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Changes in maps of language function and the integrity of the arcuate fasciculus after therapy for chronic aphasia

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Abstract

A patient with chronic aphasia secondary to unilateral stroke in the left hemisphere underwent language testing, diffusion tensor imaging (DTI), and functional imaging using magnetoencephalography (MEG) at four time points: 3 weeks prior to, immediately prior to, immediately after, and 3 months after Constraint Induced Language Therapy (CILT). Performance on language tests involving visual naming and repetition of spoken sentences improved between the immediately prior to and immediately after CILT testing sessions, but not between the pre-CILT sessions. MEG activation in putative pre-morbid language areas of the left hemisphere and homotopic areas of the right hemisphere increased immediately after therapy, as did integrity within the arcuate fasciculus bilaterally. These changes were not evident between the two pre-CILT sessions. While some of these functional, neurophysiological and structural changes had regressed 3 months after therapy, all remained at or above baseline levels. Results provide evidence for an association between improvement in functional status and the increased integrity within a white matter tract known to be involved in language function and its contralateral homologue, as well as increased neurophysiological activity in areas that have the potential to subserve language function bilaterally.

Introduction

Chronic aphasia is one of the most common sequelae of stroke, occurring in from 10% to 18% of patients (e.g. Kertesz, 1984; Pedersen, Jorgensen, Nakayama, Raaschou, & Olsen, 1995) and posing a very significant burden for patients and caretakers. While there is evidence that treatment for aphasia during the chronic period can improve function, the results are variable both within and across therapeutic approaches. With the recent advances in neuroimaging it has become possible to characterize the reorganization that occurs in the brain in response to therapy, and the conditions under which this reorganization occurs. We present here a case study in a single patient regarding changes in the integrity within the arcuate fasciculus, a white matter tract known to be involved in language function, after therapy for chronic aphasia secondary to stroke. The patient underwent language evaluation, diffusion tensor imaging (DTI), and functional imaging using magnetoencephalography (MEG) at four time points: 3 weeks prior to therapy with no intervening therapy during this time period, immediately prior to therapy, immediately after therapy and 3 months after

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therapy. Thus the first two time points serve as a control for the third, while the follow-up session serves as an indication of the stability of the findings.

DTI characterizes water molecule mobility *in vivo*, allowing for the exploration of white matter tract integrity (Basser & Pierpaoli, 1998). Highly organized fiber bundles in white matter tracts constrain motion of water molecules along a preferred direction parallel to the orientation of the tracts. The degree of facilitation of diffusion of water molecules along their main direction, or diffusion anisotropy, can be quantified, providing a scalar index, fractional anisotropy (FA), of the organization of specific white matter tracts (Le Bihan et al., 2001). FA values are generally high in white matter, and focal reductions in FA values, indicating an alteration in tract integrity, can be detected relative to controls (e.g. Werring et al., 2000) or the unaffected hemisphere (e.g. Moller et al., 2007) after stroke. In the current study we chose to focus on the integrity of the arcuate fasciculus (AF). The AF is thought to play a significant role in language function (Geschwind, 1970) and damage to the AF has been implicated in aphasia secondary to stroke in previous studies using DTI (Breier, Hasan, Zhang, Men, & Papanicolaou, 2008; Nucifora, Verma, Melhem, Gur, & Gur, 2005; Powell et al., 2006). In one of the few studies relating changes in white matter integrity as indexed by DTI to the effects of language rehabilitation Schlaug et al. (Schlaug, Marchina, & Norton, 2009) found an increase in the number of fibers and volume of the arcuate fasciculus in the right hemisphere after melodic intonation therapy for non-fluent aphasia.

MEG is a non-invasive functional imaging methodology that directly indexes neuronal discharge during task performance and has been shown to be sensitive to neurophysiological changes related to rehabilitative therapy for aphasia secondary to stroke (Breier et al., 2009; Breier, Maher, Schmadeke, Hasan, & Papanicolaou, 2007; Breier, Randle, Maher, & Papanicolaou, 2009). Functional imaging studies relating changes in patterns of brain activity associated with language function and response to aphasia therapy provide a varied picture. While some find a relationship between improvement in language function and increased activation in the right hemisphere after therapy (e.g. Musso et al., 1999; Raboyeau et al., 2008), others find increased activity in the dominant hemisphere (e.g. Belin et al., 1996; Leger et al., 2002; Meinzer et al., 2008) or bilateral increases in activation (e.g. Fridriksson & Morrow, 2005; Pulvermuller, Hauk, Zohsel, Neininger, & Mohr, 2005; Vitali et al., 2007) to be related to behavioral improvement. Breier et al. (Breier et al., 2009), in one of the larger studies of this type, found that while there was evidence for right hemisphere participation in a positive response to therapy the best response was associated with an increase in peri-infarct activity in the dominant hemisphere. There are a number of factors that potentially contribute to variance among findings, including aphasia type, lesion location and size, imaging modality, activation tasks used in the scanner, and therapy type and dosage.

Constraint Induced Language Therapy (CILT) is an approach to therapy for language dysfunction based on the principles of use-dependent learning. The approach was first described by Pulvermuller et al. (2001), and is a modification of use-dependent learning applications in motor rehabilitation, referred to as Constraint Induced Movement Therapy (Taub, 2004; Taub, Uswatte, & Pidikiti, 1999). The principles of constraint induced approaches to therapy include: (1) constraint to the impaired modality; (2) restraint of the unimpaired modality (in this case alternative modes of communication), and, (3) massed practice occurring in an enriched environment using behavioral shaping. In the case of CILT, patient's responses are limited to the speech modality only, and the patients are restrained from using any other means of communication (such as pointing, gesture, writing etc.).

Methods

Case History

The patient was a 62 year old premorbidly right-handed African American male who was employed full-time as a salesman when he suffered a stroke in the distribution of the left middle cerebral artery (MCA), including virtually all of the left frontal lobe, insula and subcortical areas up to and including the internal capsule, five years prior to administration of CILT. Initial symptoms prior to hospital admission at the time of the stroke included right-facial droop as well loss of expressive language. The patient was diagnosed with severe Broca's aphasia at the time of acute hospital admission, although he was also not able to completely and consistently follow commands, exhibiting decreased comprehension. A CT scan done at the time reportedly indicated a left frontal hypodensity consistent with an infarct in the distribution of the left MCA. The patient had undergone traditional therapy immediately after the stroke for a period of approximately five months, but none since.

CILT Methods

Although serial scanning was performed on only one subject, therapy was administered in a dyad and consisted of three-hour sessions, four days a week, for three weeks for a total of 36 hours of treatment. Constraint was operationally defined as limiting the response to spoken verbal production only. All other modes of communication were inhibited. The treatment task was a dual card task where each patient took turns either requesting a matching card from a semantic category from the other patient, or responding to that request. A visual barrier was placed on the table between the patients so they could not see each other except for eye contact.

Performance on the dual card task was used as the treatment (TX) response measure. The spoken request was scored for the number of Correct Information Units (CIUs). Each lexical item counted as one CIU except for the question phrase, for which all correct forms of the question were counted as 1 CIU, regardless of the number of words in the question phrase. For example: Do you have a short pencil? consists of a question phrase, “Do you have” = 1 CIU, an adjective, “short” = 1 CIU, and a noun, “pencil” = 1 CIU, for a total of 3 CIUs.

CIU data were collected at the same time points as the DTI and MEG scanning sessions: 3 weeks prior to, immediately prior to, immediately after, and 3 months after therapy. At each of these time periods there were three sessions, each conducted on a different day. At each session the patient was given a series of 20 cards chosen randomly from those used for CILT (10 cards containing pictures depicting high frequency adjectives and nouns and 10 cards containing pictures depicting low frequency adjectives and nouns) and asked to produce the three lexical items described above for each card.

MEG methods—At each MEG scanning session the patient was given a recognition memory task for spoken words while data were collected in the scanner. Changes in neurophysiological response to this task have been shown to correlate with positive response to CILT (Breier et al., 2009). The word list consisted of 165 English words with five words used as targets and the remaining 160 as distractors. Four blocks of 45 trials each were created for each scan, with the five targets presented in random order in each block among 40 new distractors for a total of 180 trials per scan. Two separate scans were obtained at each of the four scanning sessions. The target stimuli were presented consecutively for study immediately prior to the MEG scan as many times as was necessary for the patient to raise the left index finger to each of the five stimuli consecutively. The patient responded in the same manner during MEG data collection.

Scanning was performed in a whole-head neuromagnetometer (4D Neuroimaging, San Diego, CA.) equipped with 248 gradiometer sensors and housed in a magnetically shielded room designed to reduce environmental magnetic noise. The recorded signals were filtered online with a band pass between 0.1 and 20 Hz, and digitized at a rate of 254 Hz and adjusted relative to the mean amplitude in the 150 ms pre-stimulus period to remove DC-offset. The data were then submitted to an adaptive noise reduction procedure, and, after artifact rejection, averaged across trials within each sensor. These averaged data were submitted to a set of fully automated procedures which scanned the averaged digitized evoked magnetic fields and identified at each point in time (every 4 ms) the presence of single dipolar distributions, estimated the channel grouping that best covered each distribution, and used the portion of the flux distribution covered by such channel groupings to estimate the underlying dipolar source using the standard model (Sarvas, 1987). Up to 4 sources could be estimated at each time point. Those dipolar sources that met the criteria of acceptability (Correlation ≥ 0.9 , Confidence volume $\leq 30 \text{ cm}^3$) from each of the recording sessions were then compared according to their (a) degree of latency overlap and (b) spatial proximity in order to produce the final spatiotemporal maps corresponding to language function.

Source locations, which were initially computed in reference to the MEG Cartesian coordinate system mentioned above, were co-registered on the T1-weighted, magnetic resonance image (MRI) obtained from the patient. Transformation of the MEG coordinate system into MRI-defined space was achieved with the aid of three lipid capsules inserted into the ear canals and attached to the nasion which were easily visualized on the MRIs, using the MRI Overlay tool which is part of the 4-D Neuroimaging software. Location of individual dipoles was determined with the use of a standard MRI atlas of the human brain (Damasio, 1995).

MRI Methods

MRI Acquisition—All MRIs were performed on a Philips 3T scanner with SENSE (Sensitivity Encoding) technology using an 8 channel phase array head coil. After conventional scout and T2-weighted sequences, a three-dimensional isotropic T1-weighted sequence (MPRAGE) was performed in the coronal plane. Acquisition parameters of the isotropic 3D MPRAGE sequence were as follows: repetition time/echo time = 8.5/4.0 ms; flip angle= 6°; square field of view= 240×240 mm; matrix= 256×256; slice thickness=0.94 mm; in-plane pixel dimensions (x,y)=0.94,0.94 mm; number of excitations (NEX)=1; scan time ~ 6 minutes. The DTI sequence consisted of a single-shot spin-echo diffusion sensitized echo-planar imaging sequence with the following parameters: 21 non-collinear equally distributed diffusion encoding directions (e.g. Icosa21 (Hasan and Narayana, 2005); repetition time/echo time=6100/84 ms; b=0, and 1000 sec/mm²; square field-of-view=240×240 mm; matrix=256×256; slice thickness=3.0mm; in-plane pixel dimensions (x,y)=0.94,0.94; SENSE acceleration factor=2. Each encoding direction was repeated twice and magnitude-averaged on the scanner to enhance the signal-to-noise ratio (Conturo, McKinstry et al. 1995; Hasan 2007). Therefore, effectively 50 images were acquired for each of the 44 axial sections to cover the whole-brain. The total DTI acquisition time was approximately 7 min and resulted in a signal to noise ratio-independent DTI-metric estimation (Hasan 2007).

MRI Analyses—The DTI dataset was processed and analyzed using FSL v4.1.2 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Specifically, minor head motion and eddy currents are corrected with the Eddy Current Correction tool included in FSL's Diffusion Toolbox v2.0. Subsequently, skull-stripping and removal of non-brain tissue was performed using BET v2.1. The diffusion tensors were reconstructed using FSL's DTIFIT tool within

the Diffusion Toolbox. FSL's probabilistic tractography features required additional pre-processing using the Diffusion Toolbox, notably BedpostX.

DTI co-registration—FMRIB's Linear Image Registration Tool v5.5 (FLIRT) was used to perform co-registration between each subject's T1-weighted series and corresponding non-diffusion-weighted series from the DTI dataset (Jenkinson, Banner, Brady and Smith, 2002). The resultant transformation matrix, and the calculation of its inverse, provides the basis for co-registering the tractography results (performed in diffusion space) with the T1 volume.

Region of Interest and Fiber Tracking Analyses for DTI Data—Using FSL's ProtrackX tool, probabilistic tractography methods were used to perform fiber tracking of the arcuate fasciculus (AF). Combined use of color-coded tensor maps generated by FSL's DTIFIT tool co-registered with the high resolution anatomy available in the T1-weighted image series facilitated tractography by utilizing the seed-to-mask feature in ProtrackX where one mask is used as the seed mask and one or more masks are used as waypoints/targets. Such “masked-based” tractography reliably generates well-characterized tracts across study participants while preserving individual topology. For tractography of the arcuate fasciculus, the directionally encoded tensor map was used for manual delineation of seed and target masks. The placement of seed and target regions for tracking the arcuate fasciculus were guided by methods described by Vernooij et al., (2007). Using the directionally color-coded tensor maps (e.g. RGB maps) produced by dtifit in FSL, a seed mask was placed in the posterior parietal portion of the AF and a target mask in the descending portion of the AF in the posterior temporal lobe (see Figure 1).

The output of ProtrackX was thresholded for FA values > 0.20 to constrain the resultant pathway to white matter voxels. Since cortical gray matter and CSF voxels have lower FA values than 0.20, this thresholding step is commonly used by either the tracking algorithm itself (Faria et al., 2010) or after the algorithm has completed its probabilistic analyses of connected voxels between a seed and target. The Mean FA of the AF pathway was determined in each hemisphere by averaging all FA values across all voxels included within the AF pathway. Since a single rater (JJ) delineated all of the seed and target masks, we used FLIRT to linearly transform each mask into standard space (e.g. FMRIB58-FA-1mm) to review how well each mask delineated the same region (e.g. dorsal seed and ventral target masks) across time points (see Figure 2 where 3 weeks pre-CILT =orange; immediately pre-CILT=dark blue; immediately after CILT=green; 3 weeks post-CILT=light blue).

Results

Behavioral changes after therapy

Performance on selected language tests at the four time points relative to the administration of CILT, including the CILT outcome measure % CIUs, the Western Aphasia Battery (WAB) Aphasia Quotient (AQ) and Comprehension and Repetition AQs as well as the Action and Boston Naming Tests are presented in Table 1. There was little evidence for significant change in any of the measures between the two pre-CILT testing sessions. % CIUs increased after therapy as did the global WAB index. Most of this change was due to improved ability to repeat spoken sentences. Both verb and noun naming also increased immediately after CILT. While gains in % CIUs were lost after 3 months, gains in sentence repetition and naming were relatively stable. Comprehension was relatively intact and stable across testing sessions.

Neurophysiological changes after therapy using MEG

Early (before the resolution of the N1m) dipole activity was generally observed within primary auditory cortex. This activity was not used in the study as it represents primary sensory processing. Regions of interest in the left hemisphere were chosen based on their likely premorbid participation in language function, and included inferior frontal lobe/insula, superior and middle temporal gyri, and supramarginal and angular gyri in the left hemisphere. Homotopic areas in the right hemisphere were also chosen as potential targets for language reorganization. Maps of activity in these ROIs for the four time points relative to CILT are presented in Figure 3. The total number of thresholded dipoles summed across these areas at each of the time points relative to CILT in each hemisphere is presented in Figure 4. Prior to therapy there was no activation in the putative premorbid language areas within the left hemisphere while a very dense map was evident at both pre-therapy sessions in the posterior superior temporal gyrus in the left hemisphere. After therapy, activation was detected in the scanner in the left temporal lobe at both scanning sessions. Interestingly while immediately after the scanning session the map in the right hemisphere was essentially the same as before, activity became more diffuse at the 3-month follow-up scanning session.

Changes in the integrity of the AF after therapy using DTI

DTI scans at the four time points relative to CILT are presented in Figure 5. FA values for the AF at each time point relative to CILT are presented in Figure 6. For comparison purposes the average FA values for the AF in each hemisphere for two control subjects taken from a single scan for each (mean age 41) is included as a dashed line in the Figure 6. DTI tractography indicates increased integrity (higher FA values) in the AF in the left hemisphere immediately after therapy, although the degree of integrity in the left AF remains less than that of controls. In contrast FA values in the right AF remain stable immediately after therapy. In addition, there was evidence that the fibers of the right AF were encroaching on the left AF immediately after therapy. FA values in the left AF increase again at the 3 month post-therapy scanning session, but remain below control levels, while again FA values in the right AF remain stable and at control levels.

Discussion

The current case study afforded the unusual opportunity to evaluate neurophysiological and structural changes associated with therapy for chronic aphasia, as well as the specificity of these changes to therapy and their stability in a single patient. We observed an improvement in language function immediately after therapy, particularly in the ability to repeat spoken sentences, naming and performance on the CILT treatment task. There were essentially no changes in these measures between the two pre- and post-therapy sessions suggesting improvement in language function was specific to the effects of therapy. These behavioral changes were associated with a bilateral increase in MEG activity in the temporal lobe during a receptive language task in areas potentially involved with language function, included inferior frontal lobe/insula, superior and middle temporal gyri, and supramarginal and angular gyri in the left hemisphere and homotopic areas in the right hemisphere. In addition, there was evidence for an increase in integrity of the fibers of the arcuate fasciculus in the left hemisphere as well as the fibers that cross in the splenium of the corpus callosum between the left and right AF.

Three months after therapy naming ability and performance on the treatment task had regressed, although not back to baseline levels. Performance on the sentence repetition subtest of the WAB improved at the 3-month follow-up testing session. MEG activity was reduced bilaterally, but remained apparent in the left hemisphere and was at approximately baseline levels in the right. Interestingly the tight map in the right posterior superior

temporal gyrus at all three previous scanning sessions in the MEG data became somewhat more diffuse, becoming apparent in right SMG, and inferior frontal/insula as well as posterior STG. The FA value in the left AF increased at the 3 month follow-up session while right hemisphere values remained stable. Ours is a single case study, and the decrease in left hemisphere MEG activity at the 3 month follow-up session that accompanied the increase in FA value in the left AF may represent random variance between scanning sessions. Alternatively, areas subserving recovery of function may become more efficient after a period of time and exhibit less activation on follow-up while continued utilization of a white matter tract may result in improved integrity.

DTI studies indicate interhemispheric asymmetries in FA values after stroke (Moller et al., 2007; Thomalla, Glauche, Weiller, & Rother, 2005) and DTI has been shown to be sensitive to the time course of Wallerian degeneration after stroke in the corticospinal tract (e.g. Thomalla, Glauche, Weiller, & Rother, 2005; Werring et al., 2000). A reduction in fractional anisotropy in these tracts after stroke, indicating a decline in axonal integrity, is correlated with a reduced motor function (e.g. Liang et al., 2007; Moller et al., 2007; Puig et al., 2010). There are relatively few studies relating the integrity of white matter tracts after stroke and cognitive function, and even fewer indexing changes in relevant tracts across therapy and their relation to changes in functional status across therapy. Breier et al. (2008) found that reduced FA values in the SLF and AF were correlated with poorer sentence repetition scores in patients with chronic stroke. Zhang et al. (2009) found that reduced FA values in the left AF in patients with conduction aphasia as compared controls. Schlaug et al. (2009) found an increase in the number of fibers and volume of the arcuate fasciculus in the right hemisphere after melodic intonation therapy for non-fluent aphasia.

Data obtained from anatomical and DTI studies in humans, along with anatomical studies in non-human primates, indicate The AF is a subdivision of the superior longitudinal fasciculus. It stems from the caudal part of the superior temporal gyrus arches around the caudal end of the Sylvian fissure and extends to the lateral prefrontal cortex (Makris et al., 2005). The AF is thought to link Broca's area in the inferior frontal gyrus of the dominant hemisphere to Wernicke's area in the posterior aspect of the superior temporal gyrus in the dominant hemisphere (Geschwind, 1970). Damage to the AF due to stroke is traditionally associated with conduction aphasia, or difficulty with repetition of orally presented language despite intact comprehension and the ability to produce spontaneous speech (Geschwind, 1970). Consistent with a role for the AF in language function are findings of a greater fiber density, tract volumes and FA values in the AF/SLF in the dominant hemisphere (Nucifora, Verma, Melhem, Gur, & Gur, 2005; Powell et al., 2006).

Given the evidence for a significant role for the AF in language function, as well as previous DTI studies in patients with a history of stroke indicating a correlation between damage to the AF and language dysfunction we focused the current case study on the AF. Consistent with other studies indicating DTI's sensitivity to the relationship between damage to the AF and language function in stroke we observed a significant increase in the integrity of the AF across the application of therapy. This change was accompanied by an increase in activation during a receptive language task in the MEG scanner as well as functional improvement, particularly in sentence repetition and naming.

Functional imaging studies in aphasia rehabilitation provide a varied picture regarding the role of the each hemisphere in supporting the recovery of function. While some studies find a relationship between improvement in language function and increased activation in the right hemisphere after therapy (e.g. Raboyeau et al., 2008), others find increased activity in the dominant hemisphere (e.g. Belin et al., 1996) or bilateral increases in activation (e.g. Fridriksson, Nettles, Davis, Morrow, & Montgomery, 2006; Pulvermuller, Hauk, Zohsel,

Neininger, & Mohr, 2005; Vitali et al., 2007) to be related to behavioral improvement. While the current study is obviously limited in its generalizability, the observations are consistent with the possibility that immediate response to therapy may involve bilateral neurophysiological and structural changes working in concert. The follow-up data suggest that while regression in functional, neurophysiological and structural status may occur, some of these residual changes persist over this time period. Of course larger and temporally more protracted studies are required to confirm and extend this hypothesis.

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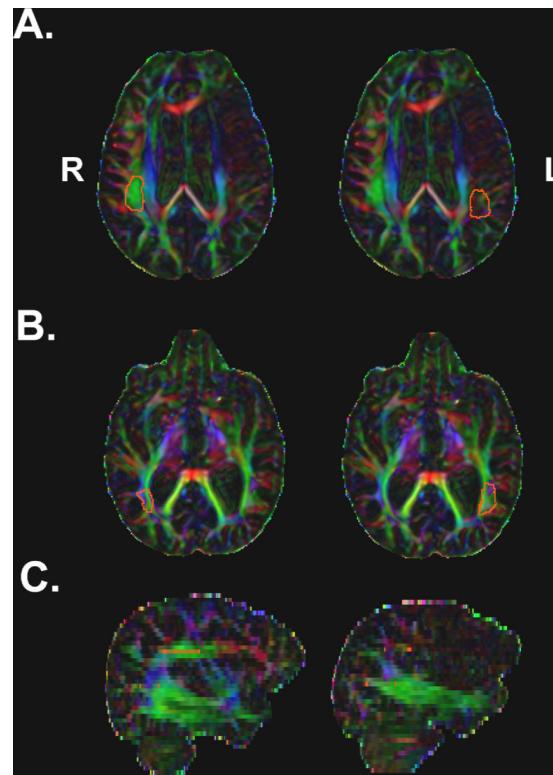
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**Figure 1.**

Demonstration of right (R) and left (L) hemisphere masks used for probabilistic tractography between two manually delineated masks (orange) on separate axial sections: a dorsal mask (seed) and ventral mask (target). Colors represent the principal orientation of white matter tracks (red = left-right; blue = superior-inferior; green = anterior-posterior). Panel A: dorsal mask. Panel B: ventral mask. Panel C: Sagittal view of right hemisphere on the left and sagittal view of left hemisphere on the right.

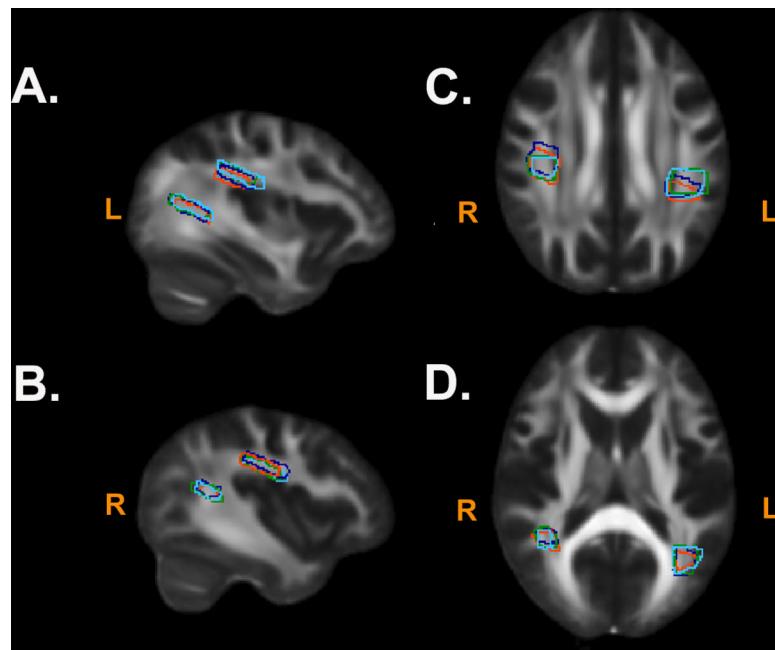


Figure 2.

Demonstration of manually delineated masks at four separate timepoints used for probabilistic tractography transformed from the subject's DTI space at each timepoint into standard space of an FA template (e.g. FMRIB58-FA-1mm) included with FSL. Timepoint 1: Orange; Timepoint 2: Dark blue; Timepoint 3: Green; Timepoint 4: Light blue.

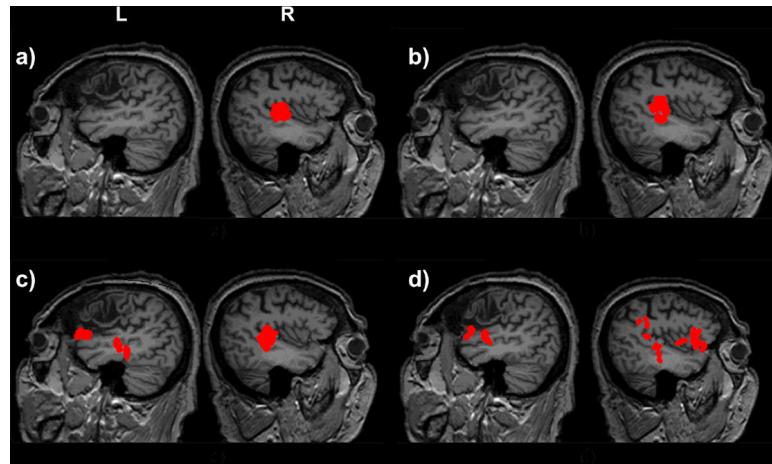


Figure 3.

MEG-MRI co-registered scans at the (a) 3 weeks prior, (b) immediately prior to, (c) immediately after, and (d) 3 months after CILT scanning sessions. Red dots represent individual dipoles thresholded in putative premorbid language areas of the left hemisphere and homotopic areas of the right hemisphere after the resolution of the N1m. Sources are projected up to 1 1/2 centimeters in the sagittal plane. The left hemisphere is on the left side at each time point.

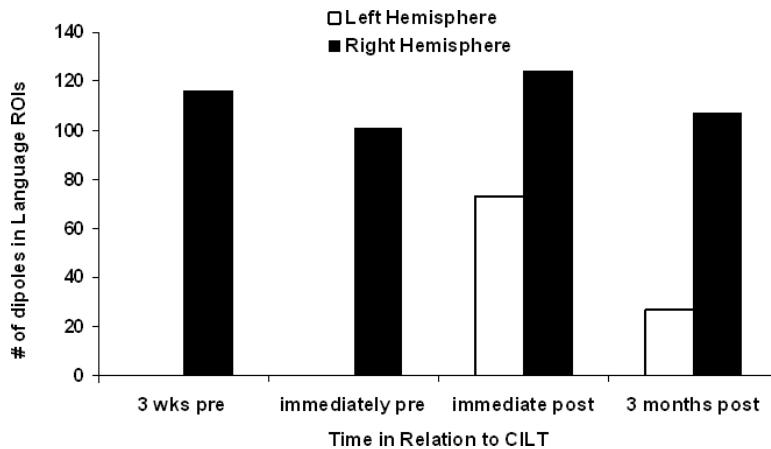


Figure 4.

Total number of late (after the resolution of the N1m) dipoles thresholded in putative pre-morbid language areas in the left hemisphere (white bars) and homotopic areas of the right hemisphere (black bars) during each scanning session.

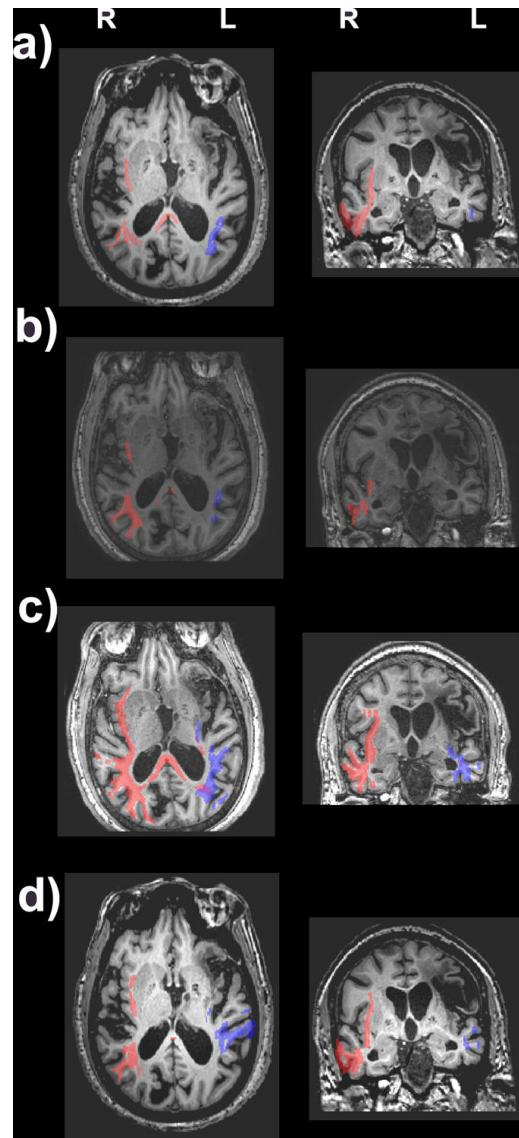
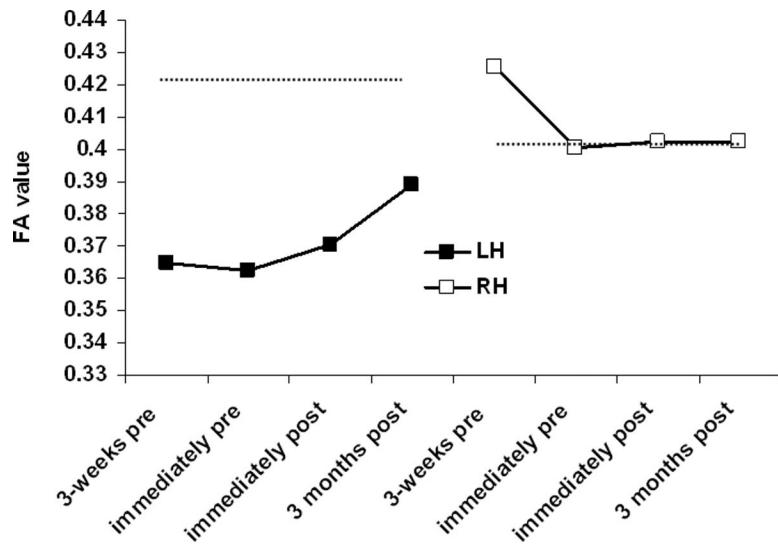


Figure 5.

DTI scans at the (a) 3 weeks prior, (b) immediately prior to, (c) immediately after, and (d) 3 months after CILT scanning sessions. Colored areas represent a thersholded FA value of 0.2 or above in the AF the left (blue) and right (red) hemispheres in the coronal and axial planes. The left hemisphere is on the left.

**Figure 6.**

FA values for the AF of the patient (solid line) in the left (black boxes) and Right (white boxes) hemispheres at each of the time points relative to CILT. The dotted line represents the average FA value for the AF for two patients in each hemisphere.

Performance on language tests before and after CLT.

Table 1

Time	% CIUs	WAB AQ	Repetition AQ	Comp AQ	Action Naming (% correct)	BNT (% correct)
3 weeks pre-CLT	20	59.2	56	89	50	17
immediately pre-CLT	27	56.2	55	84	38	22
immediately post-CLT	40	66.8	75	90	67	35
3 months post-CLT	28	68.2	82	90	62	30

CIUs = correct information units; WAB = Western Aphasia Battery; BNT = Boston Naming Test; AQ = Aphasia Quotient