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Intensive therapy induces contralateral white matter changes in chronic stroke patients with Broca's aphasia

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ABSTRACT

Using a pre-post design, eleven chronic stroke patients with large left hemisphere lesions and nonfluent aphasia underwent diffusion tensor imaging and language testing before and after receiving 15 weeks of an intensive intonation-based speech therapy. This treated patient group was compared to an untreated patient group ($n = 9$) scanned twice over a similar time period. Our results showed that the treated group, but not the untreated group, had reductions in fractional anisotropy in the white matter underlying the right inferior frontal gyrus (IFG, pars opercularis and pars triangularis), the right posterior superior temporal gyrus, and the right posterior cingulum. Furthermore, we found that greater improvements in speech production were associated with greater reductions in FA in the right IFG (pars opercularis). Thus, our findings showed that an intensive rehabilitation program for patients with nonfluent aphasia led to structural changes in the right hemisphere, which correlated with improvements in speech production.

1. Introduction

Aphasia is a common and devastating consequence of stroke that results in severe communication deficits. Although the long-term prognosis for patients with aphasia who have large left hemisphere lesions is generally poor, emerging evidence suggests that verbal communication in these patients can be improved by therapy (Robey, 1994). However, deciding which treatment to administer can be difficult, and the neural processes underlying successful treatment remain poorly understood.

To date, only a handful of studies on aphasia have examined the effects of therapy on brain reorganization (Musso et al., 1999; Saur et al., 2006; Schlaug, Marchina, & Norton, 2008; Small, Flores, & Noll, 1998; Thompson & Shapiro, 2005). Language training can increase functional activation in the right hemisphere of patients with aphasia (Raboyeau et al., 2008; Richter, Miltner, & Straube, 2008) either transiently or during the recovery process. This is because for patients with large left hemisphere lesions, the only path to regaining speech functions may be via the preserved right hemisphere (Hillis, 2007; Schlaug, Marchina, & Wan, 2011; Schlaug, Norton, Marchina, Zipse, & Wan, 2010). Within the affected left hemisphere, activity increases in perilesional frontal areas are correlated with language gains following speech therapy (Fridriksson, 2010). However, it remains unclear whether intensive language therapy also produces structural brain changes. Here, we used diffusion tensor imaging (DTI), which provides information about white matter composition and integrity by measuring diffusion properties of water molecules, to investigate therapy-induced changes in white matter structures. Derived from the diffusion tensors, fractional anisotropy (FA) is a parameter that indexes the directionality of water diffusion, and reflects the microstructural properties of fiber tracts.

Several studies have revealed changes in white matter composition in healthy individuals when comparing individuals trained in sensorimotor skills with novices (Johansen-Berg, Scholz, & Stagg, 2010). For example, a study from our group showed that singers exhibited lower FA values compared to instrumental musicians in the arcuate fasciculus (Halwani, Loui, Ruber, & Schlaug, 2011). Stronger evidence for the effects of training on white matter is available from longitudinal studies of healthy individuals. In particular, two longitudinal studies have reported FA increases after individuals learned to juggle (Scholz, Klein, Behrens, & Johansen-Berg, 2009), or underwent memory training (Engvig et al., 2011). As shown in the studies cited above, it is clear that white matter changes due to training or expertise can manifest as FA changes – either increases or decreases - and the direction of this change may depend on the brain region or the type of training involved.

We used a pre-post design to examine microstructural changes in the right hemisphere in a group of eleven chronic stroke patients with large left hemisphere lesions and nonfluent aphasia. These

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patients underwent an intensive course of intonation-based speech treatment (treated group), known as Melodic Intonation Therapy (or MIT, Albert et al., 1973), over a 15-week period. In contrast to traditional speech therapy, MIT is a treatment technique that was developed to engage right-hemisphere sensorimotor networks through the use of melodic contour, as well as tapping with the left hand. In a small case series, MIT led to fMRI changes in right-hemisphere auditory-motor regions (Schlaug et al., 2008, 2010). In the present study, our treated patient group underwent DTI scanning and speech and language assessments before and after treatment.

Given that all of our patients had relatively large lesions that encompassed the left inferior frontal gyrus (see Fig. 1), it is plausible that their only path to speech recovery is through the recruitment of homologous regions in the right hemisphere (Hillis, 2007; Rosen et al., 2000; Schlaug et al., 2010). As a control comparison, we also examined the microstructural properties of the same brain regions in nine chronic stroke patients with nonfluent aphasia, who did not receive MIT (the untreated group), but were scanned twice with a similar time interval between scans as the treated group.

All participants were scanned in a 3-Tesla General Electric scanner and the data processed and analyzed using FSL (version 4.1.4). Diffusion data were first corrected for eddy current and head motion and then fitted to a diffusion tensor model at each voxel to generate the FA image, which was then registered to FSL's FA template using linear and nonlinear algorithms. T1-weighted anatomical data were normalized to the skull-included T1 template and lesion maps were drawn by a Neurologist (GS) with experience in stroke and neuroimaging. The lesion map was used to compute an IFG lesion load, which is the percentage of the IFG (taken as the BA44 and BA45 areas of the Harvard-Oxford cortical atlas) that overlaps with the lesion ([volume of overlap]/[total volume of BA44+BA45]).

We used the whole set of Harvard-Oxford cortical ROIs on the right hemisphere, masked it with FSL's FA template at a threshold of FA > 0.25 to limit our region of interest to the white matter regions underlying the cortex, and eliminated any deep white matter regions. Using FSL's *randomise* function, the treatment group's normalized FA pre-treatment data were statistically compared against post-treatment data in a paired design. The statistically significant clusters were used as ROIs to extract FA values from treated and untreated participants. We then conducted a MANOVA with FA DIFFERENCES (FA of timepoint 2 minus FA of timepoint 1) as the dependent variable and GROUP (treated vs untreated) as the fixed effect. In addition, we conducted regressions to predict improvements in speech output by FA changes in ROIs that survived the statistical threshold, while controlling for IFG lesion load.

2. Results

2.1. Search space results

In the treated group, reductions in FA were found in seven clusters (voxels thresholded at $p < 0.005$ (tfce uncorrected) and having a cluster size >20 mm^3). One cluster survived that threshold in the opposite contrast (increase in FA).

2.2. Comparing between treated and untreated groups

Using the seven clusters as ROIs in our mixed-effects MANOVA, we found a significant reduction in FA in the treated group ($p < 0.002$), no significant changes in FA in the untreated group ($p > 0.05$), and a significant GROUP effect ($p < 0.05$) for four clusters after correcting for multiple comparisons. These clusters were centered in the white matter underlying the pars opercularis (MNI [50 17 15]) of the inferior frontal gyrus, pars triangularis (MNI [44 33 8]), posterior superior temporal gyrus (MNI [57-36 17]), and posterior cingulum (MNI [18-36 40]) (see Fig. 2). The reductions in FA were mainly due to a proportionally larger increase in radial diffusivity (see Fig. 3), although neither axial nor radial changes were significant across the two timepoints in either group.

2.3. Correlations with behavioural data

Following MIT, the treated group showed significant improvements in CIUs/min, our measure of speech fluency [$t(10) = 6.34$, $p < 0.001$]. The untreated group did not show a significant change in CIUs/min across the two assessment timepoints. These measures were derived from samples of spontaneous speech obtained in semi-structured interviews. We regressed changes in CIUs/min against changes in FA (post-treatment vs pre-treatment) within the four right-hemisphere brain regions (pars opercularis, pars triangularis, superior temporal gyrus, and posterior cingulum), while correcting for IFG lesion load. Only the pars opercularis cluster in

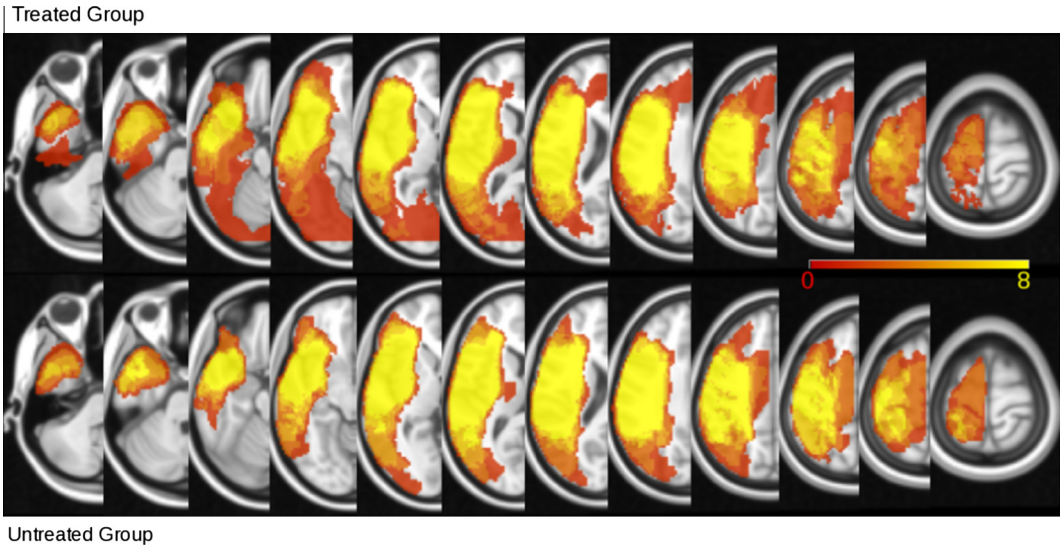

Fig. 1. Lesion density map in treated and untreated groups. Color bar indicates number of patients with lesions in a particular voxel. Bright yellow indicates voxels where at least 8 patients have a lesion.

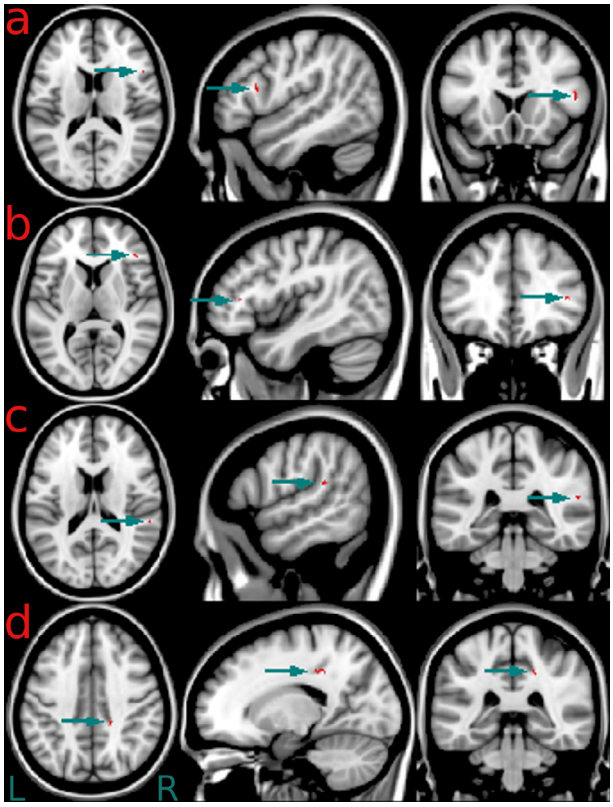

Fig. 2. Locations of significant clusters centered in the (a) IFG, pars opercularis (MNI [50 17 13]), (b) IFG, pars triangularis (MNI [44 33 8]), (c) posterior superior temporal gyrus (MNI [57 −36 17]) and (d) posterior cingulum (MNI [18 −36 40]).

the treated group showed a significant inverse correlation ($r = -0.692$; $p < 0.05$) between changes in FA and improvements in CIUs/min after correcting for IFG lesion load (see Fig. 4).

3. Discussion

Following an intensive course of Melodic Intonation Therapy, patients with chronic Broca's aphasia showed microstructural changes in a number of regions in the contralateral right hemisphere. Specifically, significant reductions in FA were found in the white matter underlying the right IFG (pars opercularis and pars triangularis), the posterior superior temporal gyrus, and the posterior cingulum. The locations of these clusters correspond with areas in and around the arcuate fasciculus. These FA changes were not observed in a group of untreated chronic aphasic patients who were scanned twice with a similar time period in between scans as the treated group.

Previous research has reported increased activation of right-hemisphere regions during language tasks in patients with Broca's aphasia (Saur et al., 2010; Schlaug et al., 2008, 2010). This is particularly relevant to our patients, who had relatively large left-hemisphere lesions, so their only path to recovery might be through the homologous language regions in the right hemisphere (Marchina et al., 2011; Rosen et al., 2000; Schlaug et al., 2008). Here, the observed FA decreases in right-hemisphere regions indicate that an intensive course of Melodic Intonation Therapy led to structural changes, and that these changes were related to improvements in speech production. It remains plausible that structural changes observed in the language regions could support therapy-induced behavioral effects that extend well beyond the treatment period. The present study was only designed to assess language outcomes immediately and up to 4 weeks after the cessation of treatment. Future studies could examine longer term effects of MIT, in particular whether the behavioral changes would last months or even years after treatment if they were supported by structural brain changes.

Both the relearning of mapping sounds to articulatory actions and the sensorimotor control of this function are particularly important for patients with Broca's aphasia who have moderate to severe speech-motor problems. The intonation component of MIT is intended to engage the right hemisphere, which has a dominant role in processing spectral information (Albert, Sparks, & Helm, 1973; Schlaug et al., 2010) and is more sensitive than the left hemisphere to the slow temporal features in acoustic signals (Abrams, Nicol, Zecker, & Kraus, 2008; Zatorre & Gandour, 2008). Both hemispheres can be involved in both singing and speaking, although singing tends to show stronger right-hemisphere activations than speaking (Bohland & Guenther, 2006; Ozdemir, Norton, & Schlaug, 2006). Thus, the slower rate of articulation associated with intonation may increase right-hemisphere involvement. MIT could potentially help aphasic patients with associated apraxia of speech, although in this study, we did not find an association between baseline level of apraxia and improvements in CIUs/min. However, this may be due to the fact that only 6 of our 11 patients in the treatment group underwent assessments of apraxia.

The left-hand tapping component of Melodic Intonation Therapy not only serves as a metronome, but can also facilitate auditory-motor mapping (Lahav, Saltzman, & Schlaug, 2007) and engage a sensorimotor network that controls both hand and articulatory movements (Meister, Buelte, Staedtgen, Boroojerdi, & Sparing, 2009). In our patients, microstructural remodelling was evident in the right inferior frontal gyrus (pars opercularis and pars triangularis), which further highlights the potential role of the right-hemisphere Broca homologue for relearning the mapping of sounds to actions. In addition to the inferior frontal gyrus, FA changes observed in the posterior superior temporal gyrus correspond to other endpoint of the arcuate fasciculus, which plays an important role in the mapping of sounds to articulatory actions as well as the sensorimotor feedback and feedforward control of vocal output (Duffau, Peggy Gatignol, Mandonnet, Capelle, & Taillandier, 2008; Glasser & Rilling, 2008; Guenther, Ghosh, & Tourville, 2006; Rilling et al., 2008; Schlaug et al., 2010). The posterior cingulum is located adjacent to the arcuate fasiculus as well as the superior longitudinal fasciculus, and could potentially indicate changes in white matter composition in areas that intersect with these major fiber bundles through the parietal lobe. Taken together, the structural changes in the present study highlight the therapeutic effects of an intensive rehabilitation program (such as Melodic Intonation Therapy) for facilitating speech production in patients with Broca's aphasia through both auditory-motor mapping and goal-directed behavior of monitoring articulatory functions and vocal output.

Several studies on healthy individuals have reported training-induced modification of white matter architecture. While some showed training-related FA increases (Engvig et al., 2011; Scholz et al., 2009), others reported FA decreases (Elmer, Hanggi, Meyer, & Jancke, 2011; Halwani et al., 2011) and this discrepancy may reflect the different mechanisms by which different brain regions can remodel. Variations in FA across and within individuals over time can be influenced by factors such as fiber density, axon diameter, myelination, axon collateral sprouting, cell membrane density, and fiber coherence (Budde et al., 2007; Hoeft et al., 2007; Sidaros et al., 2008; Song et al., 2003). Because higher FA values indicate more aligned fibers, our finding of lower FA values over time in the treated group, could indicate less alignment of fibers as well as more axonal sprouting (Sidaros et al., 2008) and more branching (Hoeft et al., 2007) in close proximity to the cortical target regions. The posterior STG and the opercular and triangular IFG

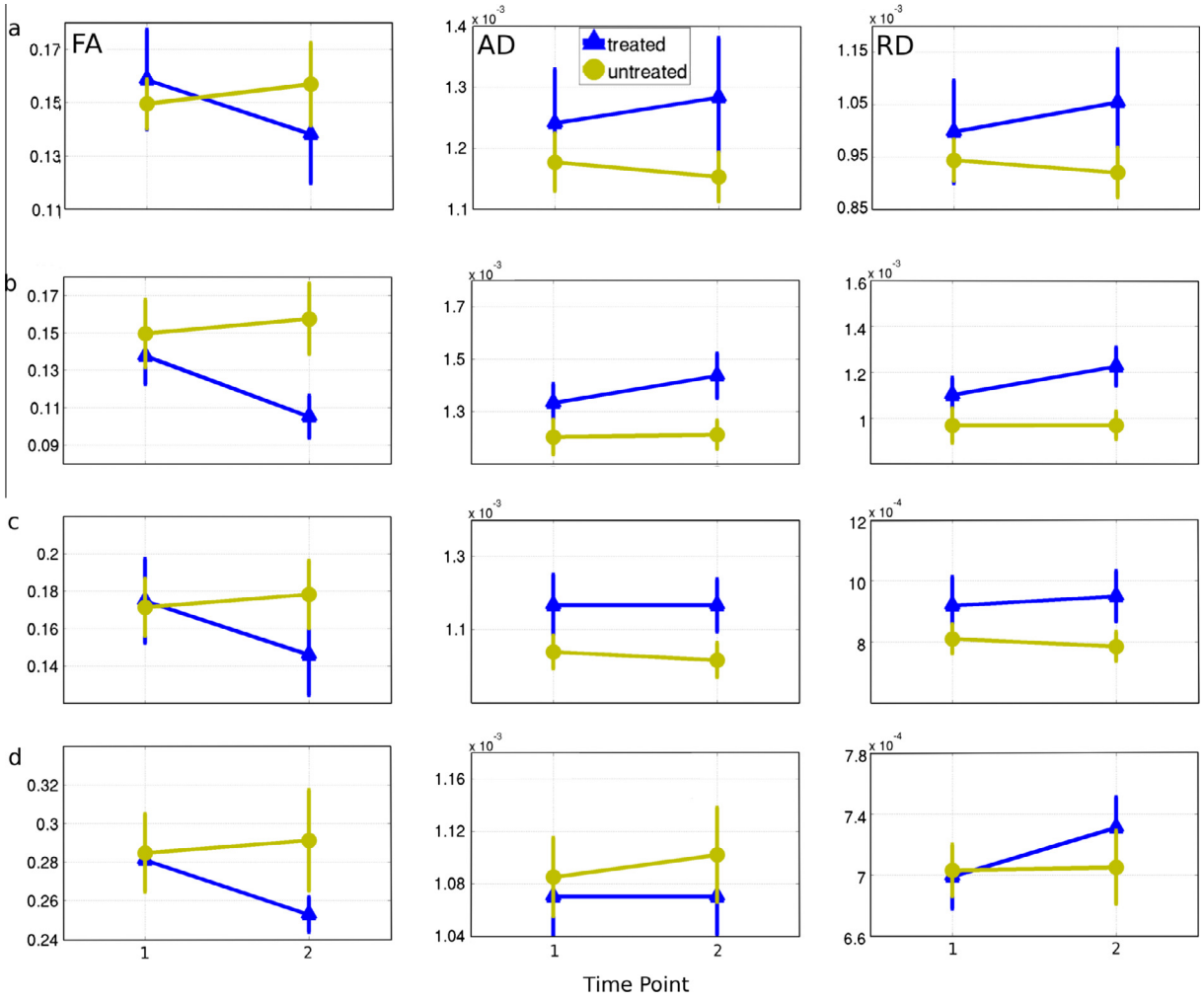

Fig. 3. Changes (with standard error bar) in mean FA, Axial Diffusivity and Radial Diffusivity (mm^2/sec) in treated patients compared to untreated patients across the two scan timepoints in the four significant clusters: (a) pars opercularis of the IFG (b) pars triangularis of the IFG (c) posterior superior temporal gyrus and (d) posterior cingulum.

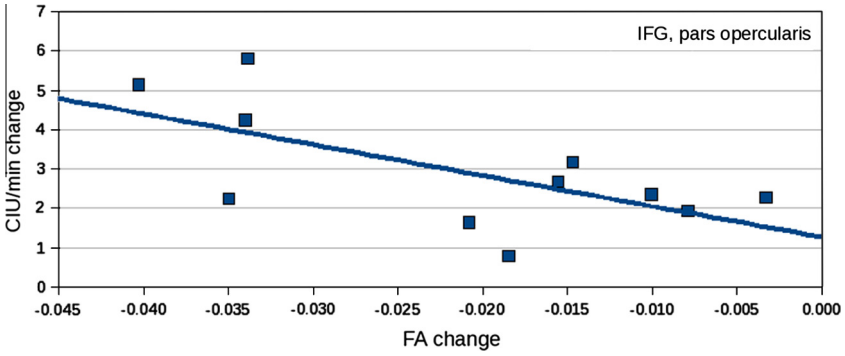

Fig. 4. Linear regression of changes in FA with changes in speech fluency (CIUs/min) in the treated patient group in the right IFG pars opercularis clusters ($r = -0.654$; $p < 0.05$).

are the cortical target regions of language tracts such as the arcuate fasciculus. The greater reduction of FA in our study was associated with a greater improvement in speech fluency.

There are a few caveats associated with the diffusion imaging method used in the present study. Among them is the use of a relatively short DTI sequence (<5 min), which was used to minimize movement artifacts in our group of moderately to severely impaired patients. This resulted in a diffusion sequence that had non-isotropic voxels, single b-values, and 25 diffusion directions. Acquiring higher resolution images with multiple b-values could improve the accuracy of parameter estimation. Nonetheless, any systematic errors associated with our DTI sequence should be equally evident across all individuals and groups (i.e., treated and untreated groups).

In summary, our pre-post study provides novel evidence for treatment-induced changes in white matter structures of the

preserved right hemisphere in chronic stroke patients, which predicted recovery of speech functions. In the future, diffusion imaging methods with higher-resolution scans, multiple *b*-values (Scherrer & Warfield, 2012), and estimated with multi-fascicle models (Taquet et al., 2014) might help in improving our understanding of the microstructural changes associated with recovery from nonfluent aphasia.

4. Method

4.1. Participants

Eleven chronic stroke patients (**mean:** *age:* 55.8 years [SD 9.4]; *months post-stroke to scan date:* 26.6 [SD 19.9]; *interscan interval:* 5.8 months [SD 1.9]; *lesion size:* 185 cc [SD 71]; 2 females) with nonfluent Broca's aphasia participated in the treated group of the study. Nine patients (**mean:** *age:* 56.7 years [SD 9.1]; *months post-stroke to scan date:* 33.0 [SD 32.6]; *interscan interval:* 6.7 months [SD 6.1]; *lesion size:* 199 cc [SD 90]; 0 females) were in the untreated group. All patients had only one ischemic stroke in the territory of the left middle cerebral artery and moderate to severe nonfluent aphasia (see Table 1 and Fig. 1).

All patients had received several courses of traditional speech-therapy prior to becoming part of this study. During the study, however, the patients did not receive any additional speech interventions other than the two treatment conditions: Melodic Intonation Therapy (for the treated group) or no treatment (for the untreated group). Each patient in the treated group underwent speech and language assessments as well as DTI before and after an intensive course of Melodic Intonation Therapy, which consisted of 1.5 h of therapy per day, 5 days per week over approximately 15 weeks, for a total of 75 sessions and at least 110 h of therapy. The patients in the untreated group underwent the same speech and language assessments and DTI twice with a similar time-period in between scans as the treated group.

4.2. Training procedure and behavioral assessment

Melodic Intonation Therapy is an intonation-based speech therapy technique that uses intoned patterns to exaggerate the normal prosodic content of speech (Albert et al., 1973). The therapist instructs the patient to intone simple phrases on two pitches while tapping their left hand with each syllable.

To assess changes in speech fluency before and after treatment, spontaneous speech samples were collected through a semi-structured conversational interview about patients' background, stroke rehabilitation, and daily activities. Videotapes of these samples were transcribed and Correct Information Units per minute (CIUs/min) (Nicholas & Brookshire, 1993), a measure of speech fluency, were determined by a researcher who had not interacted with the patients. A reliability assessment was conducted post hoc by a second rater who was blinded to the patients as well as to assessment timepoints. The inter-rater reliability was >0.9. The dependent variable was the number of correct information units that each patient produced in the first minute of their answers (CIUs/min). In addition, 6 of 11 patients in the treated group and 9 of 9 patients in the untreated group underwent subtests (Diadochokinetic Rate and Oral Apraxia) of the Apraxia Battery for Adults (ABA-2; Dabul, 2000).

4.3. Image acquisition

All patients underwent MRI scanning using a 3-Tesla General Electric (Fairfield, CT) scanner. The treated group was scanned before and after treatment; the untreated group was scanned twice, with a scan interval similar to that of the treated group. DTIs were acquired using a single-shot, spin-echo, echo-planar imaging sequence (TE = 86.9 ms, TR = 10,000 ms, FOV = 240 mm, matrix size = 128 × 128 voxels, slice thickness = 5 mm, resolution: 1.87 × 1.87 × 5.0 mm^3, no skip, NEX = 1, axial acquisition, 25 non-collinear directions with *b*-value = 1000 s/mm^2, 1 image with *b*-value = 0 s/mm^2). Anatomical scans were acquired using high-resolution strongly T1-weighted Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence (voxel size 0.93 × 0.93 × 1.5 mm).

4.4. Preprocessing of diffusion tensor imaging data

The diffusion data were preprocessed using FSL (4.1.4; http://www.fmrib.ox.ac.uk/fsl). The images were first corrected for eddy current and head motion by affine multi-scale two-dimensional registration. We then fitted a diffusion tensor model at each voxel using *dtifit* to calculate the lambda values for each principle eigenvector (λ_1, λ_2, λ_3) and FA. We then registered the diffusivity images to the FMRIB standard FA template using linear and non-linear algorithms, with the aid of lesion masks.

4.5. Preprocessing of T1-weighted data

The anatomical images were normalized to FSL's skull-included T1 template. Lesion maps were drawn on the normalized T1 images by a neurologist who has extensive experience in neuroimaging of stroke patients, and was blinded to the groups. Lesion maps were used to calculate the IFG lesion load (percentage of IFG overlapped by the lesion map). We used BA44 and BA45 areas of the Harvard-Oxford cortical ROIs atlas (www.cma.mgh.harvard.edu/fsl_atlas.html) as the IFG. The IFG lesion load is the percentage overlap of the IFG, taken as BA44 and BA45 regions of the Harvard-Oxford atlas, with the lesion mask ([volume of overlap]/[total volume of BA44+BA45]).

4.6. Defining the search space

We used the whole set of Harvard-Oxford cortical ROIs on the right hemisphere and masked it with FSL's FA template at a threshold of FA > 0.25. This provided us with a search space that was limited to the white matter regions underlying the cortex, and eliminated any deep white matter regions. Within this search space, we used the *randomise* function in FSL to statistically test for differences between the treated patients' normalized FA data pre-treatment versus post-treatment in a paired design with FSL's threshold-free cluster enhancement (TFCE) methodology (Smith and Nichols, 2009) and 10000 permutations. The statistically significant clusters, taken as uncorrected $p < 0.005$ at cluster >20 mm^3, were used as ROIs to extract the FA values from both the treated and untreated groups.

4.7. Statistical analyses

Using the cluster-extracted FA values, we conducted a MANOVA with FA DIFFERENCE (FA of timepoint 2 minus FA of timepoint 1) per cluster as the dependent variable and GROUP (treated vs untreated) as the fixed effect. In addition, we correlated changes in FA in ROIs identified as being significantly different over time between treated patients and untreated patients with improvements in speech fluency in patients, while controlling for IFG lesion load.

Table 1
Background information of the patients in both the treated (Tx) and untreated (nTx) groups. "Hd" refers to handedness. "Post Stroke" refers to the time interval between onset of stroke and scan date. "Scan Interval" refers to the time between the two scanning sessions. "IFG-LL" or IFG lesion load is the percentage of the IFG that overlaps with the lesion. "Word Discrimination", "Commands", and "Word Repetition" are subtests of the BDAE. "DDK rate" refers to the diadochokinetic rate and together with the oral apraxia score are subtests of the Apraxia Battery for Adults-Second Edition (ABA-2) battery (Dabul, 2000). "BNT" refers to the raw scores from the short form of the Boston Naming Test (max score of 15). "CIUs/min" is the speech production/fluency variable measured as correct information units per minute from a semi-structured interview with the patient. Tx-group was assessed pre- and post-treatment with a mean interval of 5.9 months. nTx-group was assessed at two timepoints (T1 and T2) with a mean interval of 6.7 months.

Treated	Gender	Age years	Hd	Post stroke months	Scan interval months	Lesion size cc	IFG-LL % overlap	Word discrim. % correct	Commands % correct	Word rep. % correct	DDK rate	Oral Apraxia Max = 50	BNT Max = 15	Fluency (pre) CIUs/min	Fluency (post) CIUs/min
1	M	55.4	R	7.8	6.7	250	92	92	27	30	5	16	5	1.3	2.9
2	M	70.7	R	12.0	9.1	73	79	100	87	10	–	–	8	1.7	7.5
3	F	54.2	R	11.7	3.9	128	23	88	70	20	3	28	6	1.9	4.3
4	M	52.5	R	25.4	4.9	212	84	62	60	70	6	34	5	5.6	10.8
5	M	66.0	R	43.6	5.1	227	78	82	73	40	2	25	3	0.5	2.8
6	M	57.7	R	55.1	6.4	123	1	–	83	64	–	–	5	0.6	2.6
7	M	55.0	R	65.9	2.5	296	96	45	–	25	–	–	1	1.1	1.9
8	F	47.7	L	11.9	5.2	261	71	60	58	60	–	–	0	0.3	2.9
9	M	56.2	R	25.8	8.1	153	37	65	67	30	6	39	7	1.1	3.4
10	M	62.7	R	23.6	5.2	112	70	80	33	70	11	26	4	1.0	5.3
11	M	35.3	R	9.5	6.5	199	64	94	100	50	–	–	4	1.3	4.4
Avg		54.8		28.1	5.9	191	65	79	67	44	5.5	28.0	5.2	1.9	4.6
Stdev		9.5		19.7	1.8	71	29	18	22	21	3.1	7.9	3.6	2.0	2.6
Not treated	Gender	Age years	Hd	Post stroke months	Scan interval months	Lesion size cc	IFG-LL % overlap	Word discrim. % correct	Commands % correct	Word rep. % correct	DDK rate	Oral Apraxia Max = 50	BNT Max 15	Fluency (T1) CIUs/min	Fluency (T2) CIUs/min
1	M	45.3	R	11.3	5.5	247	61	28	60	50	4	11	0	0.5	0.7
2	M	62.1	R	14.3	3.1	71	33	97	93	0	1	40	0	0.6	0.5
3	M	65.8	R	110.9	1.9	189	62	92	100	20	2	27	3	3.6	2.3
4	M	64.5	R	25.0	18.5	227	78	82	73	40	2	22	0	1.0	0.5
5	M	66.8	L	9.8	2.6	155	64	62	47	10	1	31	0	0.1	0.3
6	M	44.9	R	51.7	16.3	259	84	100	75	60	9	46	14	6.7	6.8
7	M	50.9	R	8.3	4.8	63	18	74	73	20	0	37	2	0.4	0.1
8	M	61.4	Amb	26.6	4.6	342	79	53	27	80	11	11	0	0.6	0.1
9	M	49.1	R	38.9	3.1	241	62	73	20	40	9	32	4	3.4	3.7
Avg		56.7		33.0	6.7	199	60	73	63	36	4.3	28.6	2.6	1.9	1.7
Stdev		9.1		32.6	6.2	91	22	23	27	26	4.2	12.2	4.6	2.2	2.3

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