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Single Case Report

Reorganized language network connectivity after left arcuate fasciculus resection: A case study

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ABSTRACT

Understanding the neural mechanisms that support spontaneous recovery of cognitive abilities can place important constraints on mechanistic theories of brain organization and function, and holds potential to inform clinical interventions. Connectivity-based MRI measures have emerged as a way to study how recovery from brain injury is modulated by changes in intra- and inter-hemispheric connectivity. Here we report a detailed and multi-modal case study of a 26 year-old male who presented with a left inferior parietal glioma infiltrating the left arcuate fasciculus. The patient underwent pre- and post-operative functional MRI and Diffusion Tensor Imaging, as well as behavioral assessments of language, motor, vision and praxis. The surgery for removal of the tumor was carried out with the patient awake, and direct electrical stimulation mapping was used to evaluate cortical language centers. The patient developed a specific difficulty with repeating sentences toward the end of the surgery, after resection of the tumor and partial transection of the arcuate fasciculus. The patient recovered from the sentence repetition impairments over several months after the operation. Coincident with the patient's cognitive recovery, we document a pattern whereby intra-hemispheric functional connectivity was reduced in the left hemisphere, while inter-hemispheric connectivity increased between classic left hemisphere language regions and their right hemisphere homologues. These findings suggest that increased synchrony between the two hemispheres, in the setting of focal transection of the left arcuate fasciculus, can facilitate functional recovery.

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1. Introduction

Some aphasic symptoms can be transient, with patients recovering in the weeks or months after a stroke or tumor resection surgery (Kertesz & McCabe, 1977; Wilson et al., 2015), while some language difficulties after acquired brain injury are permanent. At present, we have little understanding of how variance across patients in how the brain responds to injury is related to variance across patients in functional recovery. One approach, represented by a number of prior studies, is to test hypotheses about the role of the right hemisphere in supporting language recovery after left hemisphere injury. Specifically, when patients with unilateral left hemisphere lesions *do* recover, a natural question concerns the role of functional interactions between the two hemispheres in supporting that recovery. Early neuroimaging studies showed that, in patients with left hemisphere lesions, right hemisphere homologues of classic language regions, like the left inferior frontal gyrus and posterior temporal gyrus, are recruited during novel world learning tasks (Blasi et al., 2002), listening to words (Leff et al., 2002), and auditory comprehension (Saur et al., 2006). It was also found that BOLD signal in right hemisphere homologues of left hemisphere language regions was correlated with behavioral performance (Blasi et al., 2002; Saur et al., 2006). However, not all neuroimaging studies have found a supporting role for right hemisphere activation in behavioral performance—for instance, Postman-caucheteux et al. (2007) showed that increased BOLD activation in the right frontal lobe was associated with more overt naming errors in patients with chronic aphasia. Saur et al. (2006) studied patients longitudinally and found that as patients entered the chronic phase (approximately 1 year post-stroke), the peak activation shifted back to the left hemisphere and that shift was associated with improved behavioral performance. Thus, it is not clear at present whether inputs from right hemisphere regions helps or hurts language recovery after left hemisphere injury.

Over the last decade, the use of connectivity measures to study aphasia recovery has become more widespread (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005; Saur et al., 2006; Ward, Brown, Thompson, & Frackowiak, 2003; for review, see Carter, Shulman, & Corbetta, 2012). One aspect of language function that is well suited for study with measures of brain connectivity is word and sentence repetition. Within the classical Wernicke-Geschwind model, damage to the left arcuate fasciculus causes difficulty with repeating sentences, and is also associated with production of phonemic paraphasias (Tanabe et al., 1987; Yamada et al., 2007; Zhang et al., 2010). Other research has shown that preservation of the left arcuate fasciculus is associated with positive language outcome (Caverzasi et al., 2016; Hayashi, Kinoshita, Nakada, & Hamada, 2012), and that lesion load on the arcuate fasciculus is related to the severity of deficits in speech production (Marchina et al., 2011).

The anatomical definition of the arcuate fasciculus has evolved since Wernicke's description of a connection between the inferior frontal gyrus (IFG) and the posterior superior temporal gyrus (STG) (Wernicke, 1874). More modern research suggests that the arcuate fasciculus has connections extending into the middle temporal gyrus (MTG) (Catani et al., 2002) and not solely the STG, which has been confirmed with more advanced diffusion MRI techniques (Fernández-Miranda et al., 2015). In addition to the cortical endpoints, contemporary definitions of the arcuate include more than one undifferentiated tract. For example, one delineation of the arcuate (Catani et al., 2002) proposes three segments, i) the long segment, connecting the IFG and STG; ii) an anterior segment connecting the IFG to the inferior parietal lobule (IPL); iii) a posterior segment connecting the IPL to the STG. Subsequent studies have defined the arcuate fasciculus within the context of the broader network of the superior longitudinal fasciculus (SLF). For example, Glasser & Rilling (2008) suggested two pathways from the IFG—one that connects to the superior temporal gyrus and serves as a “phonological stream”, and one that connects to the middle temporal gyrus and serves as a “lexico-sematic” stream. Other proposals suggest that the anterior termination of the arcuate fasciculus may not reach the IFG at all, but rather pre-motor cortex (Bernal & Ardila, 2009).

Most prior research using functional connectivity to study aphasia recovery has used resting state fMRI (for review, see Klingbeil, Wawrzyniak, Stockert, & Saur, 2017). That work has advanced understanding of network level changes caused by brain injury, and the neural substrates of recovery. However, one issue that is unresolved by resting fMRI is the degree to which changes in functional connectivity reflect domain general changes or changes that are specific to language processing. In addition, much prior research has been carried out in stroke patients, and through a cortical-centric lens, emphasizing the relation between grey matter injury and aphasia. Thus, comparatively little is known about how subcortical injury that disrupts intra-hemispheric connectivity in the language network affects inter-hemispheric connectivity. These questions can be addressed through a clinical preparation involving subcortical pathology and which permits longitudinal measures, starting in the pre-morbid phase. Detailed studies of patients undergoing resection of low- and intermediate grade gliomas offer such a clinical model, as ***i)*** the patients can be studied pre-operatively, ***ii)*** for awake craniotomies, the emergence of aphasic symptoms can be documented in real time during surgery, and ***iii)*** it is possible to anticipate prior to surgery which white matter structures are likely to be (unavoidably) resected along with the tumor itself. Here we report a detailed and multi-modal longitudinal case study of a patient with a left inferior parietal glioma that infiltrated the posterior part of the long segment of the left arcuate fasciculus and who was studied pre-operatively, intra-operatively, and at multiple times post-operatively. The goal of this investigation was to test how changes in inter-hemispheric connectivity during language and non-language tasks relates to functional language recovery.

2. Methods

2.1. *Participants and case overview*

Patient AH was recruited as part of an ongoing longitudinal study evaluating preoperative fMRI for delineating the maximal safe surgical resection. AH was a 26 year-old right-handed male who came to clinical attention because of worsening tingling and numbness in his right hand. An MRI demonstrated a left inferior parietal glioma (Fig. 1). The patient underwent preoperative structural and functional MRI to map language, praxis, motor and somatosensory processing, and high-level visual processing. An awake craniotomy was planned with surface cortical language, motor and somatosensory mapping (direct electrical stimulation) mapping to facilitate a gross-total resection while sparing eloquent regions (see Supplementary Video 1 for example trials from intra-operative mapping). Toward the end of the tumor resection, subcortical stimulation was also used to identify the medial margin of the tumor, which preoperative imaging indicated was adjacent to the ascending/descending sensory/motor pathways. Direct electrical stimulation mapping was not used to stimulate the arcuate fasciculus in this case. However, because preoperative Diffusion Tensor Imaging suggested the tumor infiltrated the arcuate fasciculus (see Fig. 2), we informally tested his sentence repetition abilities during resection of the tumor. Throughout the surgery, the patient retained his expressive and receptive language abilities and had no difficulty repeating sentences until late in the tumor resection, when he began to struggle with sentence repetition. As will be important below, his sentence repetition difficulties were not present until late in the resection, indicating it wasn't the cortical resection to access the tumor that caused the repetition difficulties, but rather resection of the tumor itself (and putatively, the arcuate fasciculus along with the tumor). For 3–6 days after surgery, the patient presented with a global aphasia, which resolved 1 week post-op to a selective repetition impairment. On formal testing 3 weeks after surgery, the patient had difficulty repeating spoken material, but did not exhibit apraxia, agraphia, alexia, or agnosia (Table S1).

The patient completed several functional MRI experiments to map language and motor-relevant regions pre- and post-operatively, and also completed diffusion tensor imaging before and after surgery. We compare structural connectivity data from AH to 52 right-handed healthy controls (mean age 22.1, number of females = 28). All participants underwent diffusion MRI scanning. Control participants were recruited from the local University of Rochester community. Inclusion/exclusion criteria were determined prior to all data analysis, all manipulations, and all measures in the study. For details on determination of the sample size of the control subjects, see Garcea, Dombovy, & Mahon, 2013; Stasenko, Garcea, Dombovy, & Mahon, 2014. All participants provided written informed consent prior to participating in the study. All procedures were in compliance with the University of Rochester Institutional Review Board (IRB) and also met the ethical standards of the 1964 Helsinki declaration and its later amendments.

2.2. *MRI acquisition and preprocessing*

Diffusion Tensor Imaging (DTI) data were obtained on a 3T Siemens MAGNETOM Trio scanner using a single shot echo-planar sequence (60 diffusion directions with b = 1000 sec/mm^2, 10 images with b = 0 sec/mm^2, TR = 8900 msec, TE = 86 msec, FOV = 256 × 256mm^2, matrix = 128 × 128, voxel size = 2 × 2x2 mm^3, 70 axial slices). AH also completed several whole brain functional MRI scans using a BOLD echo-planar imaging pulse sequence (TR = 2000 msec, TE = 30 msec, flip angle = 90, FOV = 256 × 256mm^2, matrix = 64 × 64, voxel size = 4 × 4 × 4 mm^3, 30 axial slices). These scans included both task-based and resting-state scans. The task based scans were used as part a broader study involving picture naming, category fluency, word reading, praxis, and somatosensory and motor mapping. Patient AH also completed additional functional MRI scans for language mapping at a different site using a 3T GE Discovery MR750 scanner (General Electric, Milwaukee WI, USA). Full details of all fMRI experiments can be found in the Supplementary Materials.

Functional MRI data were analyzed with the BrainVoyager software package (Version 2.8) and in-house scripts drawing on the BVQX toolbox (MATLAB) and custom JAVA scripts. The first six volumes of each run were discarded to allow for signal equilibration (4 at image acquisition and 2 at preprocessing). Preprocessing of the functional data included, in the following order, slice scan time correction (sinc interpolation), motion correction with respect to the first volume of the first functional run, and linear trend removal in the temporal domain (cutoff: 2 cycles within the run). Functional data were registered (after contrast inversion of the first volume) to high-resolution de-skulled anatomy on a participant-by-participant basis in native space. For each participant, echo-planar and anatomical volumes were transformed into standardized space (Talairach, 1988). These analysis pipelines are described in prior work from our group (e.g., Chen, Garcea, Jacobs, & Mahon, 2018; Garcea, Chen, Vargas, Narayan, & Mahon, 2018; Mahon, Kumar, & Almeida, 2013; Shay, Chen, Garcea, & Mahon, 2018; Chernoff et al., 2018; Chen, Garcea, & Mahon, 2016; 2017; Garcea & Mahon, 2014; Garcea, Kristensen, Almeida, & Mahon, 2016; 2017).

DTI preprocessing was performed with the FMRIB Software Library (FSL; http://www.fmrib.ox.ac.uk/fsl/). FSL's brain extraction tool (BET) (Smith, 2002) was used to skull-strip each subject's diffusion weighted and T1 images, as well as the fieldmap magnitude image. The B0 image was stripped from the diffusion weighted image, and the fieldmap was prepared using FSL's prepare fieldmap tool. Smoothing and regularization was performed using FSL's fugue tool (FSL; http://www.fmrib.ox.ac.uk/fsl) and a 3D Gaussian smoothing kernel was applied (sigma = 4 mm). The magnitude image was then warped based on this smoothing, with y as the warp direction. Eddy current correction was performed using FSL's eddy_correct tool (Graham, Drobnjak, & Zhang, 2015), which takes each volume of the diffusion-weighted image and registers it to the b0 image to correct for both eddy currents and motion. Next, the deformed magnitude image was registered to the B0 image using FSL's linear registration tool (FLIRT) (Jenkinson & Smith, 2001). The resulting transformation matrix was then applied to the prepared fieldmap. Lastly, the diffusion-weighted image was undistorted using the registered fieldmap, with FSL's fugue tool. Intensity correction was also applied to this unwarping.

2.3. *Neuropsychological testing*

AH completed a broad battery of neuropsychological tests to assess language, memory, praxis, and visual and spatial

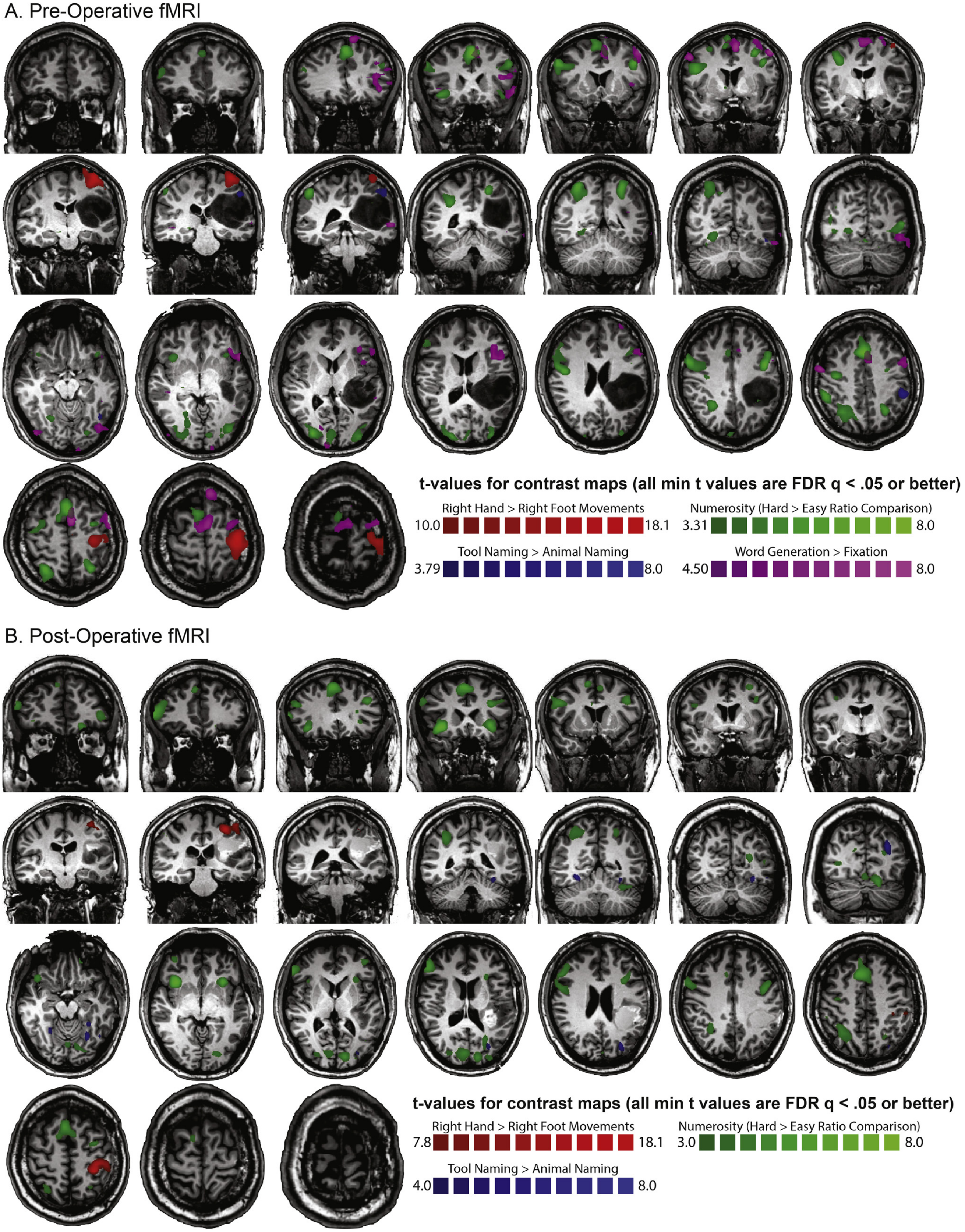

Fig. 1 – Pre-operative functional MRI. The contrast maps show the results of several contrasts identifying key functions adjacent to the glioma in Patient AH. These data were collected as part of the pre-operative workup (Panel A) in the patient, and most were collected again post-operatively (Panel B). *Blue:* Picture naming [Tools > Animals]. *Green:* Numerical processing: [Hard ratio (.8) > Easy ratio (.25)]. *Red:* Motor Localizer: [Right Hand Movement > Right Foot Movement]. *Purple:* Verbal Fluency: [Overt Word Production > Fixation]. See Supplemental Materials for detailed description of tasks and experimental design. Each map is displayed with FDR correction at q ≤ .05 or better.

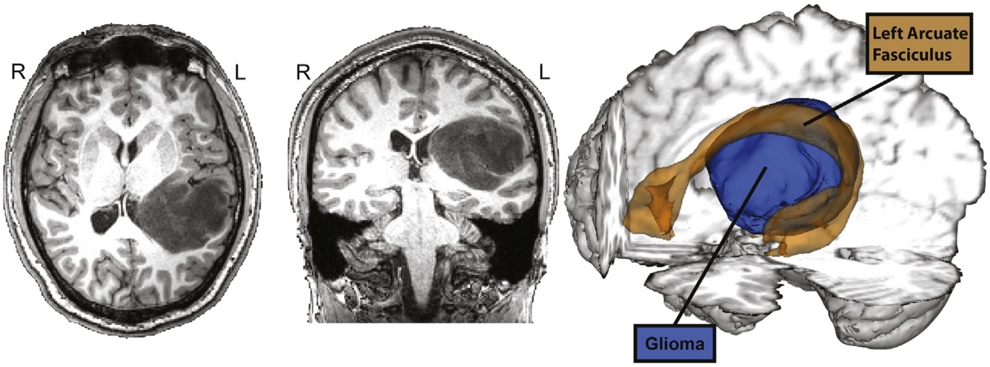

Fig. 2 – Pre-operative T1 MRI and 3D reconstruction of the left arcuate fasciculus and glioma in patient AH. The arcuate fasciculus is shown in orange at a 5% threshold with the tumor reconstruction in blue.

processing. Here we emphasize those neuropsychological tests that were completed at all time-points, and which are directly pertinent for understanding the nature of the patient's language difficulties and subsequent recovery; scores for tests which AH was not able to be complete at all time points, due to time constraints, can be found in the Supplementary Materials. Repetition ability was tested repeatedly at all post-operative time points; however, if 1 month after surgery the patient had difficulty with one of the neuropsychological tests administered prior to surgery, that test was not repeated at subsequent post-operative time points.

As noted, prior to surgery, and based on the location of the tumor, it was anticipated that tumor resection would involve transection of the arcuate fasciculus, and that a sentence repetition impairment was likely. The patient and his family were counseled on this prior to surgery. We formally tested the patient's repetition ability pre-operatively and at one month and 3.5 months after surgery using the sentence stimuli from the PALPA (Subtest 12, Kay, Coltheart, & Lesser, 1992). Performance on the sentence repetition task was quantified in two ways. First, we measured the duration of each sentence the patient repeated, as a measure of speech rate, before and after surgery. Second, we measured the average number of self-corrections the patient made per sentence, where self-corrections were operationalized as the insertion of incorrect phonemes or words, self-corrected by the patient. We used this measure because it quantifies not just speech rate but also abnormal intrusions within the patient's speech. We evaluated lexical access before and after surgery, using picture naming (Snodgrass & Vanderwart, 1980), word reading (Psycholinguistic Assessment of Language Processing in Aphasia, PALPA, subtest 33, Kay, Lesser & Colthart, 1992), pseudo-word reading (PALPA subtest 36), and Arabic number naming (one, two, and three digits). We also tested praxis by having the patient visually identify manipulable objects (e.g., screwdriver, scissors), then demonstrate how he would use the object with their dominant hand without touching the object, and finally to explain the purpose or function of use of the object. AH was also shown videos of someone pantomiming actions and asked to match the pantomime with the corresponding object. Finally, AH was shown videos of familiar and unfamiliar pantomimes and had to indicate whether they were meaningful/familiar or meaningless/unfamiliar (for details, see Garcea et al., 2013).

2.4. *Functional connectivity analyses*

Functional connectivity was computed over task based fMRI data (see Supplemental Materials for details on each experiment) in order to distinguish changes in functional connectivity associated with language versus non-language processing. All analyses were based on template-defined regions of interest (ROIs) for the left and right inferior frontal gyrus and posterior-superior temporal gyrus. We choose to focus on the left and right hemisphere inferior frontal gyrus and posterior superior temporal gyrus because they are connected by the arcuate fasciculus (cf. Bernal & Ardila, 2009). As previously discussed, the arcuate fasciculus may also connect to the middle temporal gyrus. However, the location of the patient's lesion motivated our focus on the branch of the arcuate connecting the inferior frontal gyrus to the superior temporal gyrus. Using template-based ROIs, rather than the patient's own functionally defined ROIs allowed us to put the patient and the controls on the same footing—this was particularly important for quantitatively comparing the patient to the group of healthy controls (see below). In addition to prioritizing reproducibility, using atlas-based ROI's enabled us to define right hemisphere homologues that were not identified by the functional MRI experiments. Regions of interest were defined as 2 cm diameter spheres around the peak coordinate from the Harvard–Oxford Cortical Atlas (Desikan et al., 2006). Functional connectivity among ROIs was calculated using the time-series data from all BOLD scans, using custom scripts drawing on the BVQX toolbox for MATLAB. The change in head position across volumes was regressed out of the time series data, after standard preprocessing steps described above. All functional connectivity analyses were computed over the residuals of that regression model. We did not regress the global mean time course because of prior arguments that doing so can introduce spurious patterns to the data ((Gotts, Saad, Jo, & Martin, 2013). We also coded a binary variable for each functional run that consisted of whether the task was language related (e.g., picture naming) versus not language related (e.g., finger tapping). This allowed us to test whether the Task (language, non-language) interacted with the variables ROI and Time-point.

2.5. *Tractography analyses*

We performed probabilistic tractography using FSL's probtrackx2 tool, which uses Bayesian estimation of the diffusion parameters (Behrens et al., 2003; 2007) to define and measure the left and right arcuate fasciculi. 5000 streamline samples were initiated with a curvature threshold of .2 and a step length of .5 mm. Using the network mode option in FSL, fiber tracking was initiated from each seed ROI separately and only the streamlines that passed through the other ROI were kept.

We used an iterative leave-one-out data folding approach to quantify the structural integrity of the left and right arcuate fasciculi in Patient AH relative to the distribution of healthy participants. Specifically, we defined the arcuate separately in each of the healthy control subjects (using the Harvard–Oxford Atlas), using a 5% threshold based on each subject's tractogram, and then binarized the result. We then overlaid the binarized arcuate tracts of all control participants leaving one control participant out of the analysis, and created a mask of the arcuate fasciculus using that set of n-1 healthy controls. The criterion used for generating the group-level mask (on n-1 controls) was that at least 80% of healthy controls needed to exhibit overlap at a voxel for it to be counted as 'part' of the arcuate fasciculus. The resulting arcuate "mask" was used as a waypoint to perform tractography in the left-out healthy control subject, as well as in Patient AH's preoperative and post-operative brain. This analysis was iterated 52 times, each time leaving out a different control subject, and each time re-computing AH's arcuate fasciculus; this pipeline was implemented for both left and right hemisphere arcuate fasciculi. On each iteration, for the left-out subject as well as Patient AH, we extracted the normalized number of streamlines for the arcuate fasciculus. The extracted values are plotted in the histograms of Fig. 3.

2.6. *Regions of interest*

It is important to note that we chose to use atlas-based regions of interest in order to carry out analyses that were reproducible, and to ensure that the analyses of the healthy controls were on the same footing as those for the patient. This was also important because functionally defining regions of interest, using pre-operative fMRI language tasks, does not identify right hemisphere ROIs, and an important aspect of hypothesis testing herein is to compare the left and right arcuate fasciculi. One concern associated with atlas-based ROIs in the patient is that mass effects of the tumor will not be taken into account; Supplementary Fig. 1 addresses this by overlaying tractography of the left arcuate fasciculus using functionally defined ROIs and atlas-based ROIs. The results show equivalence of the two approaches for these data: individual probabilistic tractography with atlas ROIs of cortical endpoints produces the same result as individual probabilistic tractography with fMRI defined cortical endpoints. We note that using an atlas-based reconstruction of the tract and overlaying it on the patient could be problematic due to mass effects of the tumor, which is why we elected to utilize tractography in each individual subject, including the patient. We also note, to anticipate our findings (see Fig. 3), that quantitative analysis of the patient's left arcuate fasciculus indicated that the patient was within the distribution of healthy controls pre-operatively, again suggesting that mass effects of the tumor are not a concern.

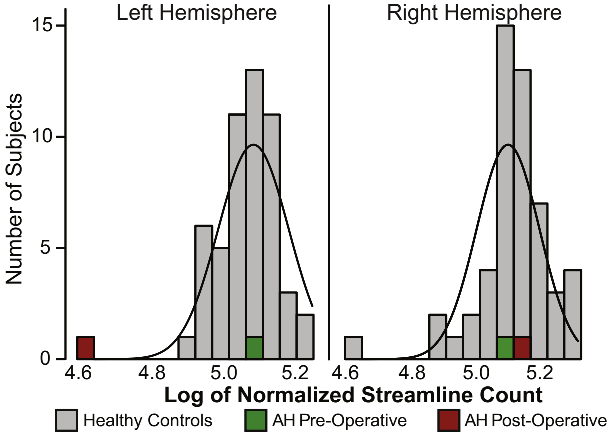

Fig. 3 – Reduction in structural integrity of the left arcuate fasciculus in AH compared to a control sample. Structural and functional connectivity analyses were carried out using atlas-defined regions of interest (ROIs) for the left and right inferior frontal gyrus and left and right posterior superior temporal gyrus. The distribution of normalized streamline counts for the left and right arcuate fasciculus are shown on a logarithmic scale for healthy controls (gray bars) and AH pre-operatively (green), and post-operatively (red). These data show that there was a reduction in structural integrity of the left, but not the right, arcuate fasciculus after surgery, compared to before surgery, and compared to healthy controls.

2.7. *Availability of data*

Raw MRI data, summary data used for analyses, and scripts to run the tractography and functional connectivity analyses are available database available using the DOI 10.1184/R1/7851515.v1 on FigShare (through Kilthub at Carnegie Mellon University). Experimental stimuli and scripts to present them are available for download here: https://openbrainproject.org/experiment-exchange/ChernoffColleagues_Cortex2019. None of the study procedures or study analyses were pre-registered in an institutional database prior to the research being conducted.

3. Results

3.1. *Neuropsychological testing*

Prior to surgery the patient had no discernable neuropsychological deficits, and his only symptom prior to surgery was occasional tingling and numbness in the right hand, likely due to the proximity of the tumor to SII. Throughout AH's surgery his productive and receptive language remained intact, as well as his ability to move and feel through the right upper and lower extremities. However, as noted, toward the end of the tumor resection, the patient exhibited difficulty repeating auditorily presented sentences on informal clinical testing during surgery (by SOS, observed by BZM and WHP). The day after surgery, AH was globally aphasic, based on clinical bedside exam by authors WHP, SOS and BZM; over the first week after surgery, the global aphasia resolved, leaving a specific difficulty with sentence repetition that persisted for several months.

Prior to formal analysis of sentence repetition data from before and after surgery, we first calculated accuracy by coding any trial with (any) phonemic paraphasias or dysfluencies as incorrect. Pre-operative accuracy was 94%. One month after surgery, accuracy was 72.2%, and three and a half months after surgery, AH was 90% correct. On further analysis, AH was worse on both measures (speech rate, number of self corrections) at the one-month post-operative time-point compared to pre-operative testing, and there was a statistically significant improvement for the 3.5 months post-operative test compared to the one-month post-operative test. The mean duration of the patient's produced sentences 1.47s pre-operatively (SD = .27). One month after surgery the mean duration doubled, to 2.84s (SD = 1.08; pre-vs. 1mo post-operative: t (34) = −5.22, $p < .001$, D = 1.74). Three and a half months after surgery, the mean duration decreased to 2.02s (SD = .54), reflecting a significant improvement compared to one month after surgery (1mo post-surgery *vs* 3.5mo post-surgery: t (26) = 2.25, $p < .04$, D = .96). A similar pattern was observed for self-corrections. Pre-operatively, the mean number of self-corrections per sentence was .06 (SD = .24). One month after surgery there was a significant increase to 1.56 (pre-vs. 1mo post-operative: t (34) = 6.29, $p < .001$, D = 1.15). Three and a half months after surgery the mean number of self-corrections decreased to .7 reflecting a significant improvement compared to 1 month after surgery (1mo post-surgery *vs* 3.5mo post-surgery: t (26) = 2.44, $p < .03$, D = 1.01). The patient's sentence repetition 3.5 months after surgery sounded clinically normal (see Supplementary Video 2 for representative example audio). The patient's naming accuracy (picture naming, word naming, and number naming) were not significantly different after surgery compared to before surgery, and there were no differences between the two post-operative time points (all t's < 1) The patient did not exhibit apraxia pre- or post-operatively, as measured by transitive and intransitive pantomiming from command, from imitation, and from video, as well as demonstrating the use and describing the function of various handheld objects (e.g., scissors, pencil). The patient's arithmetic accuracy was not significantly different post-vs. pre-operatively (t < 1). We also compared the patient's post-operative scores to a group of healthy control subjects (for details on the control sample, see Garcea et al., 2013; Stasenko et al., 2014) using Crawford t-tests (Table 1). The integrity of lexical access, praxis and numerical knowledge are important because of the cortical location of those functions adjacent to the tumor in parietal cortex (see Fig. 1); the combination of pre-operative functional MRI and the lack of specific difficulties for those functions suggests the surgery was successful in preserving those eloquent functions.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.cortex.2019.07.022.

3.2. *Tractography analyses*

Probabilistic tractography of diffusion data indicated (Fig. 3) that pre-operatively, the normalized streamline count for the left arcuate fasciculus in AH (168) was within a standard deviation of the mean of the distribution for 52 controls (mean = 163.5, SD = 12.4). Post-operatively, the normalized streamline count for the left arcuate fasciculus in AH decreased to 106, which is ~4 standard deviations below the mean for healthy controls. For comparison, the mean streamline count for the right arcuate fasciculus in AH was within a standard deviation of the mean for healthy controls (mean = 168.9, SD = 18.4) both pre- (160) and post-operatively (174). To statistically assess these changes in mean streamline count, we used the Revised Standardized Difference Test (Crawford, 2010), which is designed to measure single-case dissociations. The results demonstrated that only the post-operative left hemisphere streamline count for AH was different than the distribution of healthy controls ($t_{51} = 3.79$, $p < .0004$; all other ts < 1).

3.3. *Functional connectivity analyses*

Our core hypothesis predicted a change in functional connectivity comparing the pre- and post-operative scans, for language but not for non-language tasks. If functional connectivity is modulated as a function of surgery only for some edges among the 4 ROIs and only for language tasks, then there will be an interaction for the 3-way (2*6*2) analysis of variance (ANOVA) with factors Time-point (pre-operative | post-operative), Edge (6 levels: all connections among the 4 ROIs), and Task (language | non-language). In line with the core hypothesis, there was a significant 3-way interaction ($F_{(1,225)} = 3.88$; $p = .05$, $\eta p^2 = .02$). The main effect of Task was significant ($F_{(1,225)} = 8.88$; $p < .004$, $\eta p^2 = .03$), indicating stronger functional connectivity overall for language compared to non-language tasks; the main effects of Time-point (F < 1) and Edge (F < 1) were not significant. We then carried out hypothesis-driven tests of whether there was a significant 2-way interaction between Edge and Time-point for language tasks, but no such interaction for non-language tasks. Confirming the core prediction, the interaction was significant (Time-point*Edge) for language tasks ($F_{(1,92)} = 8.02$; $p = .006$, $\eta p^2 = .18$) but not for non-language related tasks (F < 1; See Fig. 4). As shown in Fig. 4, there was an increase in functional connectivity between left Wernicke's area and right Wernicke's area, as well as between left Broca's area and right Wernicke's area, but only for language tasks. These changes in functional connectivity, specific to language tasks, demonstrate that transection of the left arcuate fasciculus can result in increased functional coupling between dominant hemisphere language regions and their right hemisphere homologues.

Table 1 – Neuropsychological performance on primary neuropsychological tests of language function for patient AH pre- and post-operatively. Values in the table represent accuracy (% correct). Crawford *t*-tests compare the patient's post-operative score to a set of previously published healthy control subjects. The only test where the patient's scores significantly differ from controls is Object Decision, where the patient's score is significantly *higher* than the control subjects (t = 3.93, *p* = .01).

Test	Control Mean (SD)	N	Patient AH Pre-Op	Patient AH Post-Op	Crawford t-stat	*p*-value
Number Reading	98.7 (3.4)	6	100	96	−.72	.50
Object Decision	89.0 (2.0)	6	100	97.5	3.93	.01
Pantomime Discrimination	90.0 (8.0)	6	88.9	88.9	−.13	.90
Pantomime from Command						
Intransitive	100 (0)	6	91.7	100	–	–
Transitive	98.6 (1.3)	6	100	100	1.01	.36
Pantomime from Imitation	99.3 (1.2)	6	100	100	.51	.63
Picture Naming	87.3 (14.3)	42	96.2	93.7	.44	.66
Picture-Word Matching	96.0 (5.0)	96	100	100	.8	.43
Sentence Repetition	100 (0)	17	96.2	72.2	–	–
Word Reading	96 (6.0)	6	97.1	95	−.15	.88
Tactile Recognition, Object Use, and Function Knowledge						
Identifies Function	97 (2.0)	6	100	100	.93	.40
Object Use	98 (2.0)	6	100	100	1.39	.22
Object Identification	87 (2.0)	6	100	100	.93	.40

4. Discussion

The role of the right hemisphere in recovery from aphasia has been the subject of a large body of research dating back to early observations by Gowers (1887) and Barlow (1877). Here we have documented how inter- and intra-hemispheric connectivity can be modulated by transection of the left arcuate fasciculus specifically for language-related tasks. By studying a neurosurgery patient, we are able to extend findings from the stroke literature, because our longitudinal data includes pre-operative MRI and behavioral measures that were obtained when the patient was cognitively intact. Our findings demonstrate that functional connectivity among key nodes of the language network can be modulated specifically for language related tasks, and document specific changes in intra-hemispheric connectivity for language tasks that were not present for non-language tasks.

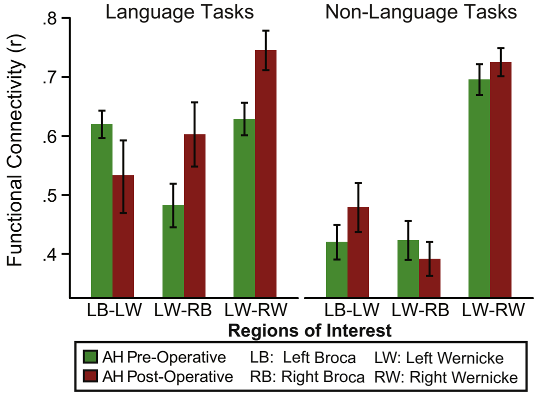

Fig. 4 – Increased intra-hemispheric functional connectivity in the language network and for language tasks. Functional connectivity over task-based BOLD fMRI for Patient AH shows there was an increase in functional connectivity between left hemisphere language regions and right hemisphere homologue regions for language-related tasks and not for non-language tasks. Error bars reflect the standard error of the mean over functional scans/runs.

Existing research into the role of the right hemisphere suggests that inter-hemispheric reorganization in the language network, as captured by fMRI, may reflect a release from inhibitory mechanisms (Turkeltaub & Messing et al., 2011; Turkeltaub, 2015). That hypothesis has motivated the use of noninvasive stimulation such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) to the right hemisphere as a therapeutic treatment for aphasia. The effectiveness of this method was first demonstrated by Naeser et al. (2005), who used rTMS on the right hemisphere homologue of Broca's area on four aphasic patients for 10 days. Those patients were 5–11 years post-stroke, and the authors found significant improvement in picture naming performance 2 months after administration of rTMS. Since then, several studies have found similar therapeutic effects of stimulation of the right inferior frontal gyrus (Turkeltaub & Coslett et al., 2011). The inhibitory mechanism proposed by Turkeltaub and colleagues is plausible given the callosal fibers that connect the left and right inferior frontal gyrus (Schlaug, Marchina, & Wan, 2011). In addition to functional MRI and TMS, functional connectivity, including dynamic causal modeling (DCM; for review, see Grefkes & Fink, 2014) has been used to study recovery after stroke in the motor (Grefkes et al., 2010; Wang et al., 2010) and language networks (Klingbeil, Wawrzyniak, Stockert, & Saur, 2017; for work with MEG see; Westlake et al., 2012). Graph-theoretic measures using functional connectivity have demonstrated the emergence of right hemisphere "hubs" in the setting of degraded left-hemisphere connectivity in patients with primary progressive aphasia (Mandelli et al., 2018), and that those changes unfold longitudinally throughout disease progression (Mandelli et al., 2016). Connectivity studies have begun to influence clinical practice in stroke patients (Silasi & Murphy, 2014) and have been shown to relate to clinical outcome (Kuceyeski et al., 2016). In addition, they have important basic science implications for studying diaschisis—how lesions in one area of the brain affect processing in anatomically remote but functionally connected regions (Carrera & Tononi, 2014).

An important issue that been a topic of concerted study over the past two decades concerns the types of lesions that are minimally sufficient, or perhaps necessary, to cause sentence repetition difficulties. Much of this work has been conducted in the context of understanding 'conduction aphasia'. For instance, Quigg and colleagues (1999; 2006) showed that cortical stimulation of the posterior perisylvian region through a grid in epilepsy patients could induce repetition errors and phonemic paraphasias (see also Anderson, Gilmore, Roper, Crosson, & Bauer, 1999). Kreisler et al. (2000) studied 107 patients with different types of aphasia caused by stroke and they found that some patients with damage to the arcuate fasciculus retained their repetition ability. A similar finding was reported by Selnes, Van Zijl, Barker, Hillis, and Mori (2002), who described a right-handed stroke patient with damage to the left arcuate fasciculus who exhibited intact repetition. Taken together, those findings suggest that while damage to the arcuate fasciculus can cause repetition impairments, it may not be necessary, and damage to structures aside from the arcuate fasciculus may also be sufficient. Bernal and Ardila (2009) proposed a reinterpretation of repetition deficits as they relate the clinical syndrome of 'conduction aphasia'. First, damage to the arcuate fasciculus is neither necessary nor sufficient to cause conduction aphasia. Second, the anterior termination of the arcuate fasciculus is not the pars opercularis of the inferior frontal gyrus, but rather the premotor and primary motor areas of the pre-central gyrus (Bernal & Ardila, 2009). Those authors argue that the proposal that damage to the arcuate fasciculus is implicated in 'conduction aphasia' derives from the incorrect assumption that Broca's area is connected by the arcuate fasciculus. Third, Bernal and Ardila argue that the arcuate fasciculus is connected to Broca's area *indirectly* via a relay station in premotor cortex (BA 6), and that the repetition impairments observed after damage to the arcuate fasciculus are consistent with an "ideomotor verbal apraxia" account of conduction aphasia—improper mapping of motor sequences for utterances (Luria, 1976). We note that our core conclusion, regarding changes in functional connectivity associated with recovery from a sentence repetition deficit, is agnostic as to whether or not patient AH had 'conduction aphasia', as there is a separate set of issues that attend how to 'define' conduction aphasia.

In the context of these prior studies, two important issues are framed by our current report. First, it may be argued that the patient's left arcuate fasciculus was not functional prior to surgery, due to infiltration by the glioma. This concern is assuaged by the fact that the patient *developed* difficulties with sentence repetition during surgery, indicating that the left arcuate fasciculus *was* functional prior to surgery. Another important concern is whether mass effects of the tumor preoperatively altered the observed measures, or tractography itself of the left arcuate fasciculus in the patient. Supplementary Fig. 1 addresses this issue by showing overlaid highly similar tractography of the patient's left arcuate when using atlas-based ROIs and functionally defined ROIs. If there such mass effects, we would expect the patient's preoperative arcuate fasciculus streamline count to be outside of the distribution of healthy control subjects, which it was not. Thus, the results shown in Supplementary Fig. 1 and in Fig. 3 collectively indicate that mass effects are unlikely to have caused any major inaccuracies in assessment of the anatomy of the pre-operative arcuate fasciculus. Another concern is whether aspects of the arcuate that extend ventral to the superior temporal gyrus may have contributed to the observed pattern. While there is reason to believe, given the location of the tumor, that the segment of the arcuate between the superior temporal gyrus and frontal regions was principally effected, it is important to note that streamlines were not restricted from traveling to adjacent cortical regions like the middle temporal gyrus, and that those connections may also be important.

Another important concern relates to whether the patient's persistent difficulty with sentence repetition after surgery was due to the subcortical resection of the arcuate fasciculus, or rather the cortical resection required to access to the glioma. The fact that the patient did not develop difficulties with sentence repetition after the cortical resection (see Supplementary Fig. 2 for location of corticectomy), but only after the deeper and anterior margin of the tumor had been resected, suggests it was not the cortical resection but rather the subcortical resection that caused the repetition difficulties. Still, future research involving the same connectivity analyses but in patients with isolated cortical lesions with no arcuate involvement will provide further insight into cortical *vs* subcortical connections, beyond the hypotheses that we tested in the present study.

It is also important to interpret the changes in streamline count that we observed in the tractography analyses with care. The constraints on streamline propagation in probabilistic algorithms are inherently different than for deterministic tractography. In addition, streamline counts may be influenced by factors such as oedema, streamline counts can be affected by diffusion weighting and reconstruction techniques that are used. In this context, it is important to note that the same acquisition parameters for diffusion MRI were used in the patient and controls, and that our core conclusion depends on longitudinal structural and functional MRI findings that fit into a coherent pattern. Nonetheless those limitations do motivate future research using diffusion spectrum imaging (DSI). Future DSI research should also examine interhemispheric connectivity in terms of possible secondary structural changes to the corpus callosum. It can be difficult to fully reconstruct the corpus callosum using simple diffusion tensor imaging without spherical deconvolution (Farquharson et al., 2013), and thus we did not pursue this direction in the current study. In addition, more fine-grained anatomical dissociations among subcomponents of the arcuate fasciculus may reveal important information about the contribution of arcuate connections to different parts of the temporal lobe (Fernández-Miranda et al., 2015) as well as the broader SLF system (Wang et al., 2016). They are key future steps to extend this research.

The findings we have reported demonstrate that changes in connectivity that occur after injury to the language network can be task-specific, which has important implications for existing theories of cortical re-organization and approaches of encouraging rehabilitation. One key issue for such future research will be to evaluate whether the modulations by task that we observed indicate or do not indicate domain-specific changes in network connectivity. For instance, future work could compare changes in functional connectivity during sentence repetition, with changes observed during tasks requiring processing of arithmetic operations (Fedorenko, Behr, & Kanwisher, 2011), or musical phrases (Garcea et al., 2017; Hickok, Buchsbaum, Humphries, & Muftuler, 2003). In addition, it would be valuable to examine whether functional connectivity varies by the type of language task (for instance, sentence repetition *vs* verbal fluency). Finally, another important direction to systematically evaluate how the type of post-injury speech rehabilitation activities in which patients engage (e.g., music therapy; Tomaino, 2012) may modulate how the network responds to focal brain injury during language processing tasks.

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Open practices

The study in this article earned Open Materials and Open Data badges for transparent practices. Materials and data for the study are available at https://kilthub.cmu.edu/s/5ac1b3821343334f3f04.

CRediT authorship contribution statement

Benjamin L. Chernoff: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Visualization. **Alex Teghipco:** Conceptualization, Formal analysis, Software, Investigation. **Frank E. Garcea:** Conceptualization, Formal analysis, Software, Investigation. **Raouf Belkhir:** Software, Visualization. **Max H. Sims:** Investigation. **David A. Paul:** Methodology. **Madalina E. Tivarus:** Investigation, Resources. **Susan O. Smith:** Conceptualization, Investigation, Resources. **Eric Hintz:** Conceptualization, Investigation, Resources. **Webster H. Pilcher:** Conceptualization, Investigation, Resources. **Bradford Z. Mahon:** Conceptualization, Methodology, Resources, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition.

Supplementary data

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