl-Meyer scores ranging from 13.5–23 and the highest quartile from 47.5–60. CST indicates corticospinal tract; FM, arm Fugl-Meyer; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; NIHSS, National Institutes of Health Stroke scale; and PLIC, posterior limb of internal capsule.

*Baseline FM was the mean of 2 FM scores taken at 2 separate visits prior to therapy.

integrity was unrelated to percent injury to CST (r=–0.23; P=0.12) or to peduncle area (r=–0.03; P=0.87), CST PLIC integrity was unrelated to percent injury to CST (r=–0.26; P=0.08) or to peduncle area (r=–0.01; P=0.94), and percent injury to CST was unrelated to peduncle area (r=–0.08; P=0.60). As expected, CST PLIC and peduncle integrity were related (r=0.68; P<0.0001). Three measures, CST peduncle integrity (r=0.55; P<0.0001), PLIC integrity (r=0.41; P=0.004), and percent injury to CST (r=–0.36; P=0.01), but not cerebral peduncle area (r=0.17; P=0.24), correlated significantly with motor status in subacute-chronic stroke, that is, baseline FM score as measured at study entry. Findings with CST peduncle and PLIC integrity and percent injury to CST were specific to motor status because these measures did not correlate with cognitive function (Mini-Mental State Examination, P>0.44) or depression (Geriatric Depression Scale, P>0.14).

Percent Injury to CST Predicts Treatment-Related Gains

From baseline to 1 month post-treatment, patients improved an average of 4.1±3.5 points on the FM scale. When the 4 measures of CST injury were examined as predictors of these treatment-related gains, only 1 was significant, percent injury to CST (r=–0.41; P=0.004; Figure 1; Table 2). Total infarct volume was not a significant predictor of treatment-related gains in arm motor status (r=–0.28; P=0.06) and neither was baseline FM score (r=0.19; P=0.21). When M1 was injured by stroke (n=23), percent injury to CST showed stronger predictive power for treatment-related arm motor gains (r=–0.44; P=0.034), and when M1 was not affected by stroke (n=24),

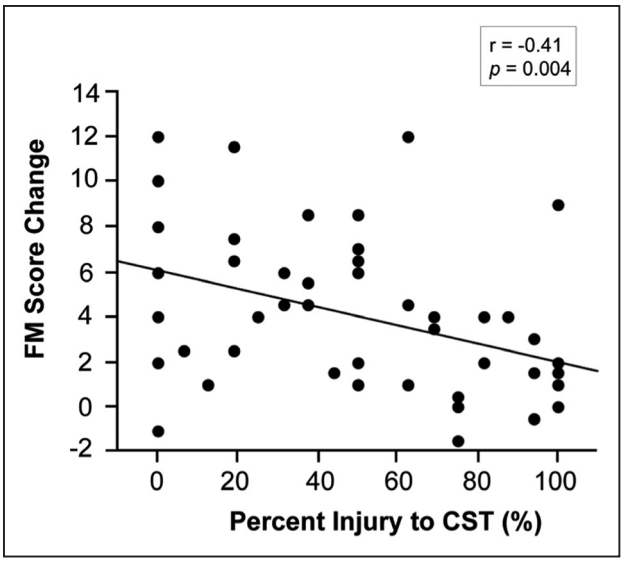

Figure 1. Greater percent injury to corticospinal tract (CST) significantly predicted poorer treatment-induced gains in arm motor status (n=47). FM indicates arm Fugl-Meyer.

percent injury to CST was no longer a significant predictor (r=–0.14; P=0.52). Adding measurements of CST peduncle integrity (P=0.62) or PLIC integrity (P=0.73) to percent injury to CST did not significantly improve prediction of treatment-related gains.

The significance of the predictive value of this measure can be further examined by contrasting 2 patient subgroups that differ according to severity of percent injury to CST. In the current population, there were 14 patients with mild injury to the CST injury (infarct injured ≤25% of the CST). Their average treatment-related gain in FM score was 5.5±4.0 points, and gains exceeded the minimal clinically important difference (MCID) of 4.25 points[25,26] in 50% of patients. There were 16 patients with severe injury to the CST (infarct injured ≥75% of the CST). Their average treatment-related gain in FM score was 1.8±2.5 points, and gains exceeded the MCID in 6.3% of patients. When directly comparing patients with mild versus severe CST injury, the odds ratio for deriving treatment-related gains exceeding the MCID was 15.0 (95% confidence interval, 1.54–147; P<0.005). These findings persisted when using a more restrictive MCID definition of 6.0 points, that is, 10% of the total arm FM scale[27] (odds ratio, 11.2; 95% confidence interval, 1.15–110; P=0.014). Figure 2

Table 2. Neuroimaging Predictors of Treatment-Related Gains

	Correlation With Treatment-Related Gains	
Injury Measure	r	P Value
Percent injury to CST	−0.41	0.004
CST peduncle integrity	0.13	0.38
CST PLIC integrity	0.14	0.34
Peduncle area	0.20	0.18
Infarct volume	−0.28	0.06

CST indicates corticospinal tract; and PLIC, posterior limb of internal capsule.

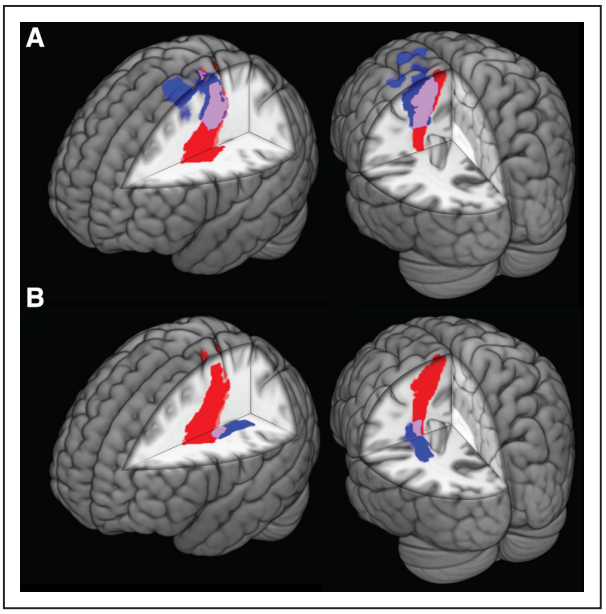

Figure 2. Percent corticospinal tract (CST) injury in 2 representative patients. Lesions are denoted in blue, the CST in red, and CST injury by the lesion in purple. **A**, Severe CST injury: 2 views of patient 1, who had lesion volume of 7.0 cc and 93.7% CST injury. **B**, Mild CST injury: 2 views of patient 2, who had lesion volume of 10.3 cc but only 18.7% CST injury. Despite similar lesion volumes, patient 1 sustained greater percent injury to CST and had lower treatment-related gains in arm Fugl-Meyer score (1.5 points) as compared with patient 2 (7.5 points).

illustrates cases of mild and severe CST injury. These findings did not persist, however, when stratifying using a behavioral measure (FM score) instead of percent injury to CST: comparing the 16 most impaired patients (baseline FM, 20.2±4.7; treatment-related gain, 2.9±3.1 points) to the 14 least impaired patients (baseline FM, 53.2±4.7; treatment-related FM gain, 3.1±2.9 points), the odds ratio for obtaining treatment-related gains exceeding an MCID of 4.25 points was 0.42 (95% confidence interval, 0.08–2.19; P=0.30).

Discussion

In a diverse population of patients with hemiparesis in the subacute-chronic phase poststroke, 3 types of CST injury measures capturing both quantity and quality of CST injury, that is, percent injury, atrophy, and integrity, were examined and found to be independent of each other. The main finding of the current analysis is that percent injury to CST was the only measure to significantly predict treatment-related gains. When directly comparing patients with mild versus severe CST injury using the percent injury to CST measure, the odds ratio was 15.0 for deriving a treatment-related gain that exceeded the MCID. Just as recent successful endovascular therapy trials used imaging to exclude patients with large ischemic cores,[1] current findings suggest that restorative trials may similarly choose to use imaging to exclude patients with severe CST injury to maximize the likelihood of detecting a treatment effect.

The percent injury to the CST caused by stroke predicted treatment-related gains in arm motor status (Figure 1). This confirms the predictive value of the same measure as described in 2 prior, independent populations where the interventions were either robotic training[10] or brain stimulation[12] and emphasizes the superior performance of percent CST injury relative to CST integrity and peduncle area in terms of predictive value in the subacute-chronic population (Table 2). Percent injury to the CST describes the fraction of descending CST fibers critically injured by stroke.[10] Abundant evidence indicates that therapies that improve motor status in the chronic stroke state generally do so by promoting plasticity in the cortex and other brain structures, and that the CST is a critical efferent pathway by which these changes are expressed.[28–30] Current findings suggest that treatment-induced changes in brain function are most likely to produce behavioral gains when CST injury is limited and that percent CST injury is a bigger factor than total infarct volume for predicting treatment response in this population. The findings further indicate that this dependence on CST is greater when M1 sustains stroke-related injury. The fact that the odds ratio is 15.0 for achieving treatment-induced arm motor gains that exceed the MCID when comparing mild versus severe percent CST injury suggests that percent injury to CST may have utility as an entry criterion in clinical trials of restorative therapies in subacute-chronic stroke because this measure enables study design to identify those patients who have a higher likelihood of achieving clinically important gains. Baseline behavior did not provide this predictive power, although most restorative trials in chronic stroke currently rely on behavioral criteria for study entry.

None of the other measures of CST injury studied (peduncle integrity, PLIC integrity, or peduncle area) was a significant predictor of treatment-related arm motor gains. This might, in part, reflect the white matter bundles assessed by each measure. The CST template used in computing percent injury to CST contained fibers originating from M1 only. However, FA values in the cerebral peduncle reflect integrity of fibers originating from cortex throughout the brain, and FA values in PLIC reflect integrity of both afferent and efferent fibers. Gains from a motor therapy that target ipsilesional M1 may be better predicted by specifically measuring injury to those fibers issued by M1 rather than by measuring injury to a heterogeneous collection of fiber tracts.

CST integrity did not predict treatment-related gains in the current cohort. The constellation of findings with CST integrity—this measure correlated with baseline motor status but not with treatment-induced motor gains—echo results of a prior study of 22 patients with chronic stroke undergoing 2 weeks of constraint-induced movement therapy.[31] CST integrity is based on FA, which describes directionality of proton diffusion,[32] and characterizes white matter integrity given that FA values are influenced by the microstructural properties of white matter, for example, myelination, axon density and diameter, and fiber organization/orientation.[33] Serial assessment of this measure may have value as a surrogate marker of treatment effects after stroke because studies in healthy rodents have found training-related increases in FA within corpus callosum[34] and white matter subjacent to M1,[35] and studies in rodents with an experimental infarct have found increases in FA within the ischemic boundary zone following neural progenitor cell therapy.[36] The peduncle area measure is calculated based on tissue loss and reflects Wallerian

degeneration.[8] Peduncular area did not correlate with degree of motor deficits in the current cohort, although this measure did in a prior study by Warabi et al[7] of 89 patients with chronic hemiplegic stroke. These divergent findings might be attributable to differences in the population studied or methods used to calculate peduncle area. Together, the findings suggest that the capacity to improve motor status in the subacute-chronic stroke state is more dependent on extent to which CST undergoes critical injury rather than the extent to which CST shows reduced integrity or Wallerian degeneration, at least in response to the current interventions.

Together, the findings across CST injury measures introduce questions important to the development of recovery biomarkers after stroke.[37] Percent injury to CST best predicted treatment-related gains, but CST peduncle integrity best explained baseline motor status. These were independent measurements because CST integrity did not correlate with percent CST injury. The findings suggest a distinction between quantity of remaining tract (percent injury) and quality of remaining tract (CST integrity). A threshold of injury that limits treatment gains may be more easily definable for quantity of injury.[38] This may be less true for CST integrity because conceivably axons may be able to conduct signals, and so support gains, across a wide range of FA reductions.

There are several strengths to the current study. Three independent types of CST injury were directly compared. Percent CST injury, which emerged as the sole measure predicting treatment-related motor gains, can be obtained using any technique that images an infarct, and so this approach could theoretically be extended to studies that used a computed tomographic scan to image the infarct. Current results emphasize the specificity of the percent injury to CST measure, that is, it correlates with behavioral deficits in motor but not other systems, and furthermore support a modality-specific approach to calculating injury after stroke[39] given that a motor system injury measure (percent CST injury) but not a global injury measure (total infarct volume) predicted treatment-related motor gains (Table 2). Performance of the CST measure predicting treatment-related gains did not vary with infarct topography because an interaction term for infarct depth (cortical versus subcortical) was not significant (P=0.64). There are also several weaknesses. Current analyses were focused only on injury measures, although measurement of both neural injury and neural function may more robustly predict motor outcomes after stroke.[11,40] The current study excluded patients with stroke in the brainstem given the complexities of CST neuroanatomy in this region. The findings may not extrapolate directly to acute stroke, where differences in the underlying neurobiology[41] necessitate separate evaluation of biomarkers. The current focus was also on neuroimaging-based CST injury biomarkers, but physiological measures, such as those obtained using transcranial magnetic stimulation, useful in predicting motor outcomes in the acute stroke setting,[16,40] may also have utility in the chronic stroke context and warrant further study in this setting. Injury was measured only to that portion of the CST descending from M1, which we have previously found to be the most important predictor of treatment gains in the chronic stroke setting,[10] and future studies can examine the performance of injury measures to additional brain structures,[42] which could potentially boost the predictive power of percent CST injury.

The findings from the current analysis may prove useful in clinical trials of restorative therapies that choose to incorporate a measure of CST injury for the purposes of optimizing patient selection and stratification. Trial design might increase the chances of detecting a treatment effect by excluding patients with severe CST injury, who might be offered enrollment in trials studying alternative interventions that are not predicted to provide poor treatment gains.

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Disclosures

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