Structural Plasticity of the Ventral Stream and Aphasia Recovery

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Restrengthening of the residual language network is likely to be crucial for speech recovery in poststroke aphasia. Eight participants with chronic aphasia received intensive speech therapy for 3 weeks, with standardized naming tests and brain magnetic resonance imaging before and after therapy. Kurtosis-based diffusion tensor tractography was used to measure mean kurtosis (MK) along a segment of the inferior longitudinal fasciculus (ILF). Therapy-related reduction in the number of semantic but not phonemic errors was associated with strengthening (renormalization) of ILF MK ($r = -0.90$, $p < 0.05$ corrected), suggesting that speech recovery is related to structural plasticity of language-specific components of the residual language network.

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Stroke is the leading cause of neurological disability and acquired language problems (aphasia).[1] For survivors with chronic aphasia, speech therapy can lead to language improvements, but the response is highly variable.[2] The neurobiological bases of therapy-mediated recovery are not completely understood, and it remains unclear why some individuals benefit whereas others exhibit little response.

A leading hypothesis suggests that restrengthening of the residual language network is crucial for recovery in poststroke aphasia.[3] The dual stream model of language suggests that ventral (parietal–temporal) networks are responsible for integrating the lexical–semantic system, whereas dorsal (parietal–frontal) networks are related to the motor–articulatory system.[4] In a pioneering work, Schlaug et al demonstrated nonspecific structural changes associated with chronic aphasia improvement[5,6]; subsequently, van Hees et al showed renormalization of the dorsal stream related to phonemic improvement.[7] However, it is unclear whether semantic improvements are supported by structural plasticity of the ventral stream. This knowledge could help guide therapy approaches targeting residual brain integrity.

We tested whether structural plasticity of the ventral stream, represented by a segment of the inferior longitudinal fasciculus (ILF), was related to linguistic improvements by examining a cohort of individuals with chronic aphasia who underwent speech therapy. We applied diffusional kurtosis imaging (DKI),[8] a diffusion magnetic resonance imaging (MRI) technique that provides more comprehensive characterization of tissue microstructure, and improves the assessment of white matter tractography.[9] In accordance with the dual stream model, we hypothesized that restrengthening of the residual ILF would be associated with semantic, but not phonemic, therapy-related improvements in naming.

Subjects and Methods

We recruited 8 participants (52 ± 7 years, 3 women) with a history of poststroke aphasia due to a single left hemisphere stroke at least 12 months (50.3 ± 29.8) prior to the study. The participants had no history of other neurological diseases and were all right-handed. This study was approved by institutional review boards at our institutions.

The participants received group-based intensive language action therapy (constraint induced)[10] for 3 weeks (5 therapy sessions per week lasting 4 hours each). They were tested for confrontational naming using a short version of the Philadelphia Naming Test[11] within 1 week before and after therapy.

MRI data were collected using a Siemens (Erlangen, Germany) 3T TIM Trio (12-channel head coil) at the University of South Carolina. DKI acquisition parameters were as follows: 2 b-values (1,000 and 2,000s/mm^2), 30 diffusion-encoding

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directions, 45 slices, voxel size = 2.7 × 2.7 × 2.7mm^3, repetition time (TR) = 6,100 milliseconds, echo time (TE) = 101 milliseconds, field of view (FOV) = 222 × 222mm^2, 2 averages, and 11 non–diffusion-weighted images. Acquisition parameters for T1-weighted images were as follows: TurboFLASH sequence, FOV = 256 × 256mm^2, 160 sagittal slices, 9° flip angle, TR = 2,250 milliseconds, TE = 4.5 milliseconds, voxel size = 1 × 1 × 1mm^3. All subjects underwent 4 MRI sessions, 2 before and 2 after treatment, within 1 week before and after therapy.

The image analysis pipeline was optimized to quantify diffusion (fractional anisotropy [FA], mean diffusivity [MD], and mean kurtosis [MK]) along a representative segment of the ILF as defined by the probabilistic Johns Hopkins University white matter atlas,[12] which travels from the coronal plane in the posterior edge of the cingulum to the temporal pole. Data from both pretreatment and post-treatment sessions were combined into a set of 121 diffusion-weighted images, linearly registered to the initial scan using SPM8 to locate the ILF for each subject. Diffusional Kurtosis Estimator was used for deterministic kurtosis-based tractography (https://www.nitrc.org/projects/dke/). A white matter seeding mask was created with SPM's Clinical Toolbox (https://www.nitrc.org/projects/clinicaltbx/), which was normalized to diffusion space by cost function masking with the stroke lesion (drawn on T1 images). Individual whole brain tractography maps were analyzed using automated fiber quantification (AFQ),[13] customized to perform analysis in diffusion space. AFQ and DKI were combined as described previously.[14] AFQ results in a set of ILF fibers, which ultimately is abridged to 1 centroid. One hundred equidistant measurements along the centroid were obtained for each metric before and after therapy. Because no significant differences were revealed between the pre- or post-treatment scans, they were averaged to reduce noise. To assess the ILF's weakest segment, the location with the highest diffusion abnormality (minimum MK or FA, maximum MD) was determined between nodes 20 and 80 of the core ILF. We called this highest abnormality the bottleneck, and a 6-node smoothing kernel was applied in this neighborhood to reduce the contribution of outliers. All further analyses were carried out in the bottleneck.

Pre- to post-treatment structural changes in the ILF were examined in relation to therapy-related improvements in both semantic and phonemic paraphasias using linear regression. Baseline metrics were also related to baseline performance. Corresponding probability values are adjusted for multiple comparisons (n = 12) using Bonferroni correction.

Results

As a group, subjects showed significant improvement in the number of correctly named items with therapy (paired t test, $p = 0.002$), which was driven by fewer semantic errors ($p = 0.01$) and a decrease of no responses ($p = 0.03$).

The left ILF was significantly different ($p < 0.001$) from the right ILF for each metric. Compared to the contralateral side, the ipsilateral ILF had a higher MD, lower FA, and lower MK (Fig 1).

Individualized perilesional changes in ILF microstructure in relation to its proximity to the stroke lesion were also noted. MK values at greater distances from the lesion were higher, gradually decreasing when closer to the lesion (Fig 2). Overlap between the lesion core and the left ILF ranged from 0.4% to 94.7% (Fig 3A).

There was a strongly significant correlation between pre- to post-therapy increment in MK (renormalization toward normal values[15] in the left ILF (at the bottleneck) and therapy-related improvement in semantic paraphasias ($r = -0.90$, $p < 0.05$; see Fig 3A). No relationships were observed for pre- to post-therapy MK changes and phonemic errors ($r = -0.11$; semantic vs phonemic R to Z comparison [Fisher transformation], $p < 0.05$) or for right ILF changes and improvement in semantic paraphasias (left-ILF vs right-ILF R to Z, $p < 0.05$). The correlations with FA and MD did not reach the significance level of $p < 0.05$. Bottleneck increases in MK with therapy are shown in the perilesional space of a representative patient (see Fig 3B; note MK color-code changes from blue to green). There was a trend toward statistical significance in the relationship between ILF MK pretreatment and the number of semantic paraphasias prior to treatment ($r = -0.82$, $p = 0.15$); this association did not increase with treatment.

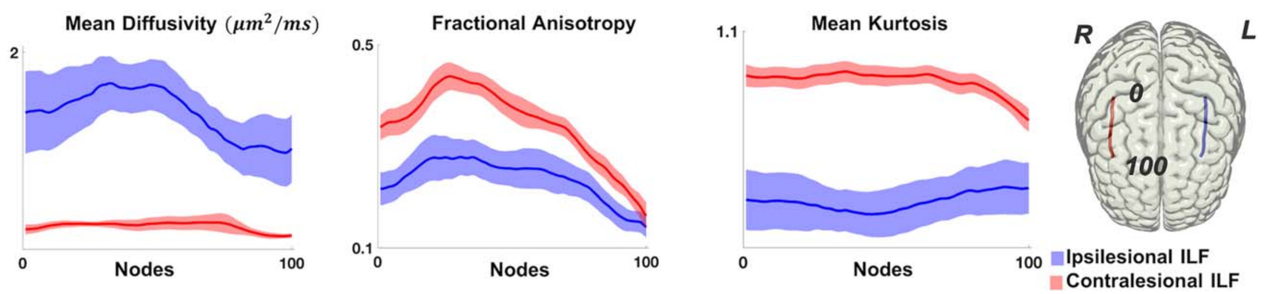


FIGURE 1: Along-tract diffusion metrics (y-axis) are demonstrated along equally spaced measurement points in the inferior longitudinal fasciculus (ILF; 0–100, posterior to anterior; x-axis). The solid lines represent the average patient value, with the standard error of the mean shown as the shaded areas. Ipsilesional ILF values are shown in blue, and contralesional ILF values are shown in red. The rightmost image illustrates an example of a participant's core right (R) and left (L) ILF.

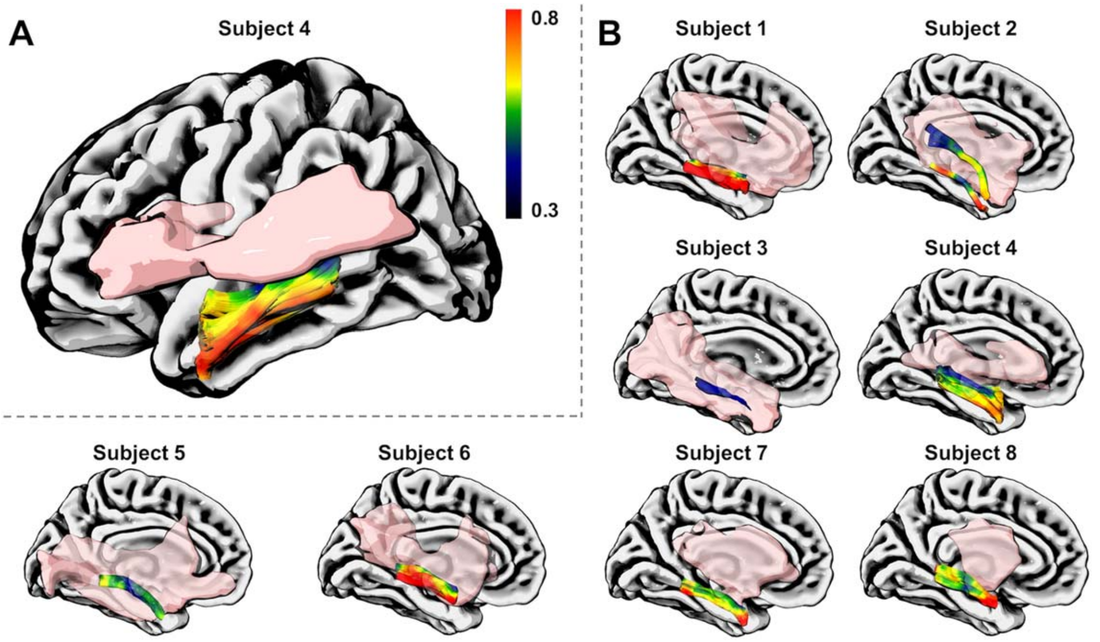


FIGURE 2: The relationship between along-tract inferior longitudinal fasciculus (ILF) mean kurtosis (MK) values and the chronic stroke lesion (in pink). (A) The data from 1 representative participant is shown in a lateral view to demonstrate the lowest MK in perilesional areas (color bar). (B) The ILF and the lesion are shown for the subject in A and all others using medial views to illustrate their anatomical relationship. Note that the lesion was excluded from the seeding mask during ILF tractography.

To investigate the effect of lesion burden on recovery, we evaluated the number of residual fibers in each patient. The number of semantic paraphasias prior to therapy was related to ILF lesion burden ($r = -0.65$, $p = 0.07$). However, lesion burden (or track integrity) was not associated with semantic recovery ($r = 0.19$, $p = 0.65$).

Discussion

The present study evaluated the relationship between structural plasticity of the ventral stream and therapy-related improvements in naming in individuals with chronic aphasia. We observed that pre- to post-treatment increases in ILF MK toward normal values,[15] specifically within the areas along the ILF with the highest degree of baseline structural compromise (the diffusion bottleneck), were strongly associated with semantic improvements.

These results leverage recent advancements in diffusion-weighted imaging and image analysis, which enable the investigation of white matter microstructure with higher sensitivity to microstructural changes.[16] MK is a biophysical measure less affected by partial volume, which can be higher in the proximity of a stroke lesion.[17] In this study, MK was the only diffusion metric that reached statistical significance, suggesting that conventional diffusion measures may be less sensitive to structural changes associated with recovery, and MK may be optimally suited for assessing poststroke neuroplasticity. Larger studies are needed to replicate these results.

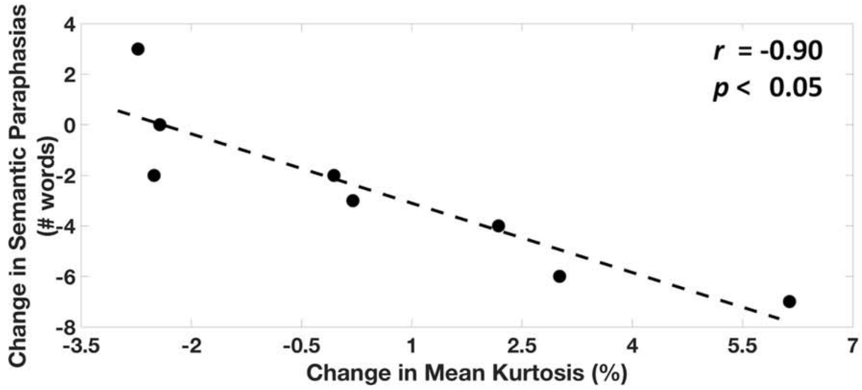
The neurobiology underlying MK changes is likely due to a combination of factors that are known to occur after strokes. Namely, axonal sprouting, changes in axon thickness, and neurogenesis can contribute to an increase in complexity in perilesional tissues, which has been demonstrated in poststroke experimental studies.[18] However, further specific biophysical tissue models are needed to completely elucidate the basis of poststroke plasticity.

Our findings provide preliminary, but theory-driven, evidence of semantic improvements being supported by structural plasticity of the ventral language processing stream. This knowledge can be used to guide therapies to recruit ventral processing pathways in individuals with residual ILF, or direct stimulation to the ILF for semantic improvement. Of note, language action therapy focuses on the improvement of communication skills in general, and future studies with a larger sample could address whether impairment-based interventions (ie, semantically based treatments for semantic paraphasias) could lead to further enhanced structural neuroplasticity.

Moreover, the residual integrity of the language network could help improve the predictions of recovery potential, together with other predictors such as lesion site, lesion load,[19] and the right language network, specifically the arcuate fasciculus, which has been implicated in recovery by previous studies.[5,20]

In conclusion, therapy-related ventral stream plasticity, quantified by MK changes within a bottleneck of damage in the ILF, is related to semantic, but not

A.



SUBJECT	LESION OVERLAP (%)	BL1	BL2	MEAN BL	FU1	FU2	MEAN FU	CHANGE MK (%)	CHANGE SEMANTIC PARAPHASIAS (#WORDS)
P8	0.8	0.53	0.53	0.53	0.53	0.49	0.51	-2.73	3
P2	10.5	0.55	0.55	0.55	0.54	0.53	0.53	-2.5	-2
P4	0.4	0.78	0.75	0.77	0.75	0.75	0.75	-2.43	0
P6	19.1	0.7	0.79	0.74	0.74	0.74	0.74	-0.06	-2
P7	13.1	0.65	0.65	0.65	0.66	0.64	0.65	0.2	-3
P1	0.5	0.86	0.82	0.84	0.85	0.86	0.86	2.18	-4
P5	66.3	0.46	0.46	0.46	0.47	0.48	0.48	3.01	-6
P3	94.7	0.39	0.40	0.40	0.43	0.41	0.42	6.13	-7

B.

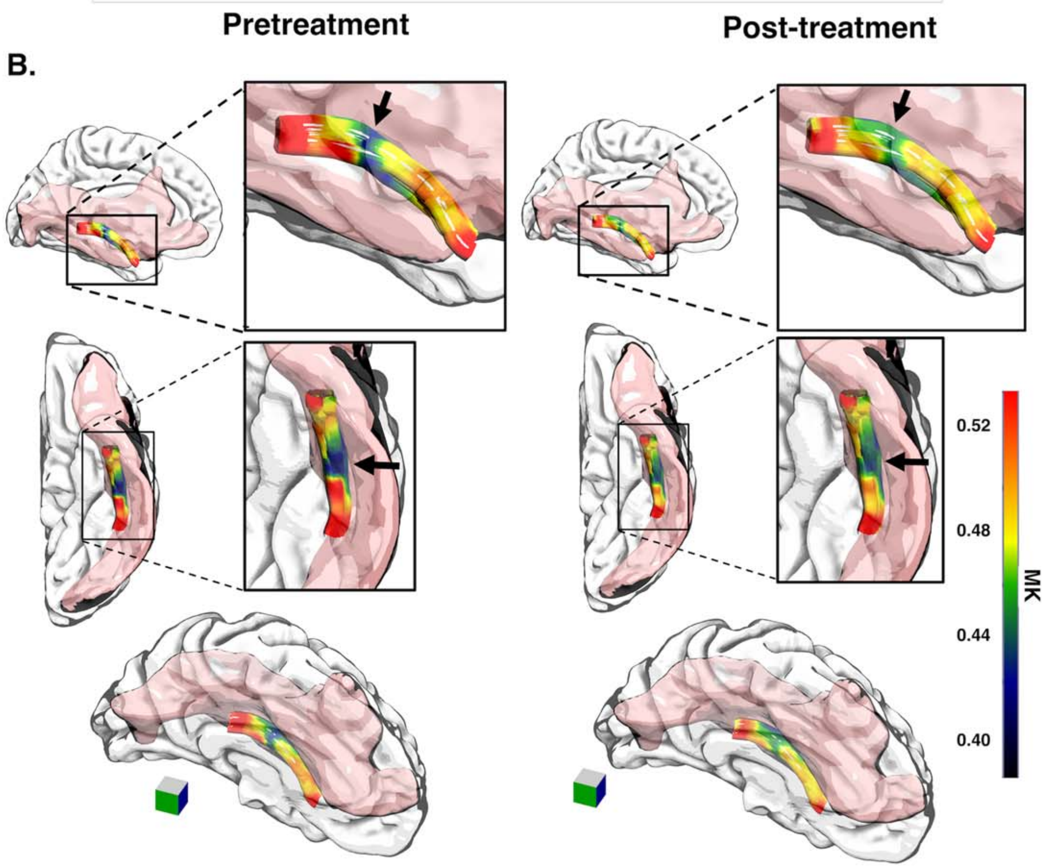


FIGURE 3: (A) Top: The scatter plot demonstrates the relationship between pre- to post-therapy changes in mean kurtosis (MK) measured at the inferior longitudinal fasciculus (ILF) bottleneck, and pre- to post-therapy changes in semantic paraphasias ($r = -0.90$ and $p < 0.05$ corrected). Bottom: Table summarizing MK values for the 4 magnetic resonance imaging acquisitions for all subjects. The table also includes individual changes in the number of semantic paraphasias with treatment (in number of words) and the percentage overlap between the stroke lesion and the ILF. The scatterplot above depicts the relationship between change in MK (second to last column) and change in semantic paraphasias (last column). BL = baseline; FU = follow-up. (B) Pre- and post-treatment MK values along the ILF from a representative participant are shown anatomically. The ILF bottleneck, which is marked with a black arrow, demonstrates an increase in MK toward normal values from before to after therapy. The stroke lesion is demonstrated in pink. This participant demonstrated a 55% improvement in semantic errors.

phonemic, improvements due to therapy. These results are in accordance with the theoretical dual stream model of language, which predicts the involvement of the ILF in semantic processing. Furthermore, kurtosis-based tractography is a promising tool for the study of the neurobiology of stroke recovery. Understanding language network integrity and its relationship with clinical performance could advance our knowledge of stroke recovery mechanisms and the basic neurobiology of language.

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Author Contributions

E.T.M., L.B., J.H.J., J.A.H., and J.F. jointly designed the study. E.T.M., G.R.G., C.R., A.B., A.Y.S., and M.V.S. aided in data collection and analysis. E.T.M. and L.B. wrote the manuscript. All authors commented on the manuscript at all stages.

Potential Conflicts of Interest

J.A.H. and J.H.J. are coinventors on patents related to diffusional kurtosis imaging.

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