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Anatomy of Stroke Injury Predicts Gains from Therapy

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Abstract

Background and Purpose—Many therapies are emerging that aim to improve motor function in people with stroke. Identifying key biological substrates needed for treatment gains would help to predict treatment effects, and to maximize treatment impact. The current study addressed the hypothesis that behavioral gains from therapy targeting distal upper extremity are predicted by the structural integrity of key motor system white matter tracts.

Methods—Twenty three subjects with chronic left-sided stroke underwent robotic therapy targeting the distal right upper extremity. MRI was obtained at baseline and used to outline the infarct. For each subject, the degree to which stroke injured each of four descending white matter tracts (from primary motor cortex, supplementary motor area, dorsal premotor cortex, and ventral premotor cortex, respectively) was determined. Correlations between tract-specific injury and behavioral gains from therapy were then examined.

Results—Numerous examples were found whereby tract-specific injury predicted treatment gains. The strongest correlations related to stroke injury to tracts descending from primary motor cortex and dorsal premotor cortex. Infarct volume and baseline behavior were weak predictors of treatment gains.

Conclusions—Extent of injury to specific motor tracts predicts behavioral gains from treatment in subjects with chronic stroke. This supports a role for these tracts in mediating treatment effects, and reinforces the importance of lesion location in stroke. Tract-specific injury was stronger than infarct volume or baseline clinical status at predicting gains, identifies subjects with sufficient biological substrate to improve from therapy, and so might be useful as an entry criterion in repair-based trials.

Keywords

corticospinal tract; stroke; prediction; standardized therapy

Stroke remains a major cause of human disability. Motor deficits are among the most common after stroke and thus a major contributor to this fact[1, 2]. Involvement of the hand can be particularly disabling given the unique role the hand plays in many daily functions. In

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response to this, a number of therapies are emerging that aim to improve hand motor function for patients in the chronic phase of stroke. Brain mapping studies[3-5] suggest that many of the effects of such therapies are mediated by the surviving motor system of the stroke-affected hemisphere, particularly ipsilesional primary motor cortex (M1), supplementary motor area (SMA), dorsal premotor cortex (PMd), and ventral premotor cortex (PMv). The extent of injury to key motor system structures[6] might therefore be a determinant of treatment effect and might also provide insight into the inter-subject variability in treatment response, which is substantial.

Cortical motor regions might exert these effects via direct corticospinal projections that have been described from each of M1, SMA, PMd, PMv[7, 8]. The primary hypothesis examined in this study is that behavioral gains during a course of standardized therapy targeting distal arm are predicted by the structural integrity of motor system white matter tracts. The corticospinal tract from M1 has the largest number of pyramidal tract neurons[9] and is the largest source of corticospinal fibers[7], and so this tract was of greatest interest.

Methods

Study design and subjects

Twenty-three subjects with hemiparesis and chronic stroke were recruited[5, 10], signed informed consent in accordance with the U.C. Irvine Institutional Review Board, received baseline behavioral assessments followed by an MRI scan, underwent 23-24 hours of robotic therapy, then underwent repeat behavioral assessment following completion of therapy. Entry criteria are described in the Supplement.

Robotic hand therapy

Therapy consisted of repeated grasp-release movements by the affected distal upper extremity using a pneumatically actuated robot that has been described previously[5].

Subject assessments

Baseline behavioral assessments were performed twice, prior to beginning therapy, 1-3 weeks apart (to insure stable baseline), then averaged for each subject. Baseline exam included assessment of medical history, NIH stroke scale (NIHSS) score, depression[11], and apraxia[12]. MRI included high-resolution (1 mm^3 voxel) T1-weighted anatomical image, followed by therapy ~1 week later, then behavioral assessments at the end of therapy. The three main behavioral assessments were arm motor Fugl-Meyer (FM) score, Box and Blocks (B&B) score, and the Action Research Arm Test (ARAT), each of which has established validity and inter-/intra- rater reliability. All assessments were performed by a single examiner.

Data analysis

The main independent measure in this study was the structural integrity of motor system white matter tracts. Because fiber tracking with diffusion tensor imaging (DTI) can be problematic in brain regions affected by stroke, tract injury for each patient was determined by examining the extent to which the infarct overlapped with the normal white matter tract[13, 14]. Areas of infarct were outlined by hand on each subject's MRI scan, from which binary stroke masks were generated. These images were then transformed into MNI (Montreal Neurological Institute) standard stereotaxic space using FSL (FMRIB Software Library).

The normal white matter tract descending from each of four motor-related cortical areas was generated from in 12 healthy right-handed healthy subjects using diffusion weighted images

obtained at 3T, as described elsewhere[14]. Each tract was generated using a unilateral seed region that covered either M1, SMA, PMd, or PMv, respectively. For each, tractographic methods were used to generate probability pathways connecting the motor cortex area to the cerebral peduncle. These tracts were then binarized, transformed into MNI space, summed to generate group probability maps, and then thresholded to include only voxels that were common to the tracts of ≥8 subjects.

Ideally, we would like to measure the percentage of axons in each tract that was injured by stroke, but MRI resolution does not permit this. Towards this approach, we divided each tract into longitudinal subsections, aiming to model the trajectory of groups of axons. The goal was to classify each subsection as injured or not; a subsection only needed to be damaged by stroke once along its length for it to be classified as injured. Therefore, for primary analyses, each tract was divided into 16 separate descending subsections (further methodological details in Supplement).

The extent of injury to each subsection of each tract was determined by measuring the volume of overlap between that subsection and the stroke mask. For each subsection we applied an empirically defined conservative threshold of 5% overlap to designate the subsection as injured by stroke. For each subject, extent of injury to each descending tract was then determined by measuring the percentage of subsections that were injured by stroke.

To address the primary study hypothesis, for each tract, the relationship between extent of injury (% of its 16 longitudinal subsections injured by stroke, at 5% injury overlap threshold) and change in behavior across the period of therapy was then examined, all using parametric statistics. Behavior was examined in three ways (FM, B&B, ARAT), and so for each tract, significance was corrected for multiple comparisons ($p < 0.0167$). The relationship between tract injury and *change in score* across treatment was examined using age and baseline score as covariates. To gain additional insight, the relationship between tract injury and *baseline score* was also examined.

Secondary analyses examined the effect of adding three clinical covariates (time post-stroke, Geriatric Depression Scale score, and a measure of apraxia) or the effect of instead combining all four measures of tract injury as predictors.

In order to examine the robustness of the methods, additional secondary analyses were performed after assumptions made in data processing were varied in two ways. First, the definition of injury was varied: the degree of overlap between the stroke mask and a tract subsection used to label that subsection as injured was varied from the primary method of 5% (above) to two more stringent definitions, 10% and 20%, and injury/behavior relationships were recalculated. Second, the number of subsections into which each tract was subdivided was changed from the primary method of 16 (above) to three alternatives: 64 subdivisions/tract (whereby each of the 16 subdivisions was quartered), 4 subdivisions/tract, and zero subdivisions/tract. For the zero subdivision approach, injury was reported as the percentage of each tract that overlapped with the stroke mask.

Results

Table 1 presents patient characteristics.

The tracts and their injury by stroke

Each of the four tracts extended from white matter immediately subjacent to the motor cortex region of interest to the cerebral peduncle[14]. Some tracts showed limited overlap, and

some cortical regions that were nearer to each other, such as PMd and PMv, showed higher overlap (Table 2).

Across the 23 stroke subjects, the range of tract injury was wide, with the extent of overlap between infarct and descending tracts ranging from 0 - 100% for M1, PMd, and PMv; and from 0 - 93.8% for SMA. The mean (± SEM) overlap between infarct and each motor tract was similar: for the tract descending from M1, an average of 71.2 ± 6.3% (i.e., approximately 11 of 16 subsections) of the tract was injured by stroke; for PMd, 71.7 ± 7.4%; for PMv, 66.1 ± 8.1%; and for SMA, 62.5 ± 6.4%.

The relation between injury and behavioral status

Primary analysis evaluated behavior in relation to tract injury, defined with each tract divided into 16 subsections, and requiring that a patient's infarct have at least 5% overlap with the tract subsection to designate that subsection as injured.

Injury and behavior at baseline—The baseline value for the three motor outcome assessments did not show a significant correlation with injury to any of the four tracts or with infarct volume. However, review of the data (Figure 1a) suggests that this lack of linearity between injury and baseline behavior is explained by the presence of several subgroups. The first subgroup of subjects had mild tract injury to M1 and mild-moderate baseline motor deficits (and maximum therapy gains, see below); among subjects with more severe tract injury, a second subgroup had severe baseline deficits (FM score ≤ 35) while a third subgroup had mild-moderate baseline deficits (FM score ≥ 44).

Injury and change in behavior across the period of therapy—Baseline scores alone did not predict change in scores, with a single exception (Table 3); nor did NIHSS score or demographic measures. However, with tract-specific injury added to the prediction model, numerous examples were found whereby change in motor status was significantly predicted (Figures 1b and 2, Table 3). Note that adding infarct volume instead did not predict change in behavior (Figure 1c, Table 3). There were some similarities in injury effects: extent of injury to tracts descending from M1, PMd, and SMA each correlated significantly with change in FM score as well as with change in B&B score, while injury to the tract descending from PMv correlated only with change in B&B score. For no tract did injury correlate with change in ARAT score.

In secondary analyses, the effect of adding covariates to the model was examined, focusing on the relationship between M1 tract injury and change in FM score. The initial model (Table 3) had r^2 of 0.42, with partial correlation coefficient between M1 injury and change in FM score of -0.65. Adding three clinical measures (time post-stroke plus measures of depression and apraxia) only increased r^2 to 0.44 with no effect on the partial correlation coefficient. Adding instead the 3 other tract injury measures increased r^2 to 0.51, but partial correlation coefficients were each ≤0.35, consistent with the partial degree of tract overlap (Table 2).

Robustness of results across methodological assumptions

Injury to the M1 tract was further studied to examine the robustness of the methods. Varying the extent to which stroke had to overlap with a subsection in order to label that subsection as injured had little effect. Changing the number of tract partitions from 16 to either 4 or 64 subdivisions/tract reduced injury/behavior correlations for B&B and had little effect on FM and ARAT; use of 0 subdivisions/tract consistently reduced injury/behavior correlations (see Table 4, Supplement).

Discussion

The main finding from this study is that the extent of injury to specific motor tracts is useful for predicting behavioral gains from therapy in subjects with chronic stroke. Tract-specific injury was stronger than infarct volume or baseline behavioral status at predicting gains; note that baseline behavioral status is often an entry criterion in stroke trials, suggesting that measures of tract injury could be useful to some clinical trials, such as for patient stratification. Tract-specific injury is a relatively simple measure to determine, and is useful to identify subjects who have sufficient biological substrate to improve from therapy.

The current results suggest that the tracts studied are important resources for deriving treatment-induced behavioral gains. The findings emphasize the value of white matter survival for achieving such gains, and so complement prior studies that focused on the role of gray matter structures to treatment-induced motor gains after stroke[5, 15, 16]. Tract-specific injury performed better than infarct volume did at predicting treatment gains, underscoring the importance of lesion location as a determinant of rehabilitation therapy effects. Tract-specific injury also predicted gains better than baseline behavior predicted gains did. A given behavioral phenotype can arise from many different brain states, but only some of these are likely to improve with therapy. The current study suggests that measures of tract-specific injury are useful for identifying treatment responders, beyond that provided by baseline behavior, and so might be useful for patient selection in clinical trials.

The current results are in general agreement with a prior study that found tract-specific injury to be a useful predictor of treatment gains[17]. In that study, Stinear et al[17] found best prediction by measuring a combination of white matter integrity via DTI and neurophysiology via transcranial magnetic stimulation. Such multimodal assessment allows for more detailed classification of tract injury. However, the current approach also has its advantages, including assessment of injury to several specific tracts and simplicity of data analysis methodology. A prior study[18] that used the tract/injury overlap approach to study gait found a limited relationship between tract injury and therapy-related gains. The reason for this disparity with current results might reflect fundamental differences in cerebral organization between hand movements (Table 3) and gait[18], or that these authors examined corticospinal tract with only zero subdivisions, which was found to perform less well than with the current approach of using 16 subdivisions (Table 4, Supplement).

The constellation of findings (Table 3) provides some insight into the relative contributions that the four motor tracts make to motor gains during post-stroke motor therapy. Injury to the tract descending from PMv predicted treatment gains less often than injury to the other descending tracts did, suggesting a smaller role of this tract in supporting gains from a robotic therapy targeting the distal arm. Injury to the tracts descending from M1 and from PMd each had approximately equal predictive power, which was of some surprise given the predominance of M1 in issuing pyramidal and corticospinal fibers, though possibly related to the fact that the majority of fibers overlapped between these two tracts (Table 2). Together, the results do suggest that all four tracts play a role in mediating gains from motor therapy in chronic stroke, though their inter-relationships makes challenging a precise estimate of each tract's role. The reason for the incomplete concordance of findings across the three behavioral scales, in particular the lack of prediction of ARAT score gains, is unclear but might reflect differences in extent to which content of each scale corresponded to content of the therapy. Further insight might be gained in future studies that use of assessments more aligned with the specific behaviors supported by each motor area, such as assessment of internal movement triggering for SMA and of external movement triggering for PMd[19].

The current analysis did not find a threshold whereby a certain level of tract injury was clearly associated with total loss of distal arm motor function at baseline, or with inability to derive gains from therapy. For example, some subjects with >90% tract injury had good baseline function and good treatment gains, whereas some had poor baseline function/gains (Figure 1). This current finding regarding *white matter tract injury* contrasts with a prior study that examined *motor cortex injury*, which did find such a threshold; in that study, injury to >37% of the hand motor map was associated with total loss of hand motor function[20]. With severe injury to motor cortex, recovery does not occur, but with severe injury to the white matter tract descending from motor cortex, recovery occurs in some patients. Together, these findings suggest that behavioral effects of large white matter injuries might be reduced by forms of plasticity that are not possible with large cortical injuries.

Strengths of the study included that the findings were robust across varied methodological assumptions such as the threshold used to define injury. All infarcts were in left brain, eliminating variance due to stroke side. There were also limits with the current approach. Clearly, numerous factors besides tract injury, such as injury to other brain structures[21], extent to which brain plasticity is exhausted at baseline[22], or psychosocial factors[23], influence behavioral response to therapy. The stroke masks obtained in the current chronic stroke cohort do not likely reflect the full nature of the acute injury; using the tract/injury overlap approach in the acute phase of stroke might find stronger relationships. The focus on left hemisphere injury does not provide specific information on right brain injury. The reason that the tract descending from M1 had lower volume than the tracts descending from PMd or SMA, despite contributing a larger proportion of axons to the corticospinal tract[7], is unclear but might reflect tract fiber density or topography[6, 24], or perhaps DTI-specific issues such as coherence. Finally, while measures of tract-specific injury correlated with change in behavior across therapy, these measures of injury showed a limited relationship with baseline behavior, in contrast to prior studies[25-27]. This is likely due to the pattern of deficits among enrollees--those with moderate-severe tract injury in the current study had a bimodal distribution, with some having mild-moderate and some having severe behavioral deficits (Figure 1a), and so the strength of the behavior/injury correlation varies with enrollee characteristics.

Many therapies are emerging that aim to improve motor function in people with stroke. Measuring the key biological substrate needed to achieve treatment gains will be useful to best match therapies with the right patients. The current report provides a robust and relatively simple method for measuring extent of injury to specific motor tracts, reinforces the importance of lesion location in stroke, and emphasizes the greater predictive value of tract-specific measures as compared to global measures of injury such as infarct volume.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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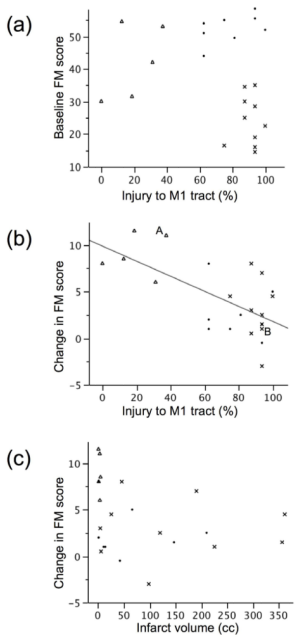

Figure 1. Relationships between injury and behavior

(a) Injury to the tract descending from M1 in relation to baseline FM score. A significant linear correlation was not present ($p > 0.25$). However, three subject clusters are apparent on inspection of the data: a subgroup of subjects with mild tract injury has mild-moderate motor deficits (marked as triangle); subjects with moderate-severe injury have either mild-moderate (marked as circles) or severe (marked as "x") deficits. This injury/behavior subgrouping was also apparent for the other three tracts.

(b) Injury to the tract descending from M1 correlates ($r=-0.65$, $p < 0.002$) with the treatment-induced change in FM score. Subjects with mild tract injury had greater gains from treatment. A and B indicate the two subjects whose images appear in Figure 2.

(c) A global measure of stroke-induced injury, infarct volume, did not show a significant relationship with the treatment-induced change in FM score ($p > 0.2$).

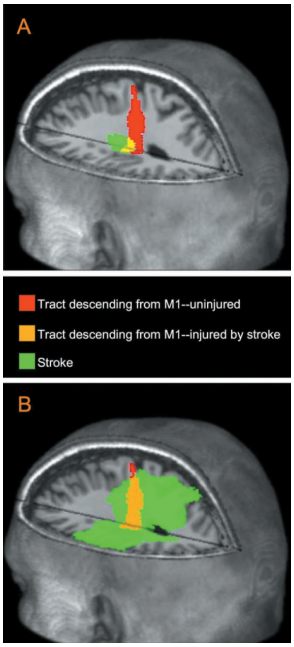

Figure 2. Examples of stroke injury to the tract descending from M1

A. This subject had 37.5% of the M1 tract injured by stroke and had a gain of 11 points on the FM scale across the period of therapy. B. This subject had 93.4% of the M1 tract injured by stroke and had a gain of 1 point on the FM scale across the period of therapy.

Table 1

Characteristics of subjects with stroke

n	23
Age (years)	59.2 ± 3.0
Gender	12 F / 11 M
Time post-stroke (years)	2.1 ± 0.5
Hypertension present?	14 Y / 9 N
Diabetes mellitus present?	3 Y / 20 N
Hypercholesterolemia present?	12 Y / 11 N
Coronary artery disease present?	3 Y / 20 N
Current cigarette smoker?	6 Y / 17 N
Geriatric Depression Scale (15Q version) score	4.2 ± 0.6
Infarct Volume (cc)	84.2 ± 23.5
NIH Stroke Scale score	5 (1-9)
Baseline FM score	37.9 ± 3.1 (15 - 59)
Baseline B&B (# blocks/60 sec)	12.9 ± 3.3 (0 - 53)
Baseline ARAT score	25.7 ± 4.3 (3 - 57)
Change in FM score across therapy	4.1 ± 0.8 (-3 to +12)***
Change in B&B across therapy	2.1 ± 0.8 (-4 to +10)*
Change in ARAT score across therapy	2.0 ± 0.6 (-5 to +9)**

In 13 patients, the stroke involved cortex (9 involving frontal, parietal, and temporal cortices, 2 frontal and parietal only, and 2 frontal only), while in 10 patients the stroke was strictly subcortical (8 striatocapsular and 2 deep white matter only). Due to acquisition of MRI images in the chronic phase, stroke pathophysiology and subtype could not be determined. Mean ± SEM, except NIH Stroke Scale, which is reported as median. All but two patients had a normal apraxia score. Values in parentheses are ranges. Improvement across therapy was significant in each case

* $p<0.02$,

** $p<0.005$,

*** $p<0.0001$, 2-tailed one-sample t-test.

Table 2

Degree to which motor tracts overlap in healthy controls

	M1	PMd	PMv	SMA
Tract volume (cc)	6.7	11.5	2.5	10.5
% of tract that overlapped with M1 tract		49.9	47.6	22.9
% of tract that overlapped with PMd tract	85.4		93.2	47.0
% of tract that overlapped with PMv tract	17.4	19.9		17.7
% of tract that overlapped with SMA tract	36.0	43.1	75.9	

Each column reflects the percentage overlap with each row. For example, in the M1 column, 36% indicates that, of the voxels in the M1 tract, 36% were also found in the SMA tract. On the other hand, in the SMA column, only 22.9% of voxels were also found in the M1 tract.

Table 3

Prediction of motor change across the period of therapy

Predictor	Change in FM score	Change in B&B (# blocks)	Change in ARAT score
Infarct volume	X	X	X
NIHSS	X	X	X
Baseline score for scale	X	0.54**	X
M1 injury	-0.65***	-0.75***	X
PMd injury	-0.67***	-0.73**	X
PMv injury	X	-0.74***	X
SMA injury	-0.56**	-0.69*	X

A measure of tract-specific injury significantly improves prediction of motor gains across therapy. Each measure was added to a prediction model that included age and baseline score. Table values are the partial correlation coefficient for the predictor, when significant, with p values corresponding to parameter estimates for the predictor

* $p < 0.05$,

** $p < 0.0167$,

*** $p \leq 0.005$.

Note that age, gender, and history of hypertension, diabetes, or hypercholesterolemia did not predict change in any of the three scales.