Altered Anterior-Posterior Connectivity Through the Arcuate Fasciculus in Temporal Lobe Epilepsy

Shigetoshi Takaya,[1,2]* Hesheng Liu,[1,2] Douglas N. Greve,[1,2] Naoaki Tanaka,[1,2] Catherine Leveroni,[2,3] Andrew J. Cole,[2,4] and Steven M. Stufflebeam[1,2]

[1]*MGH/HST Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, Massachusetts*
[2]*Harvard Medical School, Boston, Massachusetts*
[3]*Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts*
[4]*Department of Neurology, Massachusetts General Hospital, Boston, Massachusetts*

Abstract: How the interactions between cortices through a specific white matter pathway change during cognitive processing in patients with epilepsy remains unclear. Here, we used surface-based structural connectivity analysis to examine the change in structural connectivity with Broca's area/the right Broca's homologue in the lateral temporal and inferior parietal cortices through the arcuate fasciculus (AF) in 17 patients with left temporal lobe epilepsy (TLE) compared with 17 healthy controls. Then, we investigated its functional relevance to the changes in task-related responses and task-modulated functional connectivity with Broca's area/the right Broca's homologue during a semantic classification task of a single word. The structural connectivity through the AF pathway and task-modulated functional connectivity with Broca's area decreased in the left midtemporal cortex. Furthermore, task-related response decreased in the left mid temporal cortex that overlapped with the region showing a decrease in the structural connectivity. In contrast, the region showing an increase in the structural connectivity through the AF overlapped with the regions showing an increase in task-modulated functional connectivity in the left inferior parietal cortex. These structural and functional changes in the overlapping regions were correlated. The results suggest that the change in the structural connectivity through the left frontal–temporal AF pathway underlies the altered functional networks between the frontal and temporal cortices during the language-related processing in patients with left TLE. The left frontal–parietal AF pathway might be employed to connect anterior and posterior brain regions during language processing and compensate for the compromised left frontal–temporal AF pathway. *Hum Brain Mapp 37:4425–4438, 2016.*

Key words: Broca's area; Freesurfer; function; language; MRI; psychophysiological interaction; reorganization; semantic; structure; tractography

**Present address:* Shigetoshi Takaya is currently at Human Brain Research Center, Department of Neurology, Kyoto University Graduate School of Medicine, Kyoto 606-8507, Japan

Additional Supporting Information may be found in the online version of this article.

Contract grant sponsor: National Institute of Health; Contract grant numbers: R01-NS069696, P41-EB015896, U01-MH093765, T32-EB001680; Contract grant sponsor: National Science Foundation grant; Contract grant number: NFSDMS-1042134; Contract grant sponsors: Uehara Memorial Foundation, the SNMMI (Wagner-Torizuka Fellowship); Contract grant sponsor: Department of Energy; Contract grant number: DE-SC0008430

*Correspondence to: Shigetoshi Takaya, Human Brain Research Center, Department of Neurology, Kyoto University Graduate School of Medicine, Kyoto 606-8507, Japan. E-mail: shig.t@kuhp.kyoto-u.ac.jp

Received for publication 25 April 2016; Revised 4 July 2016; Accepted 7 July 2016.

DOI: 10.1002/hbm.23319

Published online 25 July 2016 in Wiley Online Library (wileyonlinelibrary.com).

INTRODUCTION

Epilepsy affects both structural and functional brain networks. In temporal lobe epilepsy (TLE), despite the localized epileptic focus, a widespread involvement of structural and functional brain networks beyond the focus has been demonstrated in neuroimaging studies [Arnold et al., 1996; Besson et al., 2014; Focke et al., 2008; Haneef et al., 2012; Keller and Roberts, 2008; Voets et al., 2012]. In concert with the extensive structural and functional abnormalities in the brain, patients with TLE exhibit a wide range of cognitive morbidity [Bartha-Doering and Trinka, 2014; Hermann et al., 1997; Oyegbile et al., 2004]. Previous studies have shown that neuropsychological measurements of memory, executive function, language abilities, and general intelligence in patients with TLE are correlated with structural changes in the white matter pathway, as measured with diffusion magnetic resonance imaging (MRI) [Diehl et al., 2008; McDonald et al., 2008a; McDonald et al., 2014; Riley et al., 2010; Winston et al., 2013; Yogarajah et al., 2008], and functional changes in the cortex, measured with [^{18}F]-fluorodeoxyglucose positron emission tomography (PET) [Jokeit et al., 1997; Takaya et al., 2006; Trebuchon-Da Fonseca et al., 2009] and functional MRI (fMRI) [Protzner et al., 2013; Protzner and McAndrews, 2011; Sanjuán et al., 2013].

Although these lines of evidence indicate that the structural changes in the white matter and the functional changes in the cortex are both associated with cognitive performance in patients with TLE, the relationship between the structural and functional changes during cognitive processing remain poorly understood. Given that the functional interaction between remote cortices during cognitive processing is mediated by the structural network in the white matter, structural changes in an association pathway may affect task-related regional cortical response as well as task-modulated functional connectivity in the remote cortices that are connected through this pathway. Investigating the functional relevance of a specific association pathway may provide insights into the neurobiological substrates of a broad spectrum of cognitive and emotional alterations that significantly affect the quality of life in patients with TLE [Giovagnoli and Avanzini, 2000; Helmstaedter et al., 2003].

The arcuate fasciculus (AF) is a major association pathway in the human brain, which is considered to mediate functional connections between remote cortices in anterior and posterior brain regions during language-related processing. The recent advent of diffusion MRI tractography enabled us to visualize the trajectory and microstructural properties of the AF in the living human brain [Dick and Tremblay, 2012]. The AF pathways connecting Broca's area/the right Broca's homologue can be divided into two subcomponents, one projecting to the temporal cortex (frontal–temporal AF pathway) and the other to the parietal cortex (frontal–parietal AF pathway). In healthy subjects, the volume of the frontal–temporal AF pathway is larger in the left hemisphere while that of the frontal–parietal AF pathway is larger in the right hemisphere [Catani et al., 2007; Catani et al., 2005; Makris et al., 2005; Parker et al., 2005; Powell et al., 2006; Thiebaut de Schotten et al., 2011]. In patients with TLE, structural changes in the AF pathway occur. In particular, the frontal–temporal AF pathway ipsilateral to the epileptic focus is vulnerable, and a decrease in volume and changes in microstructural properties have been commonly reported (Ahmadi et al., 2009; Govindan et al., 2008; Imamura et al., 2015; Kucukboyaci et al., 2012; Lin et al., 2008; McDonald et al., 2008a). However, the specific cortical regions that have changed structural connectivity with the AF in patients with TLE remain unclear. Clarifying these regions would allow examination of the changes in functional interactions between two remote cortices that are connected through this pathway.

Functional changes in language-related cortices have also been observed in patients with left TLE. Activity during language tasks decreases in the conventional language-related cortices in the left hemisphere, while additional areas are activated in both hemispheres [Adcock et al., 2003; Billingsley et al., 2001; Brázdil et al., 2005; Janszky et al., 2006; Powell et al., 2007; Thivard et al., 2005; Voets et al., 2006]. Although multiple factors could contribute to the change in cortical activity during language tasks, it has been suggested that patients with left TLE may have difficulty in recruiting the normal neural networks [Thivard et al., 2005] and the alternative network may be involved [Gaillard et al., 2011]. Considering that the frontal–temporal AF pathway connecting the anterior and posterior language-related cortices is a vulnerable pathway in left TLE, the change in structural connectivity through this pathway in the left hemisphere may underlie the change in cortical activity during language tasks in the these cortical regions. In addition, if there is another AF pathway that increases in structural connectivity, this pathway may be employed to compensate for the compromised left frontal–temporal AF pathway during language processing. More specifically, the frontal–temporal AF pathway in the

Abbreviations

ADC	Apparent diffusion coefficient,
AF	Arcuate fasciculus,
fMRI	Functional MRI,
FWHM	Full-width half-maximum,
MD	Mean diffusivity,
MPRAGE	Magnetization-prepared rapid-acquisition gradient-echo,
MRI	Magnetic resonance imaging,
PET	Positron emission tomography,
PPI	Psychophysiological interaction,
TE	Echo time,
TLE	Temporal lobe epilepsy,
TR	Repetition time

right hemisphere or the frontal–parietal AF pathways in each hemisphere might be employed to connect the anterior and posterior brain regions.

Here, we examined the structural connectivity of the AF and its functional relevance during a language task in patients with left TLE. We first examined the change in structural connectivity with Broca's area/the right Broca's homologue through the AF in the inferior parietal and lateral temporal cortices in patients with left TLE, using a surface-based structural connectivity analysis that we have developed [Takaya et al., 2015]. This method allows visualizing the cortical regions that show changes in structural connectivity of a specific fiber pathway. We then examined the association between changed structural connectivity of the AF and changes in task-related regional response and task-modulated functional connectivity during a language task in patients with left TLE. Task-modulated functional connectivity with Broca's area/the right Broca's homologue was evaluated using psychophysiological interaction (PPI) [Friston et al., 1997]. Some previous studies have compared structural changes in the white matter with functional changes during language tasks in the cortex in healthy subjects as well as patients with TLE [Perlaki et al., 2013; Powell et al., 2007]. However, these studies have extracted indices that reflect the microstructural properties from the white matter and compared them with task-related cortical activity. In contrast, the advantage of our method is that it allows direct comparison of structural connectivity, as measured using diffusion MRI, and cortical function, as measured using fMRI, within the same cortical space. To evaluate cortical function during cognitive processing, we used a single-word semantic classification task that is known to activate both Broca's area and the lateral temporal cortex in the left hemisphere. This task is used to identify the language-dominant hemisphere prior to temporal lobectomy and is thought to require functional interaction between the frontal and temporal language-related cortices, purportedly through the AF [Demb et al., 1995; Desmond et al., 1995; Glasser and Rilling, 2008; Takaya et al., 2015; Wang et al., 2014; Whitney et al., 2011].

We expected that structural and functional connectivity between the anterior and posterior language-related cortices would be altered in patients with TLE, even if no structural lesion was present in these neocortical regions. Therefore, we excluded patients with structural abnormalities between the anterior and posterior ends of the AF, including altered cortical thickness in the lateral temporal and inferior parietal cortices, which is often observed in patients with TLE [Bernhardt et al., 2010; McDonald et al., 2008b; Mueller et al., 2009].

MATERIAL AND METHODS

Subjects

We initially recruited 20 right-handed patients with medically intractable left TLE and no concomitant neurological and psychiatric diseases. Patients with neocortical or white matter lesions that were visually detected on conventional MRI were then excluded. We also measured cortical thickness using a computer-based automated algorithm (see data analysis), and excluded patients with altered cortical thickness in the lateral temporal and inferior parietal regions (outside the mean ± 2 SD of healthy controls). Based on these criteria, we excluded 3 patients out of the initial 20. We also recruited right-handed healthy controls from the community who were free from neurological and psychiatric diseases. Thus, we examined 17 patients (mean age $\pm$ standard deviation: 31.7 ± 11.1, nine male) and 17 healthy controls (mean age $\pm$ standard deviation: 29.7 ± 11.5, 6 male). The handedness was assessed using the Edinburgh Handedness Inventory. There was no significant difference between groups in terms of mean age ($P = 0.61$, two sample t-test) and sex ($P > 0.49$, Fisher's exact test). Patients had completed a comprehensive evaluation for epilepsy surgery and received a clinical diagnosis of left TLE based on seizure semiology, electroencephalography, and neuroimaging. All patients underwent long-term video electroencephalography monitoring and conventional MRI. Three of 17 patients showed atypical language lateralization, as assessed by task-activation fMRI [Labudda et al., 2012]. None of healthy subjects showed atypical language lateralization. The clinical information of all patients is listed in Table I. The study was approved by the institutional review board of our institution and each subject provided written informed consent.

Imaging Data Acquisition

All MRI data were acquired on a 3 Tesla Siemens Tim Trio scanner (Erlangen, Germany). A high-resolution three-dimensional structural image was acquired using magnetization-prepared rapid-acquisition gradient-echo (MPRAGE) sequence (voxel size: $1 \times 1 \times 1$ mm; repetition time (TR): 2,000 ms; echo time (TE): 3.37 ms; flip angle: 10°). Diffusion-weighted data were acquired using echo planar imaging (voxel size: $2 \times 2 \times 2$ mm; diffusion weighting isotropically distributed along 60 directions; b value: 700 s/mm^2).

Three runs of task-activation fMRI data were acquired using a language task involving the semantic classification of written words. Images were acquired using a gradient-echo sequence (voxel size: $3 \times 3 \times 3$ mm; TR: 2,000 ms; TE: 30 ms; flip angle: 90°; slice gap: 0.6 mm). Each run consisted of one 8-s initial block that was discarded to allow for T1-equilibration effects, followed by a 28-s fixation block and then a 36-s task block. There were three such fixation/task blocks. During the task blocks, 12 words (six concrete and six abstract words) were presented in random order for 2 s each with a 1-s interstimulus interval. In total, 108 stimuli were presented. Participants were asked to indicate if the word was

TABLE I. Demographic data of patients with left temporal lobe epilepsy

No.	Age/ Sex	Dur.	Diag.	MRI	Ictal SPECT	FDG-PET	MEG	Intracranial EEG	AEDs	Surg.	Pathology	Outcome
1	16/F	13	MTLE	MTS	med T	Med/lat T	T	+	L, Z,	MTL	MTS	I
2	19/F	11	MTLE	MTS	−	Med T	−	+	L, M, G, S	ATL	MTS	I
3	21/F	4	MTLE	MTS	−	Med/lat T	T	−	L, Z	−	−	−
4	21/M	5	MTLE	normal	med T	Med T	T	+	C, L	ATL	MTS	I
5	22/M	13	TLE	normal	−	Med/lat T	T	−	L, Z	−	−	−
6	22/M	17	MTLE	MTS	−	Med/lat T	−	+	L, M, V, R	ATL	MTS	I
7	24/F	7	MTLE	MTS	−	Normal	−	−	M, T	−	−	−
8	30/M	14	MTLE	MTS	−	Med/lat T	−	+	L, C	ATL	MTS	I
9	31/F	15	MTLE	MTS	−	Med/lat T	−	FO	M, Z	−	−	−
10	33/M	15	MTLE	T2 high (Amyg)	−	Med T	T	+	C, V	ATL	Ganglioglioma	I
11	34/F	26	MTLE	MTS	med/ lat T, P	F, T	T	+	L, T, P	ATL+ corticotomy	Gliosis	III
12	41/M	31	MTLE	MTS	−	−	−	FO	P, O	−	−	−
13	41/F	11	MTLE	MTS	−	Med/lat T	−	−	L, S	−	−	−
14	42/M	5	MTLE	normal	−	Normal	−	FO	M, V	−	−	−
15	43/M	3	TLE	normal	−	Med/lat T	T	−	L, M	−	−	−
16	45/F	12	MTLE	MTS	−	Ant T	−	−	M, Z,	-	−	−
17	54/M	20	MTLE	MTS	−	Med/lat T	−	+	M, Z	ATL	MTS	I

All abnormalities detected in neuroimaging and electrophysiological studies were observed in the left hemisphere. Amyg: amygdala; ant: anterior; ATL: anterior temporal lobectomy; Dur.: duration of epilepsy; EEG: electroencephalography; F: frontal lobe; FO: foramen ovale electrodes; lat: lateral; med: medial; MTL: medial temporal lobectomy; MTLE: medial temporal lobe epilepsy; MTS: medial temporal sclerosis; Outcome: postsurgical seizure outcome based on Engel classification; P: parietal lobe, F: frontal lobe; Surg: Surgery; T: temporal lobe; TLE: temporal lobe epilepsy. AEDs (antiepileptic drugs): C = carbamazepine, G = gabapentin, L = levetiracetam, M = lamotrigine, O = oxcarbazepine, P = phenytoin, S = lacosamide, T = topiramate, V = valproate, R =clorazepate, Z = zonisamide.

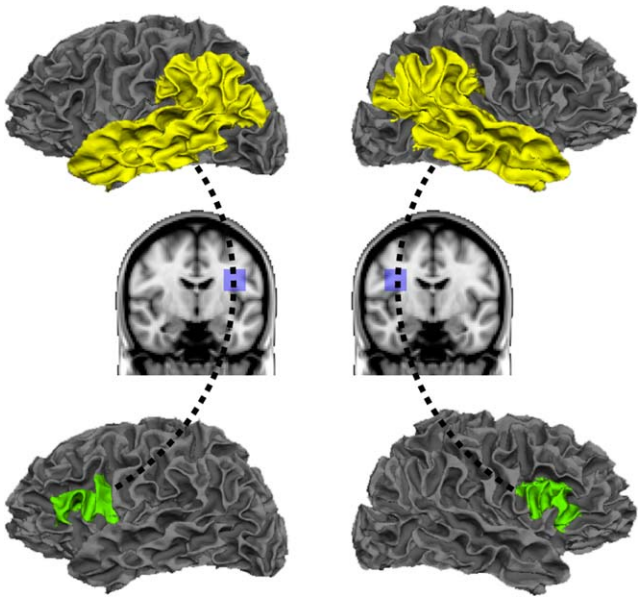

Figure 1.
Seed and target regions and white matter inclusion masks for the structural connectivity analysis of the arcuate fasciculus. Top and bottom figures: Seed (yellow) and target (green) regions at the gray-white matter boundary surface in each hemisphere of an individual brain. **Middle figures**: The symmetric white matter inclusion masks defined in each hemisphere of a standard space (blue).

concrete or abstract without articulating by pressing a key on a keyboard (left-hand key press for abstract words, right-hand key press for concrete words).

Imaging Data Analysis

Anatomical analysis

The structural MRI was analyzed in FreeSurfer (FS) version 5.3 (surfer.nmr.mgh.harvard.edu). FS creates a mesh model of the cortex as well as a thickness measurement [Fischl and Dale, 2000] and region label at each point in the cortex [Desikan et al., 2006]. It also provides surface-based intersubject registration [Dale et al., 1999; Fischl et al., 1999]. The FS anatomical analysis was used as a substrate for the integration of structural connectivity and fMRI results by mapping each of those results to a common surface-based coordinate system.

Cortical thickness measurement

Cortical thickness estimation was obtained using FS. The detailed procedures are described elsewhere [Fischl and Dale, 2000]. Briefly, after an automated procedure including skull-stripping, intensity normalization, and segmentation of subcortical white matter and deep gray matter structures, a single white matter volume for each hemisphere was obtained and covered with a polygonal tessellation. The cortical thickness at each vertex across the cortical mantle was defined by the shortest distance between the white matter surface (the gray-white boundary) and the pial surface (the gray-CSF boundary) at each vertex on the tessellated surface. The individual data were registered to the averaged cortical surface template of each hemisphere and smoothing was performed along the surface with a 10-mm full-width half-maximum (FWHM) Gaussian kernel.

Surface-based structural connectivity analysis for the AF

The tractography analysis was performed using FMRIB's Diffusion Toolbox implemented in FSL version 5.0 (www.fmrib.ox.ac.uk/fsl/fdt). Probabilistic tracts were generated between two FS-defined regions, starting from the gray-white matter boundary surface of the lateral temporal and inferior parietal cortices (seed) and terminating at the boundary surface of Broca's area/the right Broca's homologue (target, defined as the pars opercularis and pars triangularis); see Figure 1. Symmetric inclusion masks were defined in the white matter of a standard volume space (MNI 152) and registered onto the native space of each subject. The white matter inclusion mask for the left AF was located in a standard space (MNI 152) at the level of a single coronal slice at $y = -8$, extending from $x = -28$ to

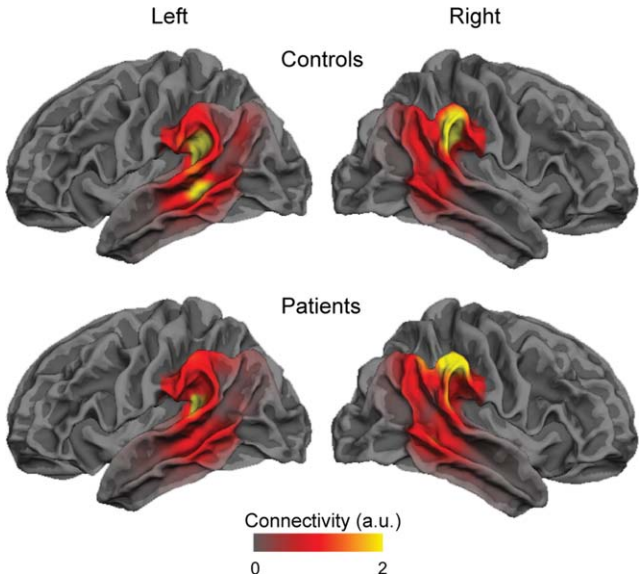

Figure 2.
Group-averaged images of the structural connectivity with Broca's area/the right Broca's homologue through the arcuate fasciculus (AF) in healthy controls (top) and patients with left TLE (bottom) on the averaged gray-white matter boundary surface. The normalized connection probability is rescaled for display purposes. a.u.: arbitrary unit.

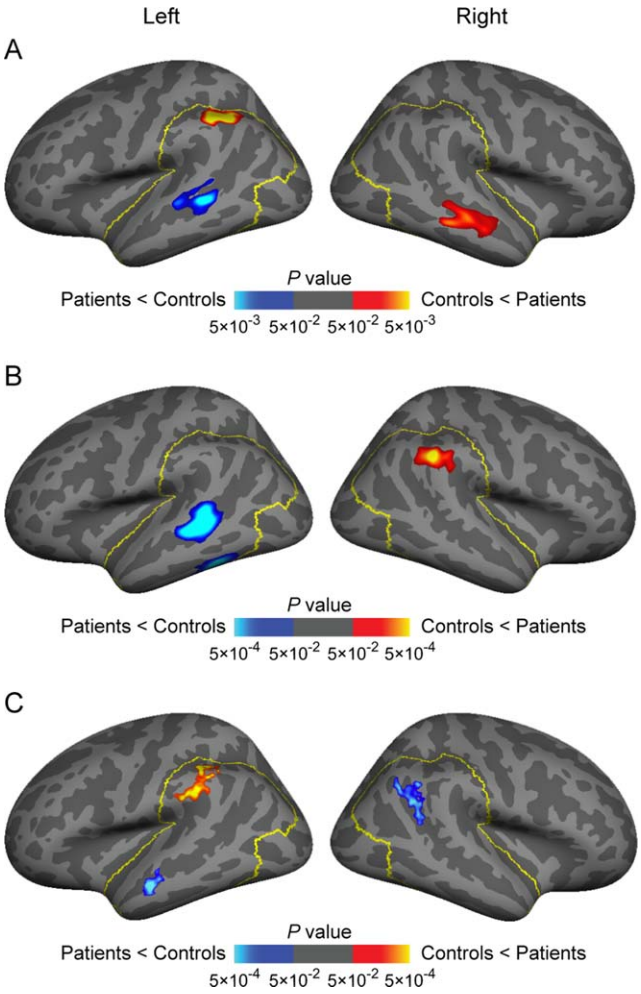

Figure 3.

Group comparison. **(A)** Clusters showing significant patient-control differences in the structural connectivity with Broca's area/the right Broca's homologue through the arcuate fasciculus, **(B)** task-related regional response, and **(C)** task-modulated functional connectivity with Broca's area/the right Broca's homologue during a semantic classification task. The results are displayed on an inflated surface of the average brain. Group comparison analyses were carried out within the inferior parietal and lateral temporal cortices (yellow-outlined region). Darker and lighter regions on the inflated surface denote the sulci and gyri, respectively.

-48, and $z = 16$ to 36. The inclusion mask for the right AF was created by flipping the masks in the left hemisphere. The exclusion mask consisted of the bilateral thalami, striatum, and midline sagittal plane.

The connection probability at a seed voxel was computed as the number of tracts that reached the ipsilateral target region from that seed voxel. The connection probability at each voxel was then normalized by dividing it by the total number of tracts that reached the target region through the white matter inclusion mask from the entire grey–white matter boundary surface in each hemisphere. The normalized connection probability maps of the AF were sampled from the volume onto the cortical surface of each individual's left and right hemispheres. Individual connection probability maps on the cortical surface were registered to the averaged cortical surface template of each hemisphere using surface-based alignment. Smoothing was performed along the surface with a 10-mm FWHM Gaussian kernel (Fig. 2 and Supporting Information Fig. 1). For more details, see elsewhere [Takaya et al., 2015].

Task-activation fMRI data analysis

Surface-based analysis was conducted for task-activation fMRI data using FS Functional Analysis Stream (FS-FAST). The details are described elsewhere (http://surfer.nmr.mgh.harvard.edu/fswiki/FsFast). Briefly, after the first four volumes were discarded to allow for T1-equilibration effects, the fMRI images were motion corrected to the middle time point. The middle fMRI time point was registered to the anatomical image for each subject using boundary-based registration [Greve and Fischl, 2009] and sampled onto the surface. Each individual image was registered to the averaged cortical surface template of each hemisphere using surface-based alignment and smoothed along the surface with a 10-mm FWHM Gaussian kernel [Hagler et al., 2006]. A general linear model was used to determine the brain regions activated in the word-classification task. A boxcar function was convolved with the SPM canonical hemodynamic response function to generate the task regressor. Six head motion parameters were used as nuisance regressors.

Task-modulated functional connectivity

To examine whether functional connectivity with Broca's area/the right Broca's homologue changed during the task in the lateral temporal and inferior parietal cortices in patients with TLE, task-modulated functional connectivity was examined using PPI analysis [Friston et al., 1997]. The PPI first-level analysis model included two psychological regressors (task and rest), one physiological regressor (a mean time course extracted from Broca's area/the right Broca's homologue) and two interaction terms between the psychological and physiological regressors. White matter/CSF signal, six head motion parameters, and the effect of task were regressed using CONN toolbox in Matlab (http://www.nitrc.org/projects/conn/).

Group comparisons

The above steps rendered cortical thickness, the structural connectivity of the AF, task-related regional response, and task-modulated functional connectivity onto the same surface-based common space where they could be compared across subjects and integrated across modalities. The group comparisons for these measurements were

TABLE II. Brain regions showing significant increases and decreases in structural connectivity, task-related response and task-modulated functional connectivity

	Side	Region	Peak coordinate[a] x	y	z	Size (mm^2)	Peak P value
Structural connectivity							
Decrease	L	STS	−50	−42	−2	691	$< 5 \times 10^{-3}$
Increase	L	SMG	−50	−46	45	1035	$< 5 \times 10^{-4}$
	R	STS	66	−32	−12	820	$< 5 \times 10^{-2}$
Task-related response							
Decrease	L	STS	−48	−39	−2	978	$< 5 \times 10^{-7}$
	L	ITS	−46	−36	−24	799	$< 5 \times 10^{-4}$
Increase	R	SMG	52	−44	35	812	$< 5 \times 10^{-5}$
Task-modulated functional connectivity							
Decrease	L	STS	−53	−12	−18	402	$< 5 \times 10^{-4}$
	R	AG	47	−53	25	685	$< 5 \times 10^{-4}$
Increase	L	SMG	−44	−36	42	850	$< 5 \times 10^{-5}$

AG: angular gyrus; ITS: inferior temporal sulcus; SMG: supramarginal gyrus; STS: superior temporal sulcus.
[a]MNI coordinate.

performed using a vertex-wise two-sample *t*-test between patients and healthy controls. We constrained the group comparison for task-activation fMRI and cortical thickness measurement within the same region that was used in the structural connectivity analysis, i.e., the lateral temporal and inferior parietal cortices (yellow outlined region in Fig. 3 and Supporting Information Figs. 2 and 3). Task-modulated functional connectivity with Broca's area and that with the right Broca's homologue were evaluated within the left and right lateral temporal and parietal cortices, respectively. Clusters were defined using a vertex-wise threshold of $P < 0.05$. Cluster-based correction for multiple comparisons was performed using a Monte Carlo simulation within this region [Hagler et al., 2006].

Structure–function relationship

We overlaid the results of group comparisons onto the same surface-based common space and examined their spatial relationship. To further examine the structure–function relationship, we calculated Spearman's correlations using the measurements of structural connectivity, task-related response, and task-modulated functional connectivity of each subject. From the spatially overlapping regions, we extracted the normalized connection probability of the AF for structural connectivity, percent signal changes adjusted by the global response (the mean percent signal change over the entire cortex in the same hemisphere) for task-related regional response, and regression coefficients for task-modulated functional connectivity.

RESULTS

The structural connectivity with Broca's area/the right Broca's homologue through the AF decreased in the left midtemporal cortex (the middle of the superior temporal sulcus), and increased in the left inferior parietal cortex (the posterior part of the supramarginal gyrus) and the right midtemporal cortex (the middle of the superior temporal sulcus) in patients with left TLE as compared to healthy controls (Fig. 3A and Table II). The language-task related response decreased in the left midtemporal cortex (the middle of the superior temporal sulcus) and the left inferior temporal cortex (the posterior fusiform gyrus), and increased in the right inferior parietal cortex (the posterior part of the supramarginal gyrus and anterior part of the angular gyrus) in patients (Fig. 3B and Table II). Task-modulated functional connectivity with Broca's area decreased in the left midtemporal cortex (the middle of the superior temporal sulcus) and increased in the left inferior parietal cortex (the supramarginal gyrus) and that with the right Broca's homologue decreased in the right inferior parietal cortex (the anterior part of the angular gyrus) in patients (Fig. 3C and Table II).

The brain region showing a decrease in the structural connectivity of the AF overlapped with the region showing a decrease in task-related response in the left midtemporal cortex (Fig. 4A left). There was a positive correlation between the structural connectivity and task-related response in the overlapping region (Spearman's $rho = 0.36$, $P = 0.037$; Fig. 4A right). The region showing an increase in the structural connectivity of the AF partially overlapped with the brain region showing an increase in task-modulated functional connectivity with Broca's area in the left inferior parietal cortex (Fig. 4B left). There was a positive correlation between the structural connectivity and task-modulated functional connectivity in the overlapping region (Spearman's $rho = 0.40$, $P = 0.020$; Fig. 4B right).

The vertex-wise group analysis of cortical thickness measurements indicated that no significant thinning or

thickening was found within these regions in patients (Supporting Information Fig. 2). Even when two patients whose epileptic focus was not determined in the medial temporal lobe or three patients who had atypical language lateralization were excluded from the analyses (Patient No. 5 and 15, and Patients No. 5, 11 and 13 in Table I, respectively), the results were substantially unaltered (Supporting Information Fig. 3).

DISCUSSION

In summary, surface-based analysis based on probabilistic tractography showed that the structural connectivity with Broca's area/the right Broca's homologue through the AF decreased in the left midtemporal cortex and increased in the left inferior parietal and right midtemporal cortices in patients with left TLE. Taking advantage of a surface-based method that enabled us to map the results across modalities on the same surface-based common space, we compared changes in the structural connectivity of the AF with changes in task-related regional responses and task-modulated functional connectivity with Broca's area/the right Broca's homologue during a semantic classification task of a single word. In particular, structural changes were associated with functional changes in the same regions in the midtemporal and inferior parietal cortices in the left hemisphere.

Changes in Structural Connectivity Through the AF in the Temporal and Parietal Cortices

The structural connectivity with Broca's area through the left frontal–temporal AF pathway decreased in the left midtemporal cortex in patients with left TLE. A widely distributed change in white matter has been reported in patients with TLE [Bernasconi et al., 2004; Focke et al., 2008]. Previous diffusion MRI tractography studies have shown that the volume and integrity of the white matter pathways connecting the frontal and temporal language-related cortices are decreased in patients with TLE [Powell et al., 2007]. Among these pathways, the AF ipsilateral to the epileptic focus is highly vulnerable [Ahmadi et al., 2009; Govindan et al., 2008; Imamura et al., 2015; Kucukboyaci et al., 2012; Lin et al., 2008; McDonald et al., 2008a]. Our result extends these previous findings by more specifically showing a regional decrease in the structural connectivity of the frontal–temporal AF pathway in the middle of the left superior temporal sulcus in patients with left TLE. The AF extending to the midtemporal cortex may be relevant to the evolution of language in the human brain because this pathway is absent in nonhuman primates [Rilling et al., 2008]. In addition, this pathway is more dominant in the left hemisphere than the right hemisphere in the healthy human brain [Catani et al., 2007; Takaya et al., 2015]. Our results indicate that the AF extending to the midtemporal cortex, which may play a substantial role during language-related processing in the healthy human brain, is likely to be affected in patients with left TLE.

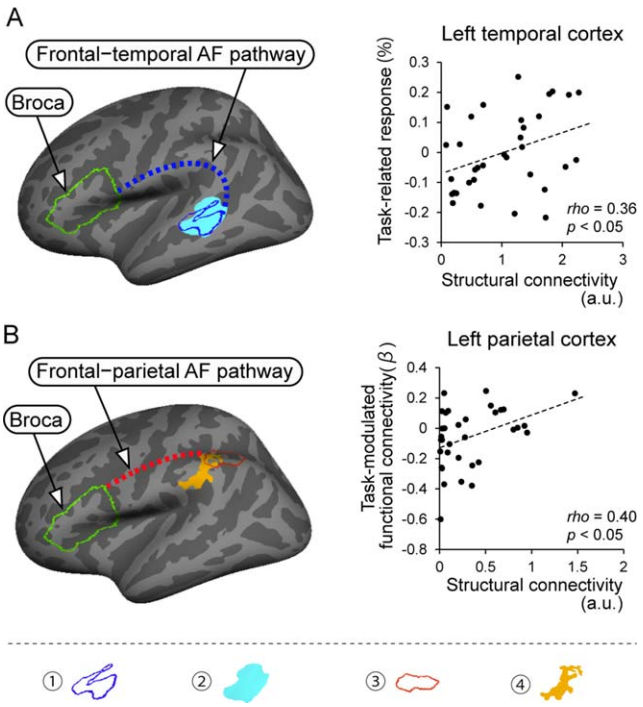

Figure 4.
Structure–function relationship. **(A)** The brain region showing a decrease in the structural connectivity through the frontal−temporal arcuate fasciculus (AF) pathway (① the blue outlined area; see also the left figure in **Fig. 3A**) overlaps with the region showing a decrease in task-related response during semantic classification task (② the blue filled area; see also the left figure in **Fig. 3B**). Structural connectivity correlates with task-related response in the overlapping region in the left temporal cortex. **(B)** The brain regions showing an increase in the structural connectivity through the frontal−parietal AF pathway (③ the red outlined area; see also the left figure in **Fig. 3A**) partially overlaps with the region showing an increase in task-modulated functional connectivity with Broca's area during a semantic classification task (④ the orange filled area; see also the left figure in **Fig. 3C**). Structural connectivity correlates with task-modulated functional connectivity in the overlapping region in the left parietal cortex. a.u.: arbitrary unit; β: regression coefficient; *rho*: Spearman's correlation coefficient.

In contrast, the structural connectivity with the right Broca's homologue through the right frontal–temporal AF pathway increased in the right midtemporal cortex in the current study. Regarding the structural changes in the right AF in patients with left TLE, various results have been reported in previous studies depending on how this pathway was evaluated. Some studies that used indices reflecting white matter integrity, such as fractional anisotropy (FA), mean diffusivity (MD) and apparent diffusion

coefficient (ADC), have claimed damage to the right AF. One such study reported that FA decreased in 9 adult patients with left TLE although MD was unchanged (McDonald et al., 2008a). Another study reported that ADC increased in 13 children with left TLE although FA was unchanged [Kim et al., 2011]. In these studies, however, the averaged indices were extracted from the AF that was defined using diffusion MRI tractography. Therefore, the results were highly dependent on how the AF was defined. In contrast, when the volume of the white matter pathway that connects the right frontal cortex including the right Broca's homologue was evaluated, the white matter volume of the pathway that projects to the temporal lobe (corresponding to the right frontal–temporal AF pathway in the current study) increased in seven patients with left TLE [Powell et al., 2007]. This method is similar to the method we used in the current study. We confirmed this prior finding with a larger number of patients and more specifically delineated a region showing an increase in the structural connectivity of the frontal–temporal AF pathway in the middle of the right superior temporal sulcus, approximately in the homologous region showing a decrease in structural connectivity in the left hemisphere.

Animal studies have shown that the brain has the capacity to anatomically rewire in the ipsilateral and contralateral hemispheres in response to brain damage [Chen et al., 2002; Dancause et al., 2005; Stroemer et al., 1995]. However, the large-scale rewiring of long tracts after brain lesion in the adult human brain has not been well demonstrated. It seems more likely that disease modifies structural organization that occurs during the course of development. In normal development, the AF shows increased FA and decreased radial diffusivity, which has been interpreted as the maturation of this pathway in development [Asato et al., 2010; Giorgio et al., 2008]. The maturation of the white matter pathway might be related to an increase in myelination that continues to occur through adolescence [Benes, 1989; Yakovlev and Lecours, 1967]. Furthermore, a recent study using post-mortem tissues of the human brain demonstrated that synaptic pruning in the prefrontal cortex continues until an individual's late twenties [Petanjek et al., 2011]. Therefore, one possible hypothesis that explains our findings is that the right AF that connects the right Broca's homologue and the right midtemporal cortex might evade the pruning and develop if the left hemisphere acquires epileptogenicity during development and the maturation of the left AF is disturbed.

An increase in structural connectivity through the left frontal–parietal AF pathway was also observed in the left inferior parietal cortex. Contrary to our result, one study has shown that the mean FA in the whole trajectory of this pathway did not increase, but decreased in the left hemisphere as compared with healthy subjects [Ahmadi et al., 2009]. However, microstructural white matter changes such as FA are distributed heterogeneously in patients with TLE. For example, while a decrease in FA has been observed in the most parts of the white matter in patients with TLE, an increase in FA has been reported in remote white matter pathways that are not directly connected with the affected temporal lobe, such as the corpus callosum [Meng et al., 2010] and the internal capsule [Wang et al., 2010]. Furthermore, even within a white matter pathway that is connected with the affected temporal lobe, such as the uncinate fasciculus, the inferior longitudinal fasciculus, and the frontal–temporal AF pathway, the microstructural white matter abnormalities are more prominent in proximal segments near the affected temporal lobe and taper off in distal segments outside the temporal lobe [Concha et al., 2012]. Possible explanations for these results are that pathological changes are more likely to occur in the vicinity of the epileptic focus and that the affected pathway is compensated by intact axons joining the pathway in distant regions [Bodini and Ciccarelli, 2013]. As an extension of these previous studies, our results might indicate that the structural connectivity of the left frontal–parietal AF pathway increases in the distal part of the projection regions from the affected temporal lobe.

Functional Changes Through the AF in the Temporal and Parietal Cortices

Although the role of the frontal and temporal cortices in the semantic network is highly controversial, the left temporal cortex may be essential for the storage of semantic information [Binder et al., 2009; Binder et al., 1997; Bookheimer, 2002; Hickok and Poeppel, 2004; Patterson et al., 2007; Vandenberghe et al., 1996; Vigneau et al., 2006; Whitney et al., 2011]. In contrast, the left inferior prefrontal cortex, including Broca's area, may serve as a central executive for retrieving and evaluating semantic information and making decisions, presumably via top-down signals to the temporal cortex [Badre et al., 2005; Binder et al., 1997; Bookheimer, 2002; Demb et al., 1995; Thompson-Schill et al., 1997; Wagner et al., 2001; Whitney et al., 2011]. In particular, the semantic classification task requires functional interaction between Broca's area and the left midtemporal cortex, supposedly through the AF [Demb et al., 1995; Glasser and Rilling, 2008; Takaya et al., 2015; Wang et al., 2014; Whitney et al., 2011]. In the current study, structural and task-modulated functional connectivity with Broca's area decreased in the left midtemporal cortices. In addition, task-related regional response decreased in the left midtemporal cortex that overlapped with a region showing a decrease in the structural connectivity with Broca's area through the AF. Furthermore, these changes were positively correlated. Therefore, we assume that the change in the structural connectivity through the left frontal–temporal AF pathway alters functional networks between the frontal and temporal cortices in patients with left TLE. This assumption is consistent with a previously proposed hypothesis that

patients with left TLE have difficulty in recruiting the frontal–temporal network in the left hemisphere during language processing [Thivard et al., 2005]. Our results support this hypothesis and suggest that changed structural connectivity of the frontal–temporal AF pathway underlies such difficulty in recruiting the functional networks between the frontal and temporal cortices in patients with left TLE.

The concomitant structural and functional changes in the left midtemporal cortex are unlikely to result simply from macroanatomical changes in this region because we excluded patients with MRI abnormalities, including significant brain atrophy, in this region. Furthermore, there was no significant change in cortical thickness in this area in the individual and group analyses. However, microscopic neocortical and white matter abnormalities that are undetectable via MRI can be found in the resected temporal lobe specimens of patients with TLE, regardless of the presence or absence of medial temporal sclerosis [Carne et al., 2004; Kasper et al., 2003; Mitchell et al., 1999]. Therefore, microstructural changes in this cortical region and/or in the white matter between the temporal and frontal cortices might have influenced the structural connectivity of the AF, task-related regional responses and task-modulated functional connectivity in this region.

Intrahemispheric and interhemispheric functional reorganization of the language-related cortices has been reported in patients with left TLE using various language tasks in fMRI studies [Adcock et al., 2003; Billingsley et al., 2001; Brázdil et al., 2005; Janszky et al., 2006; Powell et al., 2007; Thivard et al., 2005; Voets et al., 2006]. The changed cortical response during the tasks may indicate that alternative networks are involved to compensate for the compromised brain network, so as to achieve adequate task performance [Gaillard et al., 2011]. In the current study, Broca's area and the left inferior parietal cortex, which are structurally connected through the frontal–parietal AF pathway, showed an increase both in structural and task-modulated functional connectivity. In addition, there was a positive correlation between structural and task-modulated functional connectivity. These results suggest that functional coupling during the language task increased between Broca's area and the left inferior parietal cortex through the left frontal–parietal AF pathway in patients. The left frontal–parietal AF pathway, which showed an increase in structural connectivity with Broca's area, might be employed to connect the anterior and posterior language-related cortices during language processing and compensate for the compromised left frontal–temporal AF pathway in patients with left TLE. However, in the current study, such increases in structural and functional connectivity with Broca's area were not accompanied by changes in task-related responses in the left inferior parietal cortex. This might be because of a lack of sensitivity or the variability associated with group analysis. Another possibility is that an increase in functional coupling with Broca's area was not effective to induce a change in the task-related cortical response in the left parietal cortex.

Contrary to the left hemisphere, structural and functional changes were mismatched in the right hemisphere. It has been shown that in patients with left TLE as compared with healthy subjects, the functional response during some language tasks increases in multiple regions in the right hemisphere, including the right Broca's homologue [Janszky et al., 2006; Voets et al., 2006]. Thus, the right hemisphere is thought to play a substantial role in the reorganization of language function in patients with left TLE. However, despite a potential compensatory functional shift of language to the right hemisphere, this hemisphere is not as able to process language as the left hemisphere. Studies of patients who underwent left hemispherectomy in their early life have shown that language-related processing in the right hemisphere is not always carried out in the anatomical homologues of the conventional language-related cortices in the left hemisphere [Liégeois et al., 2008; Voets et al., 2006]. In the current study, while the structural connectivity of the AF in the right hemisphere increased in the homologous region showing a decrease in the structural connectivity of the AF in the left hemisphere, it was not accompanied by changes in task-related regional response or task-modulated functional connectivity. Our results indicate that structural brain networks other than the AF may underlie functional reorganization in the right hemisphere to connect the anterior and posterior brain regions during language processing.

Another point of interest is that task-modulated functional connectivity with the right Broca's homologue decreased in the right inferior parietal cortex. Studies of patients after stroke have shown that the involvement of the homologous language network in the right hemisphere may not be optimal for functional recovery after an insult in the left hemisphere [Belin et al., 1996; Rosen et al., 2000]. Furthermore, the suppression of the right homologous network may enhance the recovery of language function [Hamilton et al., 2010; Naeser et al., 2005; Naeser et al., 2011]. In patients with left TLE, an increase in task-modulated functional connectivity between the frontal and parietal cortices in the left hemisphere may enhance functional reorganization in combination with a decrease in task-modulated functional connectivity in the right homologous network.

Caveats and Future Studies

Despite the potential implications of our findings for clinical neuroscience, there are caveats regarding our study. First, whether the reorganization of the language network in patients with left TLE is adaptive or maladaptive for actual cognitive performance was not addressed. We did not evaluate performance during the fMRI scans

because our semantic classification task included ambiguous words that cannot be simply classified. In addition, we have not recorded neuropsychological measurements for all the patients in a consistent manner because the primary purpose of the current study was to examine the relationship between structural changes in the white matter and functional changes in the cortex during a cognitive task. Further studies are needed to explore the effect of the structural-functional reorganization of language network on the change in language abilities.

Second, we used a single-word classification task in contrast to a low-level non-linguistic fixation baseline. This could involve many brain regions that mediate multiple levels of language processing. Finer-grained fMRI designs and contrasts are needed to investigate structure–function relationships during specific aspects of language processing.

Third, our findings were based on cross-sectional group comparisons and the direct effect of the epileptic activity on the structure-function relationship through the AF in each patient remains unclear. Patients with left TLE usually have widespread cognitive morbidity including lower general intelligence, memory, language, and executive functions than healthy subjects [Hermann et al., 1997; Oyegbile et al., 2004]. Therefore, the use of different strategies when performing the paradigm may affect fMRI results. In addition, antiepileptic drugs may also influence fMRI results. In order to address these many confounding factors, multivariate analyses with a much larger number of subjects or longitudinal studies to evaluate the effect of epileptic activity are warranted. Given that the cortical dysfunction at rest that exists among numerous brain regions, as measured by [^{18}F]-FDG PET, improves after the selective removal of the epileptogenic lesion in patients with TLE [Dupont et al., 2001; Takaya et al., 2009], the task-related response and task-modulated functional connectivity during language-related processing may be ameliorated in the cortices that are connected through the AF after epilepsy surgery is carried out without injuring this pathway and patients become seizure free.

CONCLUSIONS

We used surface-based structural connectivity analysis based on probabilistic tractography and demonstrated altered structural connectivity with Broca's area/the right Broca's homologue through the AF in the lateral temporal and inferior parietal cortices in patients with left TLE. Taking advantage of this method to map the structural connectivity of the AF to the cortex, we then examined the relevance of the change in the structural connectivity of the AF to cortical function. Our results suggest that a decrease in structural connectivity with Broca's area through the left frontal–temporal AF pathway underlies the altered functional networks between the frontal and temporal cortices during language-related processing in the left hemisphere in patients with left TLE. In contrast, the left frontal–parietal AF pathway, which showed an increase in structural connectivity with Broca's area, might be employed to connect anterior and posterior language-related cortices during the task and compensate for the compromised left frontal–temporal AF pathway in patients with left TLE. Our study implies that the cortical interaction during cognitive processing through specific white matter pathways is altered in patients with TLE.

REFERENCES

Adcock JE, Wise RG, Oxbury JM, Oxbury SM, Matthews PM (2003): Quantitative fMRI assessment of the differences in lateralization of language-related brain activation in patients with temporal lobe epilepsy. NeuroImage 18:423–438.

Ahmadi ME, Hagler DJ Jr, McDonald CR, Tecoma ES, Iragui VJ, Dale AM, Halgren E (2009): Side matters: Diffusion tensor imaging tractography in left and right temporal lobe epilepsy. Am J Neuroradiol 30:1740–1747.

Arnold S, Schlaug G, Niemann H, Ebner A, Luders H, Witte OW, Seitz RJ (1996): Topography of interictal glucose hypometabolism in unilateral mesiotemporal epilepsy. Neurology 46: 1422–1430.

Asato MR, Terwilliger R, Woo J, Luna B (2010): White matter development in adolescence: A DTI study. Cerebral Cortex 20: 2122–2131.

Badre D, Poldrack RA, Pare-Blagoev EJ, Insler RZ, Wagner AD (2005): Dissociable controlled retrieval and generalized selection mechanisms in ventrolateral prefrontal cortex. Neuron 47: 907–918.

Bartha-Doering L, Trinka E (2014): The interictal language profile in adult epilepsy. Epilepsia 55:1512–1525.

Belin P, Van Eeckhout P, Zilbovicius M, Remy P, Francois C, Guillaume S, Chain F, Rancurel G, Samson Y (1996): Recovery from nonfluent aphasia after melodic intonation therapy: A PET study. Neurology 47:1504–1511.

Benes FM (1989): Myelination of cortical-hippocampal relays during late adolescence. Schizophrenia Bull 15:585–593.

Bernasconi N, Duchesne S, Janke A, Lerch J, Collins DL, Bernasconi A (2004): Whole-brain voxel-based statistical analysis of gray matter and white matter in temporal lobe epilepsy. NeuroImage 23:717–723.

Bernhardt BC, Bernasconi N, Concha L, Bernasconi A (2010): Cortical thickness analysis in temporal lobe epilepsy: Reproducibility and relation to outcome. Neurology 74:1776–1784.

Besson P, Dinkelacker V, Valabregue R, Thivard L, Leclerc X, Baulac M, Sammler D, Colliot O, Lehericy S, Samson S, Dupont S (2014): Structural connectivity differences in left and right temporal lobe epilepsy. NeuroImage 100:135–144.

Billingsley RL, McAndrews MP, Crawley AP, Mikulis DJ (2001): Functional MRI of phonological and semantic processing in temporal lobe epilepsy. Brain 124:1218–1227.

Binder JR, Frost JA, Hammeke TA, Cox RW, Rao SM, Prieto T (1997): Human brain language areas identified by functional magnetic resonance imaging. J Neurosci 17:353–362.

Binder JR, Desai RH, Graves WW, Conant LL (2009): Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. Cerebral Cortex 19: 2767–2796.

Bodini, B., Ciccarelli, O. (2013) Diffusion MRI in neurological disorders. In: Johansen-Berg H, Behrens TEJ, editors. Diffusion MRI, 2nd ed. London: Academic Press. pp 241–255.

Bookheimer S (2002): Functional MRI of language: New approaches to understanding the cortical organization of semantic processing. Ann Rev Neurosci 25:151–188.

Brázdil M, Chlebus P, Mikl M, Pažourková M, Krupa P, Rektor I (2005): Reorganization of language-related neuronal networks in patients with left temporal lobe epilepsy—An fMRI study. Eur J Neurol 12:268–275.

Carne RP, O'Brien TJ, Kilpatrick CJ, MacGregor LR, Hicks RJ, Murphy MA, Bowden SC, Kaye AH, Cook MJ (2004): MRI-negative PET-positive temporal lobe epilepsy: A distinct surgically remediable syndrome. Brain 127:2276–2285.

Catani M, Jones DK, ffytche DH (2005): Perisylvian language networks of the human brain. Ann Neurol 57:8–16.

Catani M, Allin MP, Husain M, Pugliese L, Mesulam MM, Murray RM, Jones DK (2007): Symmetries in human brain language pathways correlate with verbal recall. Proc Nat Acad Sci U S A 104:17163–17168.

Chen P, Goldberg DE, Kolb B, Lanser M, Benowitz LI (2002): Inosine induces axonal rewiring and improves behavioral outcome after stroke. Proc Natl Acad Sci U S A 99:9031–9036.

Concha L, Kim H, Bernasconi A, Bernhardt BC, Bernasconi N (2012): Spatial patterns of water diffusion along white matter tracts in temporal lobe epilepsy. Neurology 79:455–462.

Dale AM, Fischl B, Sereno MI (1999): Cortical surface-based analysis. I. Segmentation and surface reconstruction. NeuroImage 9:179–194.

Dancause N, Barbay S, Frost SB, Plautz EJ, Chen D, Zoubina EV, Stowe AM, Nudo RJ (2005): Extensive cortical rewiring after brain injury. J Neurosci 25:10167–10179.

Demb JB, Desmond JE, Wagner AD, Vaidya CJ, Glover GH, Gabrieli JD (1995): Semantic encoding and retrieval in the left inferior prefrontal cortex: A functional MRI study of task difficulty and process specificity. J Neurosci 15:5870–5878.

Desikan RS, Segonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS, Killiany RJ (2006): An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. NeuroImage 31:968–980.

Desmond JE, Sum JM, Wagner AD, Demb JB, Shear PK, Glover GH, Gabrieli JD, Morrell MJ (1995): Functional MRI measurement of language lateralization in Wada-tested patients. Brain: A journal of Neurology 118:1411–1419.

Dick AS, Tremblay P (2012): Beyond the arcuate fasciculus: Consensus and controversy in the connectional anatomy of language. Brain 135:3529–3550.

Diehl B, Busch RM, Duncan JS, Piao Z, Tkach J, Luders HO (2008): Abnormalities in diffusion tensor imaging of the uncinate fasciculus relate to reduced memory in temporal lobe epilepsy. Epilepsia 49:1409–1418.

Dupont S, Croize AC, Semah F, Hasboun D, Samson Y, Clemenceau S, Baulac M (2001): Is amygdalohippocampectomy really selective in medial temporal lobe epilepsy? A study using positron emission tomography with (18)fluorodeoxyglucose. Epilepsia 42:731–740.

Fischl B, Dale AM (2000): Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci U S A 97:11050–11055.

Fischl B, Sereno MI, Tootell RB, Dale AM (1999): High-resolution intersubject averaging and a coordinate system for the cortical surface. Hum Brain Mapp 8:272–284.

Focke NK, Yogarajah M, Bonelli SB, Bartlett PA, Symms MR, Duncan JS (2008): Voxel-based diffusion tensor imaging in patients with mesial temporal lobe epilepsy and hippocampal sclerosis. NeuroImage 40:728–737.

Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, Dolan RJ (1997): Psychophysiological and modulatory interactions in neuroimaging. NeuroImage 6:218–229.

Gaillard WD, Berl MM, Duke ES, Ritzl E, Miranda S, Liew C, Finegersh A, Martinez A, Dustin I, Sato S, Theodore WH (2011): fMRI language dominance and FDG-PET hypometabolism. Neurology 76:1322–1329.

Giorgio A, Watkins KE, Douaud G, James AC, James S, De Stefano N, Matthews PM, Smith SM, Johansen-Berg H (2008): Changes in white matter microstructure during adolescence. NeuroImage 39:52–61.

Giovagnoli AR, Avanzini G (2000): Quality of life and memory performance in patients with temporal lobe epilepsy. Acta Neurol Scand 101:295–300.

Glasser MF, Rilling JK (2008): DTI tractography of the human brain's language pathways. Cerebral Cortex 18:2471–2482.

Govindan RM, Makki MI, Sundaram SK, Juhasz C, Chugani HT (2008): Diffusion tensor analysis of temporal and extra-temporal lobe tracts in temporal lobe epilepsy. Epilepsy Res 80:30–41.

Greve DN, Fischl B (2009): Accurate and robust brain image alignment using boundary-based registration. NeuroImage 48:63–72.

Hagler DJ, Jr., Saygin AP, Sereno MI (2006): Smoothing and cluster thresholding for cortical surface-based group analysis of fMRI data. NeuroImage 33:1093–1103.

Hamilton RH, Sanders L, Benson J, Faseyitan O, Norise C, Naeser M, Martin P, Coslett HB (2010): Stimulating conversation: Enhancement of elicited propositional speech in a patient with chronic non-fluent aphasia following transcranial magnetic stimulation. Brain Language 113:45–50.

Haneef Z, Lenartowicz A, Yeh HJ, Engel J Jr, Stern JM (2012): Effect of lateralized temporal lobe epilepsy on the default mode network. Epilepsy Behav 25:350–357.

Helmstaedter C, Kurthen M, Lux S, Reuber M, Elger CE (2003): Chronic epilepsy and cognition: A longitudinal study in temporal lobe epilepsy. Ann Neurol 54:425–432.

Hermann BP, Seidenberg M, Schoenfeld J, Davies K (1997): Neuropsychological characteristics of the syndrome of mesial temporal lobe epilepsy. Arch Neurol 54:369–376.

Hickok G, Poeppel D (2004): Dorsal and ventral streams: A framework for understanding aspects of the functional anatomy of language. Cognition 92:67–99.

Imamura H, Matsumoto R, Takaya S, Nakagawa T, Shimotake A, Kikuchi T, Sawamoto N, Kuniedad T, Mikuni N, Miyamoto S, Fukuyama H, Takahashi R, Ikeda A. (2015) Network specific change in white matter integrity in mesial temporal lobe. Epilepsy Res 120:65–72.

Janszky J, Mertens M, Janszky I, Ebner A, Woermann FG (2006): Left-sided interictal epileptic activity induces shift of language lateralization in temporal lobe epilepsy: An fMRI study. Epilepsia 47:921–927.

Jokeit H, Seitz RJ, Markowitsch HJ, Neumann N, Witte OW, Ebner A (1997): Prefrontal asymmetric interictal glucose hypometabolism and cognitive impairment in patients with temporal lobe epilepsy. Brain 120:2283–2294.

Kasper BS, Stefan H, Paulus W (2003): Microdysgenesis in mesial temporal lobe epilepsy: A clinicopathological study. Ann Neurol 54:501–506.

Keller SS, Roberts N (2008): Voxel-based morphometry of temporal lobe epilepsy: An introduction and review of the literature. Epilepsia 49:741–757.

Kim CH, Chung CK, Koo BB, Lee JM, Kim JS, Lee SK (2011): Changes in language pathways in patients with temporal lobe epilepsy: Diffusion tensor imaging analysis of the uncinate and arcuate fasciculi. World Neurosurg 75:509–516.

Kucukboyaci NE, Girard HM, Hagler DJ Jr, Kuperman J, Tecoma ES, Iragui VJ, Halgren E, McDonald CR (2012): Role of fronto-temporal fiber tract integrity in task-switching performance of healthy controls and patients with temporal lobe epilepsy. J Int Neuropsychol Soc 18:57–67.

Labudda K, Mertens M, Janszky J, Bien CG, Woermann FG (2012): Atypical language lateralisation associated with right fronto-temporal grey matter increases–a combined fMRI and VBM study in left-sided mesial temporal lobe epilepsy patients. NeuroImage 59:728–737.

Liégeois F, Connelly A, Baldeweg T, Vargha-Khadem F (2008): Speaking with a single cerebral hemisphere: fMRI language organization after hemispherectomy in childhood. Brain Language 106:195–203.

Lin JJ, Riley JD, Juranek J, Cramer SC (2008): Vulnerability of the frontal-temporal connections in temporal lobe epilepsy. Epilepsy Res 82:162–170.

Makris N, Kennedy DN, McInerney S, Sorensen AG, Wang R, Caviness VS Jr, Pandya DN (2005): Segmentation of subcomponents within the superior longitudinal fascicle in humans: A quantitative, in vivo, DT-MRI study. Cerebral Cortex 15: 854–869.

McDonald CR, Ahmadi ME, Hagler DJ, Tecoma ES, Iragui VJ, Gharapetian L, Dale AM, Halgren E (2008a): Diffusion tensor imaging correlates of memory and language impairments in temporal lobe epilepsy. Neurology 71:1869–1876.

McDonald CR, Hagler DJ Jr, Ahmadi ME, Tecoma E, Iragui V, Gharapetian L, Dale AM, Halgren E (2008b): Regional neocortical thinning in mesial temporal lobe epilepsy. Epilepsia 49: 794–803.

McDonald CR, Leyden KM, Hagler DJ, Kucukboyaci NE, Kemmotsu N, Tecoma ES, Iragui VJ (2014): White matter microstructure complements morphometry for predicting verbal memory in epilepsy. Cortex 58:139–150.

Meng L, Xiang J, Kotecha R, Rose D, Zhao H, Zhao D, Yang J, Degrauw T (2010): White matter abnormalities in children and adolescents with temporal lobe epilepsy. Magn Reson Imaging 28:1290–1298.

Mitchell LA, Jackson GD, Kalnins RM, Saling MM, Fitt GJ, Ashpole RD, Berkovic SF (1999): Anterior temporal abnormality in temporal lobe epilepsy: A quantitative MRI and histopathologic study. Neurology 52:327–336.

Mueller SG, Laxer KD, Barakos J, Cheong I, Garcia P, Weiner MW (2009): Widespread neocortical abnormalities in temporal lobe epilepsy with and without mesial sclerosis. NeuroImage 46:353–359.

Naeser MA, Martin PI, Nicholas M, Baker EH, Seekins H, Kobayashi M, Theoret H, Fregni F, Maria-Tormos J, Kurland J, Doron KW, Pascual-Leone A (2005): Improved picture naming in chronic aphasia after TMS to part of right Broca's area: An open-protocol study. Brain Language 93:95–105.

Naeser MA, Martin PI, Theoret H, Kobayashi M, Fregni F, Nicholas M, Tormos JM, Steven MS, Baker EH, Pascual-Leone A (2011): TMS suppression of right pars triangularis, but not pars opercularis, improves naming in aphasia. Brain Language 119:206–213.

Oyegbile TO, Dow C, Jones J, Bell B, Rutecki P, Sheth R, Seidenberg M, Hermann BP (2004): The nature and course of neuropsychological morbidity in chronic temporal lobe epilepsy. Neurology 62:1736–1742.

Parker GJ, Luzzi S, Alexander DC, Wheeler-Kingshott CA, Ciccarelli O, Lambon Ralph MA (2005): Lateralization of ventral and dorsal auditory-language pathways in the human brain. NeuroImage 24:656–666.

Patterson K, Nestor PJ, Rogers TT (2007): Where do you know what you know? The representation of semantic knowledge in the human brain. Nat Rev Neurosci 8:976–987.

Perlaki G, Horvath R, Orsi G, Aradi M, Auer T, Varga E, Kantor G, Altbacker A, John F, Doczi T, Komoly S, Kovacs N, Schwarcz A, Janszky J (2013): White-matter microstructure and language lateralization in left-handers: A whole-brain MRI analysis. Brain Cogn 82:319–328.

Petanjek Z, Judas M, Simic G, Rasin MR, Uylings HB, Rakic P, Kostovic I (2011): Extraordinary neoteny of synaptic spines in the human prefrontal cortex. Proc Natl Acad Sci U S A 108: 13281–13286.

Powell HW, Parker GJ, Alexander DC, Symms MR, Boulby PA, Wheeler-Kingshott CA, Barker GJ, Noppeney U, Koepp MJ, Duncan JS (2006): Hemispheric asymmetries in language-related pathways: A combined functional MRI and tractography study. NeuroImage 32:388–399.

Powell HW, Parker GJ, Alexander DC, Symms MR, Boulby PA, Wheeler-Kingshott CA, Barker GJ, Koepp MJ, Duncan JS (2007): Abnormalities of language networks in temporal lobe epilepsy. NeuroImage 36:209–221.

Protzner AB, McAndrews MP (2011): Network alterations supporting word retrieval in patients with medial temporal lobe epilepsy. J Cognit Neurosci 23:2605–2619.

Protzner AB, Kovacevic N, Cohn M, McAndrews MP (2013): Characterizing functional integrity: Intraindividual brain signal variability predicts memory performance in patients with medial temporal lobe epilepsy. J Neurosci 33:9855–9865.

Riley JD, Franklin DL, Choi V, Kim RC, Binder DK, Cramer SC, Lin JJ (2010): Altered white matter integrity in temporal lobe epilepsy: Association with cognitive and clinical profiles. Epilepsia 51:536–545.

Rilling JK, Glasser MF, Preuss TM, Ma X, Zhao T, Hu X, Behrens TE (2008): The evolution of the arcuate fasciculus revealed with comparative DTI. Nat Neurosci 11:426–428.

Rosen HJ, Petersen SE, Linenweber MR, Snyder AZ, White DA, Chapman L, Dromerick AW, Fiez JA, Corbetta MD (2000): Neural correlates of recovery from aphasia after damage to left inferior frontal cortex. Neurology 55:1883–1894.

Sanjuán A, Bustamante JC, García-Porcar M, Rodríguez-Pujadas A, Forn C, Martinez JC, Campos A, Palau J, Gutiérrez A, Villanueva V, Avila C (2013): Bilateral inferior frontal language-related activation correlates with verbal recall in patients with left temporal lobe epilepsy and typical language distribution. Epilepsy Res 104:118–124.

Stroemer RP, Kent TA, Hulsebosch CE (1995): Neocortical neural sprouting, synaptogenesis, and behavioral recovery after neocortical infarction in rats. Stroke 26:2135–2144.

Takaya S, Hanakawa T, Hashikawa K, Ikeda A, Sawamoto N, Nagamine T, Ishizu K, Fukuyama H (2006): Prefrontal hypofunction in patients with intractable mesial temporal lobe epilepsy. Neurology 67:1674–1676.

Takaya S, Mikuni N, Mitsueda T, Satow T, Taki J, Kinoshita M, Miyamoto S, Hashimoto N, Ikeda A, Fukuyama H (2009):

Improved cerebral function in mesial temporal lobe epilepsy after subtemporal amygdalohippocampectomy. Brain 132: 185–194.

Takaya S, Kuperberg GR, Liu H, Greve DN, Makris N, Stufflebeam SM (2015): Asymmetric projections of the arcuate fasciculus to the temporal cortex underlie lateralized language function in the human brain. Front Neuroanat 9:1–12.

Thiebaut de Schotten M, Dell'Acqua F, Forkel SJ, Simmons A, Vergani F, Murphy DG, Catani M (2011): A lateralized brain network for visuospatial attention. Nat Neurosci 14:1245–1246.

Thivard L, Hombrouck J, du Montcel ST, Delmaire C, Cohen L, Samson S, Dupont S, Chiras J, Baulac M, Lehericy S (2005): Productive and perceptive language reorganization in temporal lobe epilepsy. NeuroImage 24:841–851.

Thompson-Schill SL, D'Esposito M, Aguirre GK, Farah MJ (1997): Role of left inferior prefrontal cortex in retrieval of semantic knowledge: A reevaluation. Proc Natl Acad Sci U S A 94: 14792–14797.

Trebuchon-Da Fonseca A, Guedj E, Alario FX, Laguitton V, Mundler O, Chauvel P, Liegeois-Chauvel C (2009): Brain regions underlying word finding difficulties in temporal lobe epilepsy. Brain 132:2772–2784.

Vandenberghe R, Price C, Wise R, Josephs O, Frackowiak RS (1996): Functional anatomy of a common semantic system for words and pictures. Nature 383:254–256.

Vigneau M, Beaucousin V, Herve PY, Duffau H, Crivello F, Houde O, Mazoyer B, Tzourio-Mazoyer N (2006): Meta-analyzing left hemisphere language areas: Phonology, semantics, and sentence processing. NeuroImage 30:1414–1432.

Voets NL, Adcock JE, Flitney DE, Behrens TE, Hart Y, Stacey R, Carpenter K, Matthews PM (2006): Distinct right frontal lobe activation in language processing following left hemisphere injury. Brain 129:754–766.

Voets NL, Beckmann CF, Cole DM, Hong S, Bernasconi A, Bernasconi N (2012): Structural substrates for resting network disruption in temporal lobe epilepsy. Brain 135:2350–2357.

Wagner AD, Pare-Blagoev EJ, Clark J, Poldrack RA (2001): Recovering meaning: Left prefrontal cortex guides controlled semantic retrieval. Neuron 31:329–338.

Wang XQ, Lang SY, Hong LU, Lin MA, Yan-ling MA, Yang F (2010): Changes in extratemporal integrity and cognition in temporal lobe epilepsy: A diffusion tensor imaging study. Neurology India 58:891–899.

Wang D, Buckner RL, Liu H (2014): Functional specialization in the human brain estimated by intrinsic hemispheric interaction. J Neurosci 34:12341–12352.

Whitney C, Kirk M, O'Sullivan J, Lambon Ralph MA, Jefferies E (2011): The neural organization of semantic control: TMS evidence for a distributed network in left inferior frontal and posterior middle temporal gyrus. Cerebral Cortex 21:1066–1075.

Winston GP, Stretton J, Sidhu MK, Symms MR, Thompson PJ, Duncan JS (2013): Structural correlates of impaired working memory in hippocampal sclerosis. Epilepsia 54:1143–1153.

Yakovlev, P.I., Lecours, A.R. (1967) The myelogenetic cycles of regional maturation of the brain. In: Minkowski A, editor. Regional Development of the Brain in Early Life. Oxford: Blackwell Scientific. pp 3–70.

Yogarajah M, Powell HW, Parker GJ, Alexander DC, Thompson PJ, Symms MR, Boulby P, Wheeler-Kingshott CA, Barker GJ, Koepp MJ, Duncan JS (2008): Tractography of the parahippocampal gyrus and material specific memory impairment in unilateral temporal lobe epilepsy. NeuroImage 40:1755–1764.