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Homotopic language reorganization in the right hemisphere after early left hemisphere injury

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ABSTRACT

To determine the areas involved in reorganization of language to the right hemisphere after early left hemisphere injury, we compared fMRI activation patterns during four production and comprehension tasks in post-surgical epilepsy patients with either left (LH) or right hemisphere (RH) speech dominance (determined by Wada testing) and healthy controls. Patient groups were carefully matched for IQ, lesion location and size. RH patients' activation across all tasks was greatest in right hemisphere areas homotopic to areas activated by LH and control participants. Differences in right vs. left dominant hemisphere activation were limited to homologous areas typically activated by language tasks, supporting the hypothesis that language localization following transfer to the RH is the mirror-image of localization in the absence of transfer. The similarity of these findings to those in patients with larger, peri-sylvian lesions suggests that these areas in both hemispheres may be uniquely predisposed to subserve various language functions.

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1. Introduction

The earliest and most compelling evidence for brain plasticity comes from patients with early insult to the left hemisphere who nevertheless develop low-normal to normal language. In some cases, this reflects transfer of language representation to the right hemisphere (Basser, 1962). Atypical (RH) language representation occurs in up to 53% of epilepsy patients, usually when epilepsy has a left hemisphere focus and when onset is early in life (Adcock, Wise, Oxbury, Oxbury, & Matthews, 2003; Brazdil, Zakopcan, Kuba, Fanfrdlova, & Rektor, 2003; Goldmann & Golby, 2005; Helmstaedter, Fritz, Gonzalez Perez, Elger, & Weber, 2006; Helmstaedter, Kurthen, Linke, & Elger, 1997; Janszky, Mertens, Janszky, Ebner, & Woermann, 2006; Rasmussen & Milner, 1977; Springer et al., 1999; Woermann et al., 2003). Although this is most commonly observed after large perinatal lesions, transfer can also occur post-natally and may be associated with small epileptogenic lesions in the medial temporal lobe that interfere with, but do not

destroy critical language areas (Liegeois et al., 2004). Transfer may also occur in the absence of epilepsy, associated with perinatal stroke of the left middle cerebral artery (Tillema et al., 2008), white matter damage (Lidzba, Wilke, Staudt, Krageloh-Mann, & Grodd, 2008; Staudt et al., 2001, 2002), and arteriovenous malformation – AVM (Lazar et al., 2000).

The mechanisms by which language reorganizes are still not well understood. One unresolved issue is the topography of the newly developed right hemisphere language network. Recent functional imaging studies of patients with large, perinatal vascular lesions have suggested that the right hemisphere network mirrors that of the normal left hemisphere, both in the classical language areas (Staudt et al., 2002; Tillema et al., 2008) and also in other regions such as the cerebellum (Lidzba et al., 2008). However, other studies have found differences in the topography of the right hemisphere language network as compared to the left (Liegeois, Connelly, Baldeweg, & Vargha-Khadem, 2008; Tillema et al., 2008; Voets et al., 2006).

Differences across studies may reflect true variability in right hemisphere language networks or cross-study differences in the nature or timing of the lesions or in the activation tasks used. How language transfers and where it transfers to may depend in part on the stage of neural development at the time of injury (de Bode & Curtiss, 2000). Different language tasks also produce different activation patterns, even in normal participants (Cabeza &

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Nyberg, 2000). Specific language processes may also show differential degrees and patterns of reorganization after damage. For example, Staudt et al. (2001) found extensive changes in the cortical representation of language for a production task but not for a perception task.

Inter-hemispheric transfer of language to the right hemisphere historically has been diagnosed using the intracarotid amobarbital procedure (IAP or the 'Wada test'), during which each hemisphere is independently anesthetized to determine whether it is critical for language function. Language laterality determined by fMRI is typically highly consistent with Wada results (Adcock et al., 2003; Binder et al., 1996; Carpentier et al., 2001; Rutten, Ramsey, van Rijen, Alpherts, & van Veelen, 2002; Swanson, Sabsevitz, Hammeke, & Binder, 2007; Woermann et al., 2003). Greater bilateral or right-sided fMRI activation has been associated with left sided seizure onset, early injury, and atypical speech representation on the Wada (Benke et al., 2006; Berl et al., 2005; Brazdil et al., 2003; Janszky et al., 2006; Thivard et al., 2005). However, even among patients found to be left hemisphere dominant by Wada, left-sided epilepsy is associated with more right sided fMRI activation, suggesting that fMRI may be more sensitive than the Wada to variability in inter-hemispheric reorganization of language (Adcock et al., 2003; Backes et al., 2005; Binder, 2011; Koylu et al., 2006). Variation in reorganization of expressive and receptive language processes has been observed (Backes et al., 2005; Lee et al., 2008; Thivard et al., 2005), suggesting a dissociation between reorganization in frontal and temporal networks in some cases. Although these studies have furthered our understanding of the degree and clinical predictors of inter-hemispheric transfer, they have not formally addressed the issue of localization of different language processes after transfer by comparing samples of left- and right-hemisphere language patients, using multiple fMRI language tasks.

Most prior studies have investigated language reorganization after large, perinatal, vascular lesions with or without a history of seizures or in samples with mixed lesion types. We studied this phenomenon in patients who underwent surgery for intractable epilepsy due to circumscribed, medial temporal lobe lesions to determine whether the results from studies of patients with large lesions generalize to patients with smaller, more circumscribed lesions. In the present study, we compared activation patterns in epilepsy patients with right hemisphere (RH) language dominance or left hemisphere (LH) language dominance, as established by pre-surgical Wada testing. In this setting, RH language presumably reflects inter-hemispheric transfer induced by chronic epileptic activity during a critical period of language development. We controlled for any potential effects of cognitive abilities, lesion location and size on localization of activation, by studying patients who all had left medial temporal lobe epilepsy, similar pre-surgical verbal skills, similar pathology restricted to the medial temporal lobe, and similar extent of left temporal resection. We also administered a battery of language tasks in order to examine the consistency of our findings across different language processes and to explore cortical reorganization of different aspects of language processing.

2. Materials and methods

2.1. Participants

Patients with right hemisphere (RH) ($n = 7$) and a matched group with left hemisphere (LH) ($n = 10$) speech dominance were recruited from a large cohort of medically-intractable temporal lobe epilepsy patients treated at a single center. All patients had had a left anterior temporal lobectomy at least 5 years before the study, were clinically stable and had no contraindications for

Table 1
Demographic characteristics.

	Controls ($n = 14$)	LH patients ($n = 10$)	RH patients ($n = 7$)
Age (mean/SD)	47.0/8.4	47.0/6.2	52.8/11.7
Female (%)	43	60	71
>HS educ. (%)	43	50	57
Right-handed (%)	100	90	29
Family history of atypical handedness (%)	50	50	57
NAART VIQ (mean/SD)	101.7/10.3*	92.9/9.4	90.6/6.8*
Pre-surgical VIQ (mean/SD)	–	90.6/8.3	87.1/6.3
Childhood febrile convulsions (%)	–	10*	86*
Age at 1st seizure	–	10.6*	3.5*
MTS ^a (%)	–	60	86
Seizure-free at time of study (%)	–	90	100
Years since surgery ^b	–	10.9/3.4	14.2/2.3
Surgical resection volume ^c (mean/SD)	–	2.59/0.37	2.78/0.31

^a MTS was the only abnormal finding on pre-surgical MRI.

^b All patients had tailored resections performed by the same neurosurgeon whose procedure for resecting neocortical structures did not change significantly during this period.

^c Resection size as% of total brain volume, calculated from the high resolution T1 images collected at the time of the study.

* Indicates significant differences.

MRI. Right-handed healthy volunteers (C) ($n = 14$) served as controls to identify regions normally activated by our tasks, independent of disease effects. Handedness was assessed using the Edinburgh Handedness Inventory. The North American Adult Reading Test – NAART (Uttil, 2002) estimated verbal IQ in patients and controls at the time of scanning. Informed consent was obtained from all participants according to a protocol approved by the Institutional Review Board at the University of Rochester.

Group-level information is summarized in Table 1. Subject-specific details are provided in Table S1 (online Supplementary materials). LH, RH and C groups did not differ in age, gender or education. The LH and RH groups did not differ in verbal abilities before surgery, as measured by Wechsler Adult Intelligence Scale-Revised Verbal IQ. LH and C groups did not differ on NAART Verbal IQ (VIQ) estimates at the time of the study, although the RH group performed lower than controls. RH patients were more likely to be left-handed or ambidextrous, but were just as likely as the others to have a 1st degree relative with atypical handedness. RH patients had an earlier age at initial precipitating insult, an earlier onset of habitual seizures and a longer pre-surgical duration of epilepsy. All but one patient (in the LH group) had been free of seizures for at least a year at the time of study. Patient groups were closely matched on underlying pathology, presumed etiology and extent of surgical resection. All pre-surgical lesions were restricted to the medial temporal lobe (hippocampus, amygdala and parahippocampal gyrus). Most patients had mesial temporal sclerosis (MTS) as the sole finding on pre-surgical MRI. Other findings included small lesions restricted to the mesial temporal lobe, with or without MTS (3 LH speech patients) or no visible pathology (one LH and one RH speech patient). No patient had abnormal imaging findings outside this area on pre-surgical MRI. The surgical resection area measured from the T1 images collected during the study did not differ between patient groups and represented on average 2.66% of the whole brain volume.

2.2. Language tasks

Four language tasks (verb generation – VG, passive sentence reading – PSR, definition naming – DN and semantic decision – SD) were used to sample a range of language processes (semantic, syntactic), presentation (auditory, visual) and response modalities

(passive encoding, active response, decision-making). We specifically selected tasks shown to be sensitive to variability in inter-hemispheric language representation in epilepsy patients. Task order was counterbalanced across participants. Stimuli programmed in E-Prime (Psychology Software Tools, Inc.) were presented either visually (VG, PSR) using a back projection system, or aurally (SD and DN) using pneumatic headphones. Motor responses were recorded using a custom MR safe response box. Before entering the scanner, participants practiced all tasks to ensure adequate understanding and performance. In the scanner all tasks were performed covertly to minimize head motion.

2.2.1. Verb generation

Verb generation (Petersen, Fox, Posner, Mintun, & Raichle, 1988) shows strong left language lateralization indices (LI) in right-handed healthy controls. LIs are consistent with results of more invasive methods such as Wada testing and intra-operative stimulation in patient populations (Benson et al., 1999; Harrington, Buonocore, & Farias, 2006; Ramsey, Sommer, Rutten, & Kahn, 2001; Rowan et al., 2004). Participants viewed one concrete noun every 3 s and had to silently generate a semantically related verb (e.g., 'car – drive'). Blocks of ten nouns alternated with control blocks (a string of the symbol '#', matched to the approximate length of the nouns), for a total scan time of 4 min 30 s.

2.2.2. Semantic decision

Semantic decision tasks robustly activate language-related brain areas, particularly regions contributing to speech perception and lexical-semantic processes (Binder et al., 1997). The degree of lateralization of these activated areas corresponds with Wada language asymmetry in individual epilepsy patients (Binder et al., 1996) and predict language outcome after left temporal lobectomy (Sabsevitz et al., 2003). The paradigm used here has been described in detail (Binder, 1997; Frost et al., 1999; Springer et al., 1999; Szafarski et al., 2002). During target blocks the participant heard the name of an animal and was asked to press a button if the animal is 'found in the United States' and 'used by people'. During control blocks the participant heard brief sequences of low (500 Hz) and high tones (750 Hz) and was asked to press a button for any sequence containing two high tones. Scan duration was 6 min 48 s.

2.2.3. Definition naming

Definition naming is more sensitive than visual object naming to damage or disruption of the anterior temporal lobe-ATL (Hamberger, Goodman, Perrine, & Tamny, 2001; Hamberger & Seidel, 2003). It produces strong asymmetries in activation across inferior frontal gyrus-IFG, middle frontal gyrus-MFG and posterior temporal lobe (Wernicke's area) that discriminate well between patient groups (Berl et al., 2005) and are consistent with Wada LIs (Gaillard et al., 2004). Here, we used an auditory version, with stimuli generated from a list described in detail by Hammeke, Kortenkamp, and Binder (2005). In the target condition, participants heard descriptions of an object (e.g., 'jewelry you wear on your finger') and were instructed to covertly name the object ('ring') and push a button when they had thought of the answer. In the control condition, subjects indicated whether they heard a specific combination of complex synthetic sounds within a longer sequence by pressing a button on the response box. A jittered inter-stimulus fixation (3–15 s) was also included. Scan time was 8 min 57 s.

2.2.4. Passive sentence reading

Passive reading provides LIs for language processing regions that differs between postoperative epilepsy patients and healthy controls (Backes et al., 2005). We presented participants with blocks of target and control conditions alternating with a fixation cross. In the target condition each block consisted of 30 9-word

conjoined sentences (e.g. 'The kitten was little and it attacked the mouse'). Each control block consisted of 30 false font sentences, matched in length to the sentences in the target condition. To control for attention, six trials in each condition were followed by a matching task. Participants were asked to respond via button press if a picture matched the content of the previous sentence or if a false font item was in the previous control trial. This scan lasted 7 min.

2.3. MRI data acquisition

Images were acquired on a Siemens 3T Trio MRI system, equipped with an 8-channel head coil. High-resolution T1 weighted images were acquired using MPRAGE (TR = 2350 ms, TE = 3.4 ms, FOV = 256 mm, resolution $1 \times 1 \times 1 \text{ mm}^3$). A series of BOLD EPI scans (GE EPI, TR = 3 s, TE = 30 ms, resolution $4 \times 4 \times 4 \text{ mm}^3$, FOV = 256 mm) were acquired during each of the language paradigms described above.

2.4. fMRI data analysis

The imaging data were analyzed using FEAT (fMRI Expert Analysis Tool) part of FSL software (Smith et al., 2004).

2.4.1. fMRI preprocessing

Data preprocessing consisted of motion correction (Jenkinson, Bannister, Brady, & Smith, 2002), slice-timing correction, non-brain signal removal (Smith, 2002), Gaussian spatial smoothing (FWHM 5 mm), and high-pass temporal filtering. The estimated motion was within acceptable limits for most runs. Mean displacements (MD) were calculated for each group ($MD_{LH} = 0.29 \text{ mm}$ ($SD = 0.21$), $MD_{RH} = 0.31 \text{ mm}$ ($SD = 0.19$), $MD_C = 0.27 \text{ mm}$ ($SD = 0.14$)) and no significant differences between the three groups were found (RHvsLH: $p = 0.66$; RHvsC: $p = 0.43$; LHvsC: $p = 0.43$). Due to motion (greater than the voxel size in one LH patient or time-correlated with the stimulus for two control participants) and other technical problems (failure of audio equipment for three control participants), some data were not included in the group analyses, resulting in different numbers of participants in each group across tasks (see Fig. 1). Registration of BOLD images to structural T1 images and to the Montreal Neurological Institute (MNI) standard template was also carried out using a combination of linear (FLIRT – FSL's Linear Image Registration Tool) and non-linear (FNIRT-FMRIB's Non-linear Image Registration Tool) registration. First, a 12 degrees-of-freedom affine transformation was applied to align the functional images to each participant's structural T1 image, and then the T1 image to the MNI template, using FLIRT (Jenkinson et al., 2002; Jenkinson & Smith, 2001) to achieve a global matching of brain size and shape with respect to the template. The registration of high-resolution structural image to standard template was then further refined using FNIRT (Andersson, Jenkinson, & Smith, 2007a, 2007b). The non-linear method compensates for local deformations due to brain surgery, resulting in a more precise alignment. Finally, the warping field estimated by FNIRT was applied to resample the functional data into standard space. All transformed images were inspected carefully for possible misalignments and all registrations were found to be acceptable (Supplementary materials Fig. S2).

2.4.2. Individual and average activation in each group

First level statistical analysis was carried out using FILM (FMRIB's Improved Linear Model) and higher level analyses (group averages and group comparisons) were carried out using FLAME (FMRIB's Local Analysis of Mixed Effects) stage 1 and stage 2 with automatic outlier detection (Beckmann, Jenkinson, & Smith, 2003; Woolrich, 2008; Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004). Average activation maps were obtained for each group

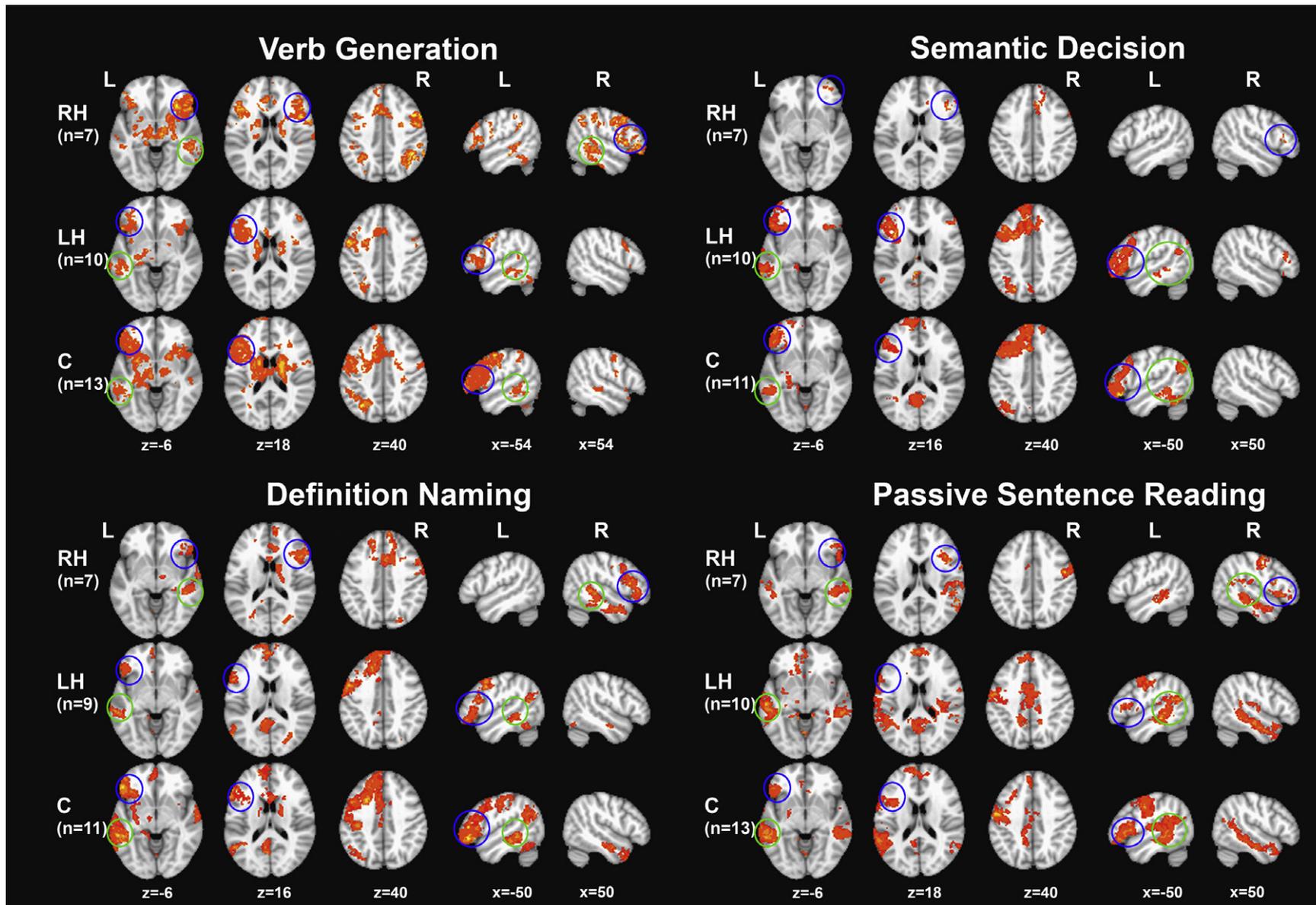


Fig. 1. Group activation maps during the four tasks for left (LH) and right (RH) hemisphere speech dominant patients and healthy controls (C). Circles showing frontal (blue) and posterior (green) language areas and their right hemisphere homologues, along with the x and z-axis coordinates in MNI standard space, emphasize the mirrored distribution of language networks in the two hemispheres.

separately. A union mask including the resection areas in all patients was created and used to mask out the left ATL in all group analyses for both patient groups and control subjects. Besides removing potential bias associated with different resection size and shape, this process also reduced the number of voxels tested, thus making the multiple comparison correction less stringent. All Z statistic images were thresholded using clusters determined by $Z > 2.3$ and a corrected cluster significance threshold of $p = 0.05$, with the exception of VG task. This test elicited very strong activation in all three groups, therefore each group's Z statistic images were thresholded using clusters determined by $Z > 3$ and a corrected cluster significance threshold of $p = 0.05$. Also, in the case of SD task, due to few voxels surviving the cluster correction for the RH patient group, additional uncorrected ($p = 0.05$) maps were created for this group. The same analyses were repeated while controlling for VIQ to demonstrate that the findings were not mediated by this variable.

2.4.3. Lateralization Indices-LI

Lateralization indices were calculated to confirm group membership as established by the Wada test. Equally sized regions of interest (ROI) were defined in the right and left hemisphere using the probabilistic Harvard-Oxford structural atlas available in FSL. Large ROIs were created to account for possible atypical activation in the patient groups and included areas known to be involved in language processing: all gray matter of the frontal lobe, posterior half of the inferior, middle and superior temporal lobe, and temporo-parietal regions, angular gyrus and supramarginal gyrus (Backes et al., 2005; Binder et al., 2008; Sabsevitz et al., 2003; Szaflarski et al., 2002). In order to avoid bias induced by variability in size of left ATL resection, the anterior part of both temporal lobes was not included in these ROIs. LIs were calculated for each participant and each task, using $[L - R]/[L + R]$, where L and R are the number of voxels significantly activated ($Z > 2.3$, $p = 0.05$) in the ROIs in each hemisphere. As in previous studies, we considered $LI \geq 0.20$ to indicate left hemisphere dominance, $LI \leq -0.20$ to indicate right hemisphere dominance and intermediate values to indicate bilateral activation (Backes et al., 2005; Szaflarski et al., 2002). In order to verify correct group assignment and correlation with Wada test, a two-sample t -test was computed between the LIs of LH and RH patient groups. To verify that the LIs obtained were not threshold-dependent, individual LIs were also calculated for a range of threshold values (uncorrected $Z > 0$, $Z > 1.9$, $Z > 2.3$, $Z > 2.9$, $Z > 3.1$). In addition, to establish that these values were not significantly affected by the choice of ROI, a whole hemisphere LI was calculated using all activated voxels at various thresholds in each hemisphere. In order to avoid bias induced by lack of tissue in the left anterior lobe of the patient groups, this area was masked out in both hemispheres.

2.4.4. Patient group comparisons

In order to quantify similarities and differences in language localization in LH and RH patients, we directly compared their dominant hemisphere activation (left hemisphere in the LH group, right hemisphere in the RH group) on all four tasks. For this purpose, the functional and structural data of RH patients were flipped along the x axis (left to right), thus superimposing the right hemisphere of the RH patient group onto the left hemisphere of the LH group, using a procedure similar to that of Staudt et al. (2002). In order to avoid the confound of comparing dominant hemispheres with and without missing tissue (the operated left ATL of the LH group vs. the un-operated right ATL of the RH group), the ATL was masked bilaterally using the union mask described in Section 2.4.2 and its mirror image. Direct comparisons between the two patient groups were computed using two-sample unpaired t -tests and all Z statistic images were thresholded using clusters

determined by $Z > 2.3$ and a (corrected) cluster significance threshold of $p = 0.05$.

3. Results

3.1. Task performance

All participants reached an acceptable level of performance on all tasks on pre-scan practice as observed by the trainer. Performance during scanning was only recorded for the semantic decision task. For this task, accuracy on correct task trials (animal names) was $A_{RH} = 64.5\%$ ($SD = 11.8$), $A_{LH} = 60.6\%$ ($SD = 11.3$), $A_C = 78\%$ ($SD = 8.1$), and for correct tone discrimination trials $A_{RH} = 82.5\%$ ($SD = 16.3$), $A_{LH} = 81.7\%$ ($SD = 22$), $A_C = 93.8\%$ ($SD = 6.6$). There were no significant differences between groups in accuracy for tone trials [$F(2,24) = 1.64$, $p = 0.21$]. There were, however, significant differences between groups in performance for the semantic decision task [$F(2,24) = 7.58$, $p < 0.005$]. Post-hoc comparisons indicated that the mean accuracy for the C group was significantly greater than either the RH ($p < 0.01$) or LH ($p < 0.05$) groups but that there were no significant differences between the two patient groups. Reaction times (RT) to the task and tone trials were also analyzed. For the correct task trials, the average RTs were: $RT_{RH} = 1.7$ s ($SD = 0.3$), $RT_{LH} = 1.5$ s ($SD = 0.2$), $RT_C = 1.6$ s ($SD = 0.1$) while for the tone task they were $RT_{RH} = 2.2$ s ($SD = 0.6$), $RT_{LH} = 2.5$ s ($SD = 0.2$), $RT_C = 2.5$ s ($SD = 0.1$). A one-way ANOVA was used to test for RT differences between groups. No significant group differences were found for correct task [$F(2,23) = 1.26$, $p = 0.30$] or tone [$F(2,23) = 2.25$, $p = 0.13$] trials. For false alarms the average RTs were: $RT_{RH} = 1.6$ s ($SD = 0.08$), $RT_{LH} = 1.5$ s ($SD = 0.6$), $RT_C = 1.8$ s ($SD = 0.1$) while for the tone trials they were $RT_{RH} = 1.5$ s ($SD = 0.7$), $RT_{LH} = 1.5$ s ($SD = 1.3$), $RT_C = 1.7$ s ($SD = 1.1$). There were no significant group differences in false alarms RTs for task [$F(2,22) = 1.45$, $p = 0.25$] or tone [$F(2,12) = 0.07$, $p = 0.93$] trials.

3.2. Average group activation

The patterns of activation for the C group resemble those previously reported in the literature. For the patients, activation was in similar areas as that of controls (for the LH patients) or in homologous areas in the right hemisphere (for the RH patients) (Fig. 1). Overall, in both patient groups, the extent of activation was smaller and more bilateral than in the healthy control group. Similar results were obtained when controlling for VIQ (Fig. S3). Task-specific patterns were as follows.

3.2.1. Verb generation

Both patient groups had bilateral activation in the IFG and MFG extending into the precentral gyrus, with greater activation on the left (LH group) or right (RH group). Activation was also found in the left posterior middle (MTG) and superior (STG) temporal gyri, supramarginal and angular gyri as well as superior parietal lobe (SPL), for the LH group, or their right homologues for the RH group. Similar areas of activation also appeared bilaterally in insula, basal ganglia and supplementary motor area (SMA) in both patient groups. The RH group had more bilateral and widespread activation than the LH group.

3.2.2. Semantic decision

RH group activation was minimal for this task, probably due to task difficulty and larger group variability. When a similar thresholding method was used for all groups (cluster $Z > 2.3$; corrected $p < 0.05$), the only areas activated in the RH group were in the right IFG and SFG, homologous to areas active in the left hemisphere for the LH group. However, when using uncorrected

Table 2
Lateralization indices.

	Controls mean LI (SD)	LH patients mean LI (SD)	RH patients mean LI (SD)
Verb generation	0.40 (0.29)	0.35 (0.27)	-0.09 (0.27)
Definition naming	0.68 (0.23)	0.53 (0.15)	-0.23 (0.36)
Semantic decision	0.56 (0.22)	0.32 (0.21)	-0.21 (0.34)
Passive sentence reading	0.46 (0.3)	0.33 (0.35)	-0.22 (0.26)

threshold ($p < 0.05$) for the RH group, we found activation in the right hemisphere homologues of the left posterior MTG, angular gyrus, SPL, MFG and precentral cortex activated in the LH group (Fig. S1, Supplementary materials). STG and planum temporale (PT) were not active, due to the low-level, auditory processing demands of the non-linguistic control task (tone decision), consistent with prior studies (Binder, 1997).

3.2.3. Definition naming

Activation in the IFG, MFG, superior frontal gyrus (SFG), precentral gyrus, MTG and superior temporal sulcus in the RH group mirrored the activation in these areas for the LH group. Additional areas of activation were observed in the left angular gyrus and posterior cingulate cortex (PCC) for the LH group, right basal ganglia for the RH group and bilateral anterior cingulate cortex (ACC), SMA and right ATL for both groups. Again, absence of STG and PT

activation probably reflects the low-level auditory processing demands common to the target and control tasks.

3.2.4. Passive sentence reading

Similar areas were active in the IFG, posterior STG, PT, supra-marginal/angular gyri and precentral gyrus in both patient groups in their respective dominant hemispheres. Bilateral activation was also observed in the MTG extending anteriorly in the right ATL for both patient groups. Other activation was found for the LH group in the left MFG, ACC, PCC and left basal ganglia.

3.3. Inter-hemispheric transfer and task differences: Summary

Activation maps for the RH patient group reveal a network that mirrors the activation in the IFG (Broca’s area) and posterior temporal lobe (including Wernicke’s area in some tasks) for the LH control group. In addition to these classic language areas, similar homotopic activation was observed in other regions of the brain that mediate language processing. In the VG task, this was evident in the parietal lobe and premotor cortex. For the SD and DN tasks the RH speech dominant group showed activation in the right MFG, SFG and SPL that mirrored the activation observed in these regions in the left hemisphere for the LH group. For the PSR task mirror right hemisphere activation was observed in the premotor cortex. Although RH patients mostly show inter-hemispheric transfer, there is also some maintenance of language activation in the left hemisphere, in particular for posterior temporal activation on some tasks (verb generation, semantic decision) as observed from the group maps in Figs. 1 and S1. The LH group also shows some evidence of partial transfer to the right hemisphere as revealed by activation in the right IFG for SD task and PT for the PSR task, areas not activated in the healthy control group (Fig. 1).

3.4. Lateralization indices

Average LIs (significance threshold $Z > 2.3$, corrected cluster significance $p = 0.05$) for each patient group and each task were mostly consistent with the Wada test. LH and C groups had mean LI ≥ 0.20 and the RH group had LI ≤ 0.20 except that RH LIs were in the bilateral range for the VG task (Table 2). LIs were significantly different for the LH and RH groups on all tasks (VG, $p < 0.003$; DN, $p < 0.0005$; SD, $p < 0.002$; PSR, $p < 0.001$). LIs for LH and C groups differed on DN ($p < 0.04$) and SD ($p < 0.009$), but not VG ($p < 0.33$) or PSR ($p < 0.17$). This indicates a weaker left lateralization for the DN and SD tasks in the LH patient group, possibly due to partial transfer to the right hemisphere for the SD task, as described in Section 3.3, or weaker dominant hemisphere activation for the DN task. As with the extent of activation, LH and RH LIs were less asymmetric than C LIs for all tasks. These findings were not threshold or ROI dependent (see Table S2 in Supplementary materials).

3.5. LH and RH group comparisons

Results of the quantitative comparisons of dominant hemisphere activation in the RH and LH groups support the hypothesis that language localization following transfer to the RH is the mirror-image of localization in the absence of transfer. First, RH patients did not show greater activation than LH patients anywhere in the brain on three out of the four tasks (Fig. 2, left panel). Thus, areas in RH patients that are homologous to language-activated areas in the LH patients were similarly active during most language tasks and there were no areas that fall outside these regions that were more activated for the RH patients. For the one task that showed differences (DN) (Fig. 2, left panel), greater RH activation was observed in IFG, precentral gyrus and posterior MTG, areas that fall within regions activated by this task in the group maps

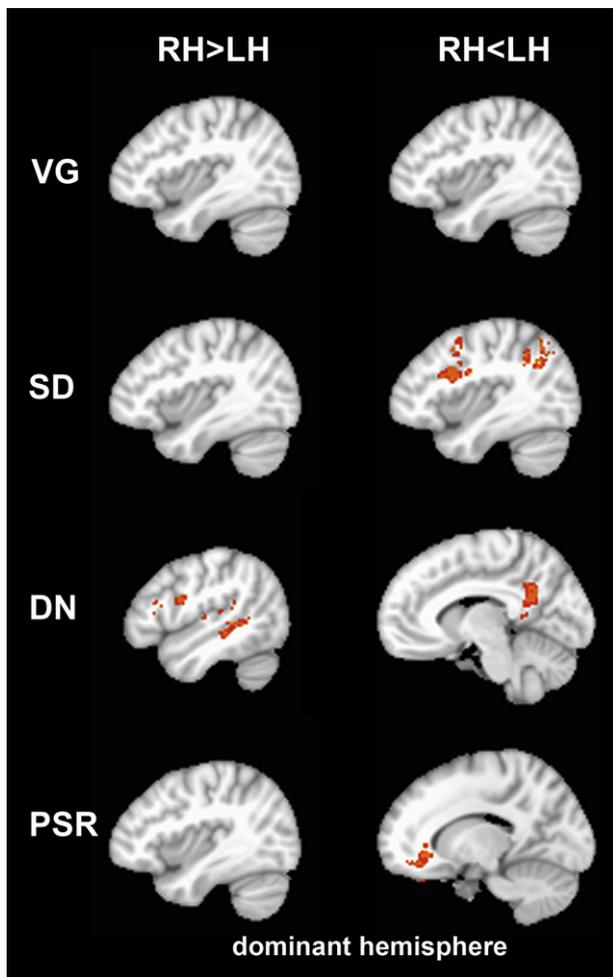


Fig. 2. Direct comparisons of dominant hemisphere activation in the RH and LH patient groups ($Z > 2.3$, $p < 0.05$).

(Fig. 1). STG and PT were also more active. These fall within traditional posterior language areas, but likely were not active on the group maps due to the nature of the control task, as discussed in Sections 3.2.2 and 3.2.3. Similar results were observed when controlling for VIQ, except from increased RH group activation in dominant, supplementary motor cortex (Fig. S4). This area was activated in the dominant hemisphere group maps for both the LH and RH patients (Fig. 1), suggesting the difference reflects between-groups differences in the level, but not location of activation.

The RH group showed less dominant hemisphere activation than the LH group (Fig. 2, right panel) in the IFG, MFG, precentral gyrus, supramarginal gyrus and SPL for the SD task and in the regions of the frontal medial cortex (PSR task) and PCC (DN task). These areas were active on these tasks in the average maps for the LH and C groups, but less so for the RH group. Results controlling for VIQ were essentially unchanged. Thus, across all four tasks, there were either no differences in activation levels between the groups or any differences that were observed fell within areas activated by these tasks in the normally dominant left hemisphere or within areas that normally participate in early stages of language processing. In other words, these quantitative comparisons show that the activation in the right hemisphere of our RH-dominant patients indeed occurs in the homologous areas to those activated in the left hemisphere of LH and C groups. The comparisons failed to demonstrate that any of four tasks, covering a range of language functions, differentially activated novel language areas in patients who transferred language to the right after early injury.

In the non-dominant hemisphere contrasts (results not shown), there was greater non-dominant (left) hemisphere activation for the RH group in areas that were also activated by these tasks in the dominant (left) hemispheres of the LH and C groups (IFG, MFG, precentral cortex, supramarginal/angular and SPL for DN task, and SPL for PSR task). Overall, these results suggest some degree of incomplete transfer from left hemisphere language areas to the right hemisphere after early insult. None of the tasks showed greater non-dominant (right) hemisphere activation for the LH group in any region, consistent with the results of the LI analyses that LH patients are strongly lateralized to the left.

4. Discussion

4.1. Findings of the present study

In this study we examined the topography of language reorganization by studying two groups of patients with well matched medical histories and baseline verbal abilities (to control for effects of disease and treatment) and with known speech dominance as determined by pre-surgical Wada testing. Thus, any differences between the two patient groups in hemispheric language organization is likely to reflect the effect of transfer due to the earlier developmental timing of the initial insult and/or the longer history of seizures in the RH group, and not the effects of different degrees or types of brain insult or cognitive deficits. A battery of language tasks was employed in order to examine consistency of functional reorganization patterns across a range of language processes, including both production and comprehension. All groups showed significant activation in classical language areas or their right hemisphere homologues, as well as in a network of other regions that mediate language processing. The two patient groups showed decreased and more bilateral activation than the healthy control group, reflecting effects of left temporal lobe epilepsy and surgery, as reported by others.

Our primary findings indicate that when language transfers to the right hemisphere, it does so primarily to homotopic areas, in accord with some of the previous research (Lidzba et al., 2008;

Staudt et al., 2002; Tillema et al., 2008), although there may be task- or person-dependent differences in activation levels within these areas. This is true not only for classical language areas (IFG, posterior temporal lobe and temporo-parietal areas) but also for other brain regions that support language processing (Lidzba et al., 2008). These conclusions are based both on visual inspection of group activation maps and direct quantitative comparisons of activation in the dominant hemisphere of the RH and LH patients. The quantitative comparisons revealed no significant greater activation for the RH patients on three out of the four tasks. Thus, for the majority of tasks, localization of language representation following transfer was the mirror image of representation in the absence of transfer. On the one task where RH patients showed greater dominant hemisphere activation (DN, Fig. 2), this was confined to IFG, MTG, STG and PT. It is not clear whether the relatively increased activation in these areas reflects group differences in activation during the target task, the control task, or both. For present purposes, it is sufficient to note that these areas fall well within the boundary of language regions as traditionally defined and as demonstrated in our sample. The lack of activation of traditional Wernicke's areas by DN and SD on the group average maps is accounted for by the fact that the DN and SD target and control tasks each elicit lower-level, non-linguistic auditory processing mediated by these areas (Binder et al., 1997) and thus cancel out their activity in the contrasts. RH patients also show decreased dominant hemisphere activation compared to LH patients in IFG, MFG, angular gyrus and superior parietal lobe for the SD task, medial frontal cortex for the PSR task and PCC for the DN task. But, again, these areas were also active in the average maps for the LH and C groups, suggesting that they are normally involved in these processes. It is unclear whether this difference reflects overall reduced level of activation for the RH group (in the case of the SD task) or greater variability or lower power (due to fewer subjects in the RH group). It may be that these areas are indeed less involved after transfer, but we cannot discriminate among these explanations, given our data. Regardless, these findings are consistent with the observation that RH vs. LH differences in activation on these four language tasks are confined to areas homologous to those activated in persons with typical patterns of language dominance; there are no areas of RH language activation that fall outside areas homologous to those activated in LH language patients and controls.

Some previous studies have suggested subtle differences between the networks in the two hemispheres in both frontal and posterior language areas (Liegeois et al., 2008; Tillema et al., 2008; Voets et al., 2006). It has been unclear whether these variations reflect a different right hemisphere network or are simply due to heterogeneity of lesions, the varied timing of the insult, or differences in language proficiency between patients and healthy controls. These confounding effects were minimized in our study: both LH and RH dominant groups had similar underlying lesions, education and verbal IQ. It has also been argued that in patients, the pathology and treatment can disturb the blood oxygenation level dependent (BOLD) mechanism (Lazar et al., 2000; Lehericy et al., 2002; Ulmer et al., 2004), and thus bias fMRI findings when comparing patients with healthy controls. Our comparisons were between two groups of patients that were quite homogeneous in regards to their presumed etiology, pathology and surgical treatment.

Previous research has been limited to investigating one or two language tasks. Most of these studies investigated word generation tasks, with only a small number of studies examining reorganization of both language production and perception. One found changes in cortical representation of language due to left hemisphere damage for production but not perception (Staudt et al., 2001). The authors consider that, due to the variability and decreased lateralization of the temporo-parietal activations

observed with receptive language tasks (Just, Carpenter, Keller, Eddy, & Thulborn, 1996; Lehericy et al., 2000), differences between patients and control participants in the asymmetries of language perception might have been too small to detect. By comparing two groups of well-matched patients, we were able to demonstrate that reorganization in the right hemisphere language areas homologues also takes place for perception tasks (PSR). These findings are in accord with previous research examining sentence comprehension after left ATL resection, which found that reading skills were preserved by recruitment of right hemisphere regions that are not normally activated in control participants (Noppeney, Price, Duncan, & Koeppe, 2005).

We also observed some task-dependent maintenance of left hemisphere activation for the RH speech dominant group in both frontal and temporal areas. When examining the group activation maps, we found maintenance of left hemisphere activation in RH patients for the VG task (language production) and residual left posterior temporal lobe activation for the SD task (comprehension) and PSR (perception). Results of comparisons of activity in the non-dominant hemispheres of the two groups showed greater activity in the non-dominant (left) hemispheres of the RH patients, in regions also activated by these tasks in the dominant (left) hemispheres of the LH and C groups. This suggests that, despite being classified as “right hemisphere dominant” by Wada test, transfer of language may have been incomplete in some RH patients, consistent with the RH group having LIs closer to zero than the LH and C groups. The specific Wada procedure used to classify these patients’ language dominance relies primarily on the occurrence of expressive speech errors (paraphasias) and thus may not be sensitive to variability in lateralization of other language or language-dependent functions.

Based on visual inspection of the group average maps and the LI analyses, the LH patient group also showed evidence of some inter-hemispheric transfer of language to the right hemisphere, while maintaining left hemisphere dominance. Production tasks (DN and VG) did not show any evidence of inter-hemispheric transfer. However SD, a comprehension based task, showed right hemisphere activation in LH patients, compared to healthy controls. These findings support prior studies demonstrating that fMRI is more sensitive to variability in language reorganization than the Wada (Adcock et al., 2003; Backes et al., 2005; Binder, 2011; Koylu et al., 2006). Indeed, LIs from the SD task are a better predictor than the Wada test of post surgical language and verbal memory outcome (Binder et al., 2008; Sabsevitz et al., 2003). Weighing the risk of verbal memory decline in left ATL surgery candidates is of utmost importance because verbal memory decline following surgery is well documented in these patients (Baxendale, Thompson, Harkness, & Duncan, 2006; Lee, Yip, & Jones-Gotman, 2002; Sabsevitz, Swanson, Morris, Mueller, & Seidenberg, 2001). Therefore, lateralization decisions made primarily on the basis of performance on expressive language tasks during Wada test may not be sufficient for pre-surgical planning. The use of fMRI employing different types of tasks, including production, comprehension and perception may better describe the gradient of shift in the language network that occurs with left hemisphere epilepsy.

4.2. Limitations

There are a number of potential limitations to our primary results. First, all patients were scanned post-surgically. Given the scarcity of RH patients with small, homogeneous lesions, accruing a sufficient sample with pre-surgical scanning would be prohibitively difficult. It is possible that surgery resulted in some additional reorganization within the right hemisphere, making our sample not strictly revealing of reorganization from the original pre-surgical injury itself.

Second, it is possible that the RH activation patterns in our patients reflect genetically-based RH dominance rather than the effects of reorganization. This is unlikely, given that RH dominance after early left insult is fairly common and the three groups did not differ in familial left-handedness.

Third, the RH sample may have not been large enough to produce sufficiently reliable results on all tasks, as indicated by the lack of activation in SD task at a threshold sufficient for the other tasks. Larger samples of well-matched LH and RH patients will be needed to confirm and extend these results or identify more subtle differences than we were able to detect.

Lastly, due to limited performance data collected during scanning, it is difficult to completely rule out an effect of potential performance differences on the final results.

4.3. Implications of the current literature for further research into mechanisms of plasticity and reorganization

Our observation (that language transfers largely to inferior frontal and posterior temporal areas in the RH after small, circumscribed, medial temporal lobe lesions) and the similar, intra-hemispheric pattern of localization observed in prior studies in patients with larger, destructive, left hemisphere lesions raises two interesting questions that have broader implications for understanding the underlying processes and limitations of brain plasticity. First, what level or type of disruption of normal function is necessary to induce cortical reorganization? With large, perinatal, destructive lesions, the neural substrate available to support language in the left hemisphere is presumably limited. A parsimonious assumption is that, in some cases, massive early injury induces transfer to the hemisphere with structurally more viable language substrate. However, the occurrence of transfer associated with seizure activity in structurally remote regions suggests that plasticity can be induced by mechanisms other than massive tissue damage. Understanding the range of mechanisms that induce plasticity has important implications for promoting functional recovery. If plasticity can only be stimulated by destroying tissue, this would limit options for treatments to promote recovery. However, if plasticity can be induced by less permanent and destructive changes, there may be similar treatment approaches that can promote plasticity in the context of disease or damage. Indeed, different types and locations of lesions in animals result in marked differences in cortical and subcortical sensory-motor plasticity at the regional and cellular level, suggesting a spectrum of mechanisms that might lead to varying degrees of plasticity (Goddard, 1967; Gonzalez & Kolb, 2003; Nishibe, Barbay, Guggenmos, & Nudo, 2010).

Second, the consistency of results across samples with very different types and locations of lesions suggests that inferior frontal and posterior temporal areas in the right and left hemispheres may be particularly predisposed to subserve language. It may be that these areas have privileged access to auditory and oro-motor cortices that subserve speech perception and production. However, these same areas subserve sign language perception and production in deaf native signers with limited access to auditory input (MacSweeney, Capek, Campbell, & Woll, 2008; Newman, Supalla, Hauser, Newport, & Bavelier, 2010), suggesting that privileged access to auditory and oro-motor cortices may be sufficient but is not necessary for language specialization.

Alternatively, their distinct cytoarchitecture may confer advantages for language processing. Cytoarchitectonic asymmetries in Broca’s area develop later than asymmetries in primary motor cortex, with a time course that roughly parallels language development (Amunts, Schleicher, Ditterich, & Zilles, 2003). While it is unclear why language is controlled preferentially by either the left language network or its right hemisphere homologue, our results

add to evidence that this preference dominates the nature of reorganization after early insult.

4.4. Conclusions

When language reorganization occurs as a result of early left hemisphere injury, it does so in some cases by shifting to homotopic areas in the right hemisphere. Language reorganization to the right hemisphere can occur with early left temporal lobe seizure activity, even when the classical language areas of the left hemisphere are undamaged. Although this transfer occurs across all language tasks, the degree of inter-hemispheric transfer is somewhat task and patient dependent, as indicated by residual left hemisphere activation in RH speech dominant patients or partial right hemisphere transfer for the LH speech dominant patients. The primary clinical implication is that fMRI reveals more variability in language reorganization than the Wada test, consistent with studies showing that fMRI language lateralization is more predictive of cognitive outcome than Wada language lateralization. On the other hand, lateralization was task-dependent, suggesting that the superior predictive validity of fMRI is also likely to be task dependent and that clinical applications of fMRI need to use activation tasks with established predictive validity. The primary implication for understanding functional recovery is that, in some cases, considerable plasticity can be induced by lesions that are structurally remote from, but functionally connected to areas critical for language functions. Understanding the mechanisms that underlie this effect may lead to therapeutic methods to induce plasticity in the central nervous system without creating undue collateral damage. Finally, our results support prior studies that suggest that specific contralateral brain regions may be uniquely predisposed to mediate language when there is damage to the dominant hemisphere. Understanding the unique structural and functional properties of these areas may provide further insights into how language is instantiated in the brain.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.bandl.2012.06.006>.

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