Title

Intrinsic functional organization of putative language networks in the brain following left cerebral hemispherectomy.

Journal

Brain structure & function, 222(8)

ISSN

1863-2653

Authors

Ivanova, Anna
Zaidel, Eran
Salamon, Noriko
et al.

Publication Date

2017-11-01

DOI

10.1007/s00429-017-1434-y

Peer reviewed

Published in final edited form as:
Brain Struct Funct. 2017 November ; 222(8): 3795–3805. doi:10.1007/s00429-017-1434-y.

Intrinsic functional organization of putative language networks in the brain following left cerebral hemispherectomy

Anna Ivanova[1], **Eran Zaidel**[2], **Noriko Salamon**[3], **Susan Bookheimer**[3], **Lucina Q. Uddin**[1,4,*], and **Stella de Bode**[5]

[1]Department of Psychology, University of Miami, Coral Gables, FL

[2]Department of Psychology, UCLA, Los Angeles, CA

[3]Department of Radiology, UCLA David Geffen School of Medicine, Los Angeles, CA

[4]Neuroscience Program, University of Miami Miller School of Medicine, Miami, FL

[5]The Brain Recovery Project, Los Angeles, CA

Abstract

In rare cases of severe and intractable epilepsy, cerebral hemispherectomy is performed to arrest seizure activity and improve quality of life. The remaining hemisphere is often capable of supporting many cognitive functions post-surgery, although the outcome depends on the underlying etiology, hemisphere removed, and age of resection. The mechanisms underlying this massive reorganization are at present unknown. Here we examined intrinsic functional connectivity of putative language brain networks in 4 children after left cerebral hemispherectomy using resting state functional magnetic resonance imaging (rsfMRI). We compared these functional systems to intrinsic language networks in 15 neurotypical controls using region-of-interest (ROI) based functional connectivity analyses. In 3 out of 4 hemispherectomy patients, the ROI placed in the right inferior gyrus revealed a functional network that strongly resembled the right hemisphere intrinsic language network observed in controls. This network typically comprised inferior frontal gyrus, superior temporal sulcus, and premotor regions. Quantitative ROI-to-ROI analyses revealed that functional connectivity between major nodes of the language network was significantly altered in all 4 examined patients. Overall, our data demonstrate that the pattern of functional connectivity within language networks is at least partially preserved in the intact right hemisphere of patients who underwent left hemispherectomy.

Keywords

plasticity; laterality; hemispheric specialization; epilepsy; Broca's area; resting state fMRI

---

[*]**Corresponding author:** Lucina Q. Uddin, Ph.D, Department of Psychology, University of Miami, P.O. Box 248185, Coral Gables, FL 33124, USA, l.uddin@miami.edu, Fax: +1 305-284-3402, Phone: +1 305-284-3265.

Introduction

The fundamental laws guiding brain plasticity and reorganization after major lesions remain an area of intensive investigation. An extreme but under-studied example of such rewiring is brain recovery after hemispherectomy, a surgical procedure resulting in the removal of one cerebral hemisphere to alleviate intractable epilepsy (Jonas et al., 2004). During post-surgery recovery, the remaining hemisphere is often able to take over some cognitive and sensorimotor functions, although a number of deficits such as hemiparesis and hemianopsia remain (Althausen et al., 2013; Moosa et al., 2013; Samargia & Kimberley, 2009). Previous studies have shown that core brain regions in the remaining hemisphere tend to retain their original function, although some reorganization does take place to partially compensate for the missing contralateral hemisphere (Paiement et al., 2008;HYPERLINK \l "bookmark41" Zhang et al., 2013). It is not clear which functions are reassigned to the remaining hemisphere and what laws guide the hierarchy of rescued functions (Cummine, Borowsky, Winder, & Crossley, 2009).

The most studied cognitive function following left hemispherectomy is spoken, and to a lesser degree written, language. Many patients after left hemispherectomy produce fluent speech and about 40% learn to read (de Bode, Chanturidze, Mathern, & Dubinsky, 2015; Moosa et al., 2013), even though most brain regions supporting language functions in the neurotypical population are located in the left hemisphere (Grosmaitre et al., 2015; Liegeois et al., 2010; Stark & McGregor, 1997). The neural principles underlying this functional restitution remain largely unknown due to the fact that results of lesion studies cannot be directly applied to this population. It has been shown that the right hemisphere becomes more actively involved in language tasks following a lesion on the opposite side, but the recruited brain regions are not fully homologous to those on the left (Gupta, 2014; Saur et al., 2008; Voets et al., 2006).

Resting state fMRI (rsfMRI) analysis can serve as a powerful tool for determining functional brain network rearrangement after hemispherectomy, as the approach allows for detection of canonical, intrinsic connectivity networks (ICNs) as well as discovery of novel brain regions that they might include. The past decades of research have demonstrated that functional connectivity of brain regions at rest exhibits specific patterns that often correspond to the task-induced activation of these areas (Biswal, Yetkin, Haughton, & Hyde, 1995; Smith et al., 2009; van den Heuvel & Hulshoff Pol, 2010). Such interconnected regions form functional networks, which tend to be reproducible within and between subjects (Damoiseaux et al., 2006; Shehzad et al., 2009; Tomasi & Volkow, 2012). Resting state fMRI is considered to be a promising tool for neurosurgery, in particular for preoperative planning (Branco et al., 2016) but its applications require further investigation (Lang, Duncan, & Northoff, 2014). While the function of spontaneous blood-oxygen-level-dependent (BOLD) signal that gives rise to ICNs is not yet completely understood, it has been suggested that these signals serve to organize and coordinate neuronal activity (Fox & Raichle, 2007).

Several recent **studies** have confirmed the existence of a lateralized language ICN, which is comprised of the typical fronto-temporo-parietal left-hemisphere (LH) language centers, but also includes some regions within the right hemisphere (RH) (Tie et al., 2014; Zhu et al., 2014). According to the analysis by Muller and Meyer (Muller & Meyer, 2014), areas comprising the language network in the RH are not mirror images of their LH counterparts, although they do tend to be located within homologous structures, including inferior frontal gyrus, superior temporal sulcus, and precentral gyrus.

Here we present the results of seed region-of-interest (ROI) based analyses on four patients who underwent left hemispherectomy. Our aim was to identify putative RH language networks in these patients. We hypothesized that the ICN obtained by placing a seed ROI in right inferior frontal gyrus would include some of the core regions constituting the language network, including inferior frontal gyrus, superior temporal sulcus, and/or precentral gyrus. Previous fMRI studies examining children who have undergone left hemispherectomy identified BOLD responses to language tasks in the right inferior frontal gyrus (IFG), as well as in temporal and dorsal precentral regions; some have noted an increased recruitment of the frontal areas, as well as variation within the intact IFG (Hertz-Pannier *et al.*, 2002; Liégeois *et al.*, 2008; Danelli *et al.*, 2012). The current study is the first to evaluate the potential of rsfMRI to identify consistent patterns in the functional organization of putative language ICNs following left hemispherectomy.

Methods

Data collection

We analyzed resting state fMRI data collected from four children who had undergone left hemispherectomy (3 female, age at testing 11 to 21 years, mean age = 15.25, *SD* = 4.35), collected by researchers at The Brain Recovery Project (http://brainrecoveryproject.org/research). The participants were recruited via advertisements through the support groups for families with children after hemispherectomy. The Office of the Human Research Protection Program of the University of California, Los Angeles, approved this study and all participants gave informed consent to participate in the study. Patients and their families signed research informed assent and consent forms including Health Insurance Portability and Accountability Act (HIPAA) authorizations. In recruiting patients for this study, we made an effort to include individuals whose etiology would allow an isolated right hemisphere the greatest potential to develop language skills, i.e. the situation when language has unfolded in the RH from the very beginning. This selection process excluded individuals with progressive lesions, such as those having Sturge Weber Syndrome or Rasmussen Encephalitis and individuals with ongoing seizures that are not controlled by anti-epileptic drugs (AED). All participants underwent functional hemispherectomy, meaning that every connection to the LH was severed. In addition, all motor cortex in the LH was physically resected. Clinical history and neuroimaging results were reviewed both pre- and post-surgically by a medical team including a neuroradiologist and a neurosurgeon to check for the presence of any missed connections remaining between the two hemispheres and on the status of the remaining RH. The RH of all participants in this study was described as normal, with no overt signs of any mentioned pathologies.

A group analysis based on randomly selected data from 15 healthy controls was used for comparison with the subjects who underwent hemispherectomy. The control data were obtained from data collected at New York University made publicly available through the Autism Brain Imaging Data Exchange (http://fcon_1000.projects.nitrc.org/indi/abide/) (Di Martino et al., 2014). The age range of healthy, right-handed subjects (5 female, 10 male) was 11 to 18 years (mean age = 15.32, *SD* = 3.54). The control participants scored within the normal range on the WASI (Full-scale IQ average = 107.3, *SD* = 12.2; Verbal IQ average = 107.6, *SD* = 10.2).

Image acquisition

Whole-brain resting state fMRI data were collected for participants after hemispherectomy, using an echo-planar imaging (EPI) sequence (3T Allegra, 28 slices, slice thickness 3 mm, TR = 2500 ms, TE = 35 ms, flip angle = 90°, FOV = 200 mm, voxel size 3.1 × 3.1 × 3.0 mm, 166 volumes). A matched bandwidth high-resolution structural image was acquired for each participant (TR = 5000 ms; TE = 33 ms; rotation = 0°; 28 slices; 1 volume FOV = 200 mm).

The rsfMRI scans for controls were also collected on a 3T Allegra (33 slices, slice thickness 4 mm, TR = 2000 ms, TE = 15 ms, flip angle = 90°, FOV = 240 mm, voxel size = 3 mm × 3 mm × 4 mm, 180 volumes). A high-resolution T1-weighted anatomical image was acquired using a magnetization prepared gradient echo sequence (TR = 2530 ms; TE = 3.25 ms; flip angle = 7°; 128 slices; 1 volume FOV = 256 mm). All details regarding scanning protocols for control participants can be found in (Di Martino et al., 2014).

Preprocessing

We preprocessed the data using Data Processing Assistant for Resting-State fMRI (DPARSF), which is based on Statistical Parametric Mapping (SPM8) and the toolbox for Data Processing & Analysis of Brain Imaging (DPABI) (Yan, Wang, Zuo, & Zang, 2016). The first 10 volumes of the functional scans were deleted for all participants to avoid artifacts associated with their acquisition. The preprocessing steps included slice-timing correction, brain extraction of structural images, co-registration of the structural and the functional data for control participants, and segmentation using SPM priors for cerebrospinal fluid (CSF) and white matter (WM). We used the WM and CSF mean time series as nuisance regressors in the general linear model (GLM) to reduce the influence of physiological noise (Margulies et al., 2007). Global signal regression was not used (Saad et al., 2012). Additionally, we regressed out nuisance covariates related to motion using the Friston 24-parameter model (Friston, Williams, Howard, Frackowiak, & Turner, 1996) and applied a band pass filter capturing the fMRI signal between the frequencies 0.01–0.1 Hz. The data were spatially smoothed with a 6 mm full-width half-maximum Gaussian kernel. To further reduce motion-related artifacts we applied the cut (delete) “scrubbing” option available in the DPABI-A toolbox using the following parameters: framewise displacement (FD) threshold for bad time points = 0.5, time points deleted before bad time points = 1, time points deleted after bad time points = 2 (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). The original dataset included functional scans from six patients with hemispherectomy, but two had unacceptably high levels of motion (with more than 50% of points removed after scrubbing) and thus were excluded from subsequent analyses. No time points were removed for participants 1F and 2F; participant 3M had 48% of time points removed after scrubbing, and participant 4F had 38% removed. After scrubbing, control data were registered to the standard MNI template. Due to significant structural changes in brains after hemispherectomy, the patient data were not registered to a common template.

Seed ROI-based functional connectivity analysis

Individual functional connectivity analyses were performed in DPARSF. In order to identify the putative language network in the lone RH, we placed a spherical 6 mm-radius ROI in the pars orbitalis of the right inferior frontal gyrus (IFG, MNI coordinates 50 28–10). A matching location for each hemispherectomy patient was defined interactively, using anatomic landmarks within the IFG, a technique previously proven reliable by Kelly et al. (2010). In each participant, the seed was located within the posterior part of right pars orbitalis, immediately below pars triangularis. We selected the right IFG as the optimal region for seed ROI placement based on previous task-based fMRI studies in hemispherectomy patients demonstrating consistent involvement of this brain region in language function (Danelli et al., 2013; Hertz-Pannier et al., 2002; Liegeois, Connelly, Baldeweg, & Vargha-Khadem, 2008; Voets et al., 2006). Another region that tends to be recruited during language tasks in both neurotypical participants (Binder, 1997) and participants with hemispherectomy (Liégeois et al., 2008) is the middle temporal gyrus; however, exploratory analyses of functional connectivity of the middle temporal gyrus in control participants revealed a network that included several brain regions not specific to language function, so it was not considered further. We verified that the ICN obtained from our seed in the right IFG was indeed the putative language ICN by qualitatively comparing it with (a) the networks described in the literature (e.g., Muller & Meyer, 2014), (b) the Neurosynth map corresponding to the term "language" (Yarkoni et al., 2011), and (c) a language ICN in control participants, obtained by placing a seed ROI within the left IFG (MNI coordinates −53 20 15).

The control data were further analyzed on a group level. A group map was obtained via one-sample *t*-test, performed with the Resting-State fMRI Data Analysis Toolkit (REST) (Song et al., 2011). The result was corrected for multiple comparisons using Gaussian Random Field Theory Multiple Comparison Correction (voxel-level *p*-value = .00005; cluster-level *p*-value = .05), also implemented in REST.

ROI-to-ROI correlation analysis

In order to quantify the degree of connectivity between the seed ROI and the nodes that are functionally linked to it, we computed ROI-to-ROI correlation coefficients for both control participants and patients with hemispherectomy. **We used functional connectivity maps of individual participants (as opposed to the group map) in order to account for possible variability within the neurotypical population.** Significant clusters included at least 10 voxels and had a Fisher's z score of 0.55 or above. **The z score threshold we selected was based on the constraint that the IFG cluster should be separate from clusters in other brain regions, such as superior temporal sulcus. Based on these criteria, we identified regions in the RH that were present in at least a third of the participants (5 out of 15). The analysis revealed that four RH regions exhibited strong functional connectivity with the right IFG:** superior temporal sulcus, precentral gyrus, frontal pole, and right cerebellum. Additionally, we considered the cluster in the left cerebellum, which was present in four control participants. We subsequently defined a spherical 6 mm ROI within each of the chosen regions, centered on the voxel with the highest z score on the group map computed from control participants. Corresponding ROIs were defined for each of the patients based on anatomic landmarks. We then calculated correlation scores between the original seed and the obtained ROIs in each subject using Pearson's R (Song et al., 2011) and plotted them using the Anaconda software (http://docs.continuum.io/anaconda/). Due to the fact that the IFG seeds in the LH and in the RH are not fully homologous, a quantitative comparison of RH seed connectivity scores in hemispherectomy patients with LH seed connectivity scores in controls was not conducted.

Results

Participants: Clinical cohort description

Clinical variables and language scores of receptive vocabulary, reading and comprehension of a written text for the four participants are presented in Table 1. Histopathology results were consistent with a middle cerebral artery (MCA) stroke *in utero* in three individuals (1F, 2F & 3M), and with cortical dysplasia (CD) in the last one (4F). All participants with prenatal infarct were born with hemiparesis, but seizures started later in childhood following four to nine years of seizure-free development. In contrast, seizures in participant 4F started immediately after birth, congruent with her diagnosis of CD. All subjects were seizure-free following hemispherectomy, and AEDs were discontinued. Figure 1 shows high resolution anatomical MRIs of 3 of the 4 participants.

All participants had age-appropriate spoken language, with two patients (1F & 2F) who were also able to read and comprehend in the average range (Table 1). All four individuals were from monolingual English-speaking families. Pre-surgical evaluations of language abilities were not available due to severe seizure activity. Interviews were conducted with each participant's parents in order to obtain an account of the participant's language and literacy acquisition. Parents of participants after prenatal stroke (1F, 2F and 3M) stated that, after an initial delay, their child's language development seemed appropriate from about 24 months of age, until seizures became uncontrolled and language deterioration began. These three participants could barely speak at the time of their surgery and retained only a few words and signs. Language recovery was described as fast, and within 3–4 weeks post-surgery children had attained their pre-surgery, pre-seizure levels.

In contrast to individuals post-stroke who had prolonged seizure-free development before hemispherectomy, participant 4F started having severe AED-resistant seizures at birth and developed language skills following surgery only. Currently, 4F is a fluent speaker with significantly delayed cognitive and emotional development. In our study she received the lowest reading scores and could identify only a few sight words, being functionally illiterate.

Functional connectivity: Neurotypical individuals

After examining whole-brain connectivity of the left IFG seed (MNI coordinates −53 20 15), we obtained the group functional connectivity map representing the language ICN, shown on the top panel of Figure 2. The bottom panel of Figure 2 shows the group functional connectivity map obtained by placing the seed in the right IFG, specifically, within the pars orbitalis (MNI coordinates 50 28–10). Connectivity patterns derived from these two analyses were similar, suggesting that both represent portions of the same network. The clusters composing the network are listed in Table 2. Importantly, the ICN obtained by placing a seed in the right pars orbitalis included typical language regions, namely IFG, left angular gyrus, superior temporal sulcus, and clusters in both precentral gyri (Muller & Meyer, 2014). Within the RH, consistent patterns of connectivity were observed between the IFG and precentral gyrus, superior temporal sulcus, angular gyrus, temporal pole, left and, to a lesser extent, right cerebellum, and frontal pole. The analysis of the ICN obtained in neurotypical individuals demonstrated that the chosen ROI was effective at revealing the language network described in the previous studies (Muller & Meyer, 2014; Tie et al., 2014; Zhu et al., 2014). Thus, ROIs in the right IFG could be used as a starting point for exploring compensatory language networks in patients after hemispherectomy.

Functional connectivity: Hemispherectomy patients

The results of the seed-based analysis in individual hemispherectomy patients are presented in Figure 3. The seed ROI, located in pars orbitalis of the right IFG, was functionally connected with other parts of the IFG, specifically, with pars triangularis in all four participants and with pars opercularis in participants 3M and 4F. Three out of the four patients exhibited functional connectivity between the right IFG, right precentral gyrus, and right superior temporal sulcus, a pattern typical for the language network. The only exception was participant 3M, whose functional network did not include any cortical areas outside the IFG. Functional connectivity with the left cerebellum was present in participants 2F, 3M, and 4F, while connectivity with the right cerebellum was observed in 1F and 2F. Novel connectivity patterns that were not present in the ICNs of control participants include clusters in the superior parietal lobule (1F, 2F, and 4F), and the postcentral gyrus (4F). Functional connectivity results are summarized in Table 3.

ROI-to-ROI Analyses

We analyzed correlations in BOLD signal between our seed ROI and spherical ROIs centered at activation peaks of five major clusters of the RH language network identified in neurotypical individuals. The results are presented in Figure 4. For the control group, the strongest correlation values between cortical areas were observed between inferior frontal gyrus and (i) superior temporal sulcus, followed by (ii) precentral gyrus, and (iii) the frontal pole. Activity in the seed was also significantly correlated with activity in the ROIs in left and right cerebellum.

The description of functional connectivity results for participants who underwent hemispherectomy can be found in Table 4. Connectivity scores between the IFG and the superior temporal sulcus in 3M and 4F were comparable to scores of neurotypical controls, but 1F had an unusually high connectivity score, and 2F had an unusually low score. Connectivity scores between the IFG and the precentral gyrus were unusually high for 4F but within the normal range for other patients. Frontal pole connectivity values were higher than average in 2F and 4F but were close to zero in 1F and 3M. Right cerebellum connectivity score was unusually low in 3M, while the scores of the other participants were within the normal range. All four participants exhibited non-extreme functional connectivity scores between the IFG seed and left cerebellum ROIs.

Discussion

We demonstrate for the first time patterns of functional connectivity of the right inferior frontal gyrus in patients who have undergone left hemispherectomy for surgical treatment of epilepsy. Using seed ROI-based analysis of rsfMRI data, we identified intrinsic connectivity networks that partially resembled those observed in control subjects. These results demonstrate the potential utility of using rsfMRI to reveal functional organization of intrinsic connectivity networks following drastic brain surgery.

IFG connectivity patterns post-hemispherectomy are partially preserved

Our analyses indicate that functional connectivity between right inferior frontal gyrus and other regions typically contributing to language is at least partially preserved in patients with a lone RH. In three out of four patients, the networks revealed by the seed ROI analysis include most of the regions observed in neurotypical controls, such as pars triangularis, precentral gyrus, and the superior temporal sulcus (see Table 2). The only exception was participant 3M, who also exhibited the highest levels of in-scanner motion: the seed in his pars orbitalis showed remarkably low connectivity with the brain regions outside of IFG. Given the lack of the interaction with temporo-parietal regions, this network would not be able to carry out such a complex function as language (Friederici et al., 2011). We conclude that participant 3M likely relies on additional brain regions for language processing, which do not involve our ROI seed. The lack of involvement of pars orbitalis in the language ICN of this participant is not too surprising, as even in neurotypical individuals this region is not always involved in language function (Fedorenko, Duncan, & Kanwisher, 2012). In the remaining participants, however, the overall connectivity patterns are similar to the patterns observed in neurotypical individuals and can be indicative of a putative language ICN in the right hemisphere.

Patients with a lone right hemisphere demonstrate aberrant connectivity scores

Quantitative ROI-to-ROI analysis demonstrates that the RH network in participants with hemispherectomy exhibits altered connectivity patterns, with some scores lying outside the neurotypical variation range (see Figure 4 and Table 4). While the RH network includes most of the areas belonging to a traditional language ICN, it appears that some of the pathways within the network must undergo reorganization in order to compensate for the damage done to the left hemisphere.

Interestingly, high connectivity scores in these participants do not necessarily indicate functional recovery. Participants 1F and 2F have normal spoken and written language despite the fact that the ROI in superior temporal sulcus of participant 2F exhibits low connectivity scores, and right IFG in participant 1F has unusually low connectivity between right IFG and precentral gyrus, as well as between right IFG and the frontal pole. Meanwhile, written language function in 4F is impaired even though the nodes of this patient's network are highly correlated. It is possible that preserving the neurotypical network organization is, in fact, counterproductive when one hemisphere has to perform the functions of the two and that significant changes in connectivity are required for proper functional development. Although more studies are needed to determine the neural markers predicting operation outcome in this population, quantifying the degree of correlation between IFG and other major nodes of the language ICN pre- and post-surgery can reveal important information about the organization and efficiency of the network.

Resting state fMRI analysis complements information from task-based studies

To date, four studies have used fMRI to assess functional recovery in left hemispherectomy patients during language tasks. In the study of Hertz-Pannier et al. (2002), only the left hemisphere was shown to be involved in language tasks prior to the surgery, but functional scans of the right hemisphere after the operation revealed a network with high activation levels in the frontal areas, namely the right IFG and the right precentral gyrus, similar to the ICNs observed in our patients. Danelli and colleagues (2013) also report an increased recruitment of RH frontal regions post-surgery. In the study of Voets et al. (2006), activation is observed almost exclusively in the right IFG (although both frontal and temporal activation was present before the surgery), which may indicate the underconnectivity of this region, similar to the situation in participant 3M. Finally, three participants in the experiment by Liegeois et al. (2008) demonstrate an activation pattern consistent with the results we obtained for participants 1F, 2F, and 4F: all patients in that study recruit posterior temporal regions, as well as the dorsal part of the precentral gyrus. All three participants in Liegeois *et al.* (2008) demonstrate functional subdivision within the IFG, which can be observed for **one out of four** participants in our study. Overall, there is a high degree of correspondence between the task-based studies and our current analysis; in particular, three of the four discussed papers indicate the increased recruitment of frontal regions, as demonstrated in two of our subjects, although individual outcomes likely depend on the participants’ age and disease history.

Some previous studies assume that the compensatory network in the right hemisphere is a “neural blueprint” of its left counterpart (Danelli et al., 2013; Hertz-Pannier et al., 2002), while others point out the differences in anatomical location of new activation patterns (Liegeois et al., 2008; Voets et al., 2006). Our data seem to support the latter view, demonstrating that there are some differences in the location of right-hemisphere network clusters in patients compared to those in controls, and that these sites vary between participants. In future studies, rsfMRI analysis may be used to reveal regions in the right hemisphere that are functionally connected with major language centers and, therefore, have the potential to take over language functions after surgery (as suggested by Hertz-Pannier et al. (2002)).

Task-based fMRI is an important tool for directly evaluating brain regions involved in a specific function and has been used as a pre-surgical tool in patients with epilepsy to assess the feasibility of hemispherectomy (Gould et al., 2016). However, it is often insufficient for determining the nature and the extent of brain network reorganization (Reid, Boyd, Cunnington, & Rose, 2016). Moreover, disease manifestations before the surgery often make conducting task-based studies impossible, as was the case with our participants, none of whom were able to speak immediately before the surgery. Resting-state fMRI provides a useful complement to task-based methods and permits tracking changes in the ICNs before and after surgery.

Limitations and future directions

To date, only task-based fMRI studies have been used to assess the relationship between functional recovery and rearrangement of the language network in hemispherectomy patients. Our work complements these studies by investigating the rearrangement of the intrinsic connectivity network centered in the right IFG. While this type of network analysis is better suited to describe brain plasticity overall, only a combination of resting-state and task-based data can match a specific function to a given network (Poldrack, 2006). Given the differences in functional rearrangement that are observed between patients, performing both types of analysis on the same subjects would reveal the most reliable image of functional reallocation and recovery.

Although all participants were seizure-free following surgery, suggesting relative integrity of the remaining hemisphere, the putative language networks described here resulted from a number of factors including an original lesion, seizures and cerebral hemispherectomy. This makes it difficult to link specific changes underlying reorganization to one particular event. Moreover, this reorganization has influenced multiple cognitive functions, with language being only one of them. Nevertheless, our study is the first examination of substantial rewiring within the RH language network that occurs when an isolated hemisphere has to support functions of two, and different pathways it may adopt.

In the future, a larger sample size could be used to link individual differences in network rearrangement with language performance. Functional recovery usually depends on such factors as age of operation and the preceding course of the disease, and it is important to determine what age is most preferable for performing the operation (Hartman & Cross, 2014;HYPERLINK \l "bookmark23" Moosa et al., 2013). Resting state fMRI analysis, performed both before and after the operation, can be used to assess network autonomy and the potential for rearrangement. These data could then be used to optimize surgical planning and guide the recovery process for individuals undergoing this drastic operation.

Acknowledgments

This work was supported by awards K01MH092288 and R01MH107549 from the National Institute of Mental Health, a Slifka/Ritvo Innovation in Autism Research Award from the International Society for Autism Research, and a NARSAD Young Investigator Award to LQU.

References

Althausen A, Gleissner U, Hoppe C, Sassen R, Buddewig S, von Lehe M, Helmstaedter C. Long-term outcome of hemispheric surgery at different ages in 61 epilepsy patients. J Neurol Neurosurg Psychiatry. 2013; 84(5):529–536. DOI: 10.1136/jnnp-2012-303811 [PubMed: 23268362]

Binder JR, Frost JA, Hammeke TA, Cox RW, Rao SM, Prieto T. Human brain language areas identified by functional magnetic resonance imaging. J Neurosci. 1997; 17(1):353–362. [PubMed: 8987760]

Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med. 1995; 34(4):537–541. [PubMed: 8524021]

Branco P, Seixas D, Deprez S, Kovacs S, Peeters R, Castro SL, Sunaert S. Resting-State Functional Magnetic Resonance Imaging for Language Preoperative Planning. Front Hum Neurosci. 2016; 10:11.doi: 10.3389/fnhum.2016.00011 [PubMed: 26869899]

Cook SW, Nguyen ST, Hu B, Yudovin S, Shields WD, Vinters HV, Mathern GW. Cerebral hemispherectomy in pediatric patients with epilepsy: comparison of three techniques by pathological substrate in 115 patients. J Neurosurg. 2004; 100(2 Suppl Pediatrics):125–141. DOI: 10.3171/ped.2004.100.2.0125

Cummine J, Borowsky R, Winder FS, Crossley M. Basic reading skills and dyslexia: three decades following right versus left hemispherectomy for childhood-onset intractable epilepsy. Epilepsy Behav. 2009; 15(4):470–475. DOI: 10.1016/j.yebeh.2009.05.018 [PubMed: 19553160]

Damoiseaux JS, Rombouts SA, Barkhof F, Scheltens P, Stam CJ, Smith SM, Beckmann CF. Consistent resting-state networks across healthy subjects. Proc Natl Acad Sci U S A. 2006; 103(37):13848–13853. [PubMed: 16945915]

Danelli L, Cossu G, Berlingeri M, Bottini G, Sberna M, Paulesu E. Is a lone right hemisphere enough? Neurolinguistic architecture in a case with a very early left hemispherectomy. Neurocase. 2013; 19(3):209–231. DOI: 10.1080/13554794.2011.654226 [PubMed: 22519521]

de Bode S, Chanturidze M, Mathern GW, Dubinsky S. Literacy after cerebral hemispherectomy: Can the isolated right hemisphere read? Epilepsy Behav. 2015; 45:248–253. DOI: 10.1016/j.yebeh.2015.01.007 [PubMed: 25819796]

Di Martino A, Yan CG, Li Q, Denio E, Castellanos FX, Alaerts K, Milham MP. The autism brain imaging data exchange: towards a large-scale evaluation of the intrinsic brain architecture in autism. Mol Psychiatry. 2014; 19(6):659–667. DOI: 10.1038/mp.2013.78 [PubMed: 23774715]

Dunn, LM., Dunn, DM. Peabody Picture Vocabulary Test. Fourth. San Antonio, TX: PsychCorp; 2007.

Fedorenko E, Duncan J, Kanwisher N. Language-selective and domain-general regions lie side by side within Broca's area. Curr Biol. 2012; 22(21):2059–2062. DOI: 10.1016/j.cub.2012.09.011 [PubMed: 23063434]

Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci. 2007; 8(9):700–711. [PubMed: 17704812]

Friederici AD, Brauer J, Lohmann G. Maturation of the language network: from inter- to intrahemispheric connectivities. PLoS One. 2011; 6(6):e20726.doi: 10.1371/journal.pone.0020726 [PubMed: 21695183]

Friston KJ, Williams S, Howard R, Frackowiak RS, Turner R. Movement-related effects in fMRI time-series. Magn Reson Med. 1996; 35(3):346–355. [PubMed: 8699946]

Gould L, Mickleborough MJ, Wu A, Tellez J, Ekstrand C, Lorentz E, Borowsky R. Presurgical language mapping in epilepsy: Using fMRI of reading to identify functional reorganization in a patient with long-standing temporal lobe epilepsy. Epilepsy Behav Case Rep. 2016; 5:6–10. DOI: 10.1016/j.ebcr.2015.10.003 [PubMed: 27330987]

Grosmaitre C, Jambaque I, Dorfmuller G, Rodrigo S, Ville D, Delalande O, Bulteau C. Exceptional verbal intelligence after hemispherotomy in a child with Rasmussen encephalitis. Neurocase. 2015; 21(2):144–147. DOI: 10.1080/13554794.2013.878724 [PubMed: 24471481]

Gupta SS. fMRI for mapping language networks in neurosurgical cases. Indian J Radiol Imaging. 2014; 24(1):37–43. DOI: 10.4103/0971-3026.130690 [PubMed: 24851003]

Hartman AL, Cross JH. Timing of surgery in rasmussen syndrome: is patience a virtue? Epilepsy Curr. 2014; 14(1 Suppl):8–11. DOI: 10.5698/1535-7511-14.s2.8 [PubMed: 24955069]

Hertz-Pannier L, Chiron C, Jambaque I, Renaux-Kieffer V, Van de Moortele PF, Delalande O, Le Bihan D. Late plasticity for language in a child's non-dominant hemisphere: a pre- and post-surgery fMRI study. Brain. 2002; 125(Pt 2):361–372. [PubMed: 11844736]

Jonas R, Nguyen S, Hu B, Asarnow RF, LoPresti C, Curtiss S, Mathern GW. Cerebral hemispherectomy: hospital course, seizure, developmental, language, and motor outcomes. Neurology. 2004; 62(10):1712–1721. [PubMed: 15159467]

Kelly C, Uddin LQ, Shehzad Z, Margulies DS, Castellanos FX, Milham MP, Petrides M. Broca's region: linking human brain functional connectivity data and non-human primate tracing anatomy studies. Eur J Neurosci. 2010; 32(3):383–398. DOI: 10.1111/j.1460-9568.2010.07279.x [PubMed: 20662902]

Lang S, Duncan N, Northoff G. Resting-state functional magnetic resonance imaging: review of neurosurgical applications. Neurosurgery. 2014; 74(5):453–464. discussion 464–455. DOI: 10.1227/NEU.0000000000000307 [PubMed: 24492661]

Liegeois F, Connelly A, Baldeweg T, Vargha-Khadem F. Speaking with a single cerebral hemisphere: fMRI language organization after hemispherectomy in childhood. Brain Lang. 2008; 106(3):195–203. DOI: 10.1016/j.bandl.2008.01.010 [PubMed: 18329093]

Liegeois F, Morgan AT, Stewart LH, Helen Cross J, Vogel AP, Vargha-Khadem F. Speech and oral motor profile after childhood hemispherectomy. Brain Lang. 2010; 114(2):126–134. DOI: 10.1016/j.bandl.2009.12.004 [PubMed: 20096448]

Margulies DS, Kelly AM, Uddin LQ, Biswal BB, Castellanos FX, Milham MP. Mapping the functional connectivity of anterior cingulate cortex. Neuroimage. 2007; 37(2):579–588. DOI: 10.1016/j.neuroimage.2007.05.019 [PubMed: 17604651]

Moosa AN, Jehi L, Marashly A, Cosmo G, Lachhwani D, Wyllie E, Gupta A. Long-term functional outcomes and their predictors after hemispherectomy in 115 children. Epilepsia. 2013; 54(10):1771–1779. DOI: 10.1111/epi.12342 [PubMed: 23980759]

Muller AM, Meyer M. Language in the brain at rest: new insights from resting state data and graph theoretical analysis. Front Hum Neurosci. 2014; 8:228.doi: 10.3389/fnhum.2014.00228 [PubMed: 24808843]

Paiement P, Champoux F, Bacon BA, Lassonde M, Gagne JP, Mensour B, Lepore F. Functional reorganization of the human auditory pathways following hemispherectomy: an fMRI demonstration. Neuropsychologia. 2008; 46(12):2936–2942. DOI: 10.1016/j.neuropsychologia.2008.06.009 [PubMed: 18602934]

Poldrack RA. Can cognitive processes be inferred from neuroimaging data? Trends Cogn Sci. 2006; 10(2):59–63. S1364-6613(05)00336-0[pii]10.1016/j.tics.2005.12.004. [PubMed: 16406760]

Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage. 2012; 59(3):2142–2154. S1053–8119(11)01181-5 [pii] 10.1016/j.neuroimage.2011.10.018. [PubMed: 22019881]

Reid LB, Boyd RN, Cunnington R, Rose SE. Interpreting Intervention Induced Neuroplasticity with fMRI: The Case for Multimodal Imaging Strategies. Neural Plast. 2016; 2016:2643491.doi: 10.1155/2016/2643491 [PubMed: 26839711]

Saad ZS, Gotts SJ, Murphy K, Chen G, Jo HJ, Martin A, Cox RW. Trouble at rest: how correlation patterns and group differences become distorted after global signal regression. Brain Connect. 2012; 2(1):25–32. DOI: 10.1089/brain.2012.0080 [PubMed: 22432927]

Samargia SA, Kimberley TJ. Motor and cognitive outcomes in children after functional hemispherectomy. Pediatr Phys Ther. 2009; 21(4):356–361. DOI: 10.1097/PEP.0b013e3181bf710d [PubMed: 19923976]

Saur D, Kreher BW, Schnell S, Kummerer D, Kellmeyer P, Vry MS, Weiller C. Ventral and dorsal pathways for language. Proc Natl Acad Sci U S A. 2008; 105(46):18035–18040. [PubMed: 19004769]

Shehzad Z, Kelly AM, Reiss PT, Gee DG, Gotimer K, Uddin LQ, Milham MP. The resting brain: unconstrained yet reliable. Cereb Cortex. 2009; 19(10):2209–2229. doi: bhn256 [pii]10.1093/cercor/bhn256. [PubMed: 19221144]

Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, Mackay CE, Beckmann CF. Correspondence of the brain’s functional architecture during activation and rest. Proc Natl Acad Sci U S A. 2009; 106(31):13040–13045. 0905267106 [pii]10.1073/pnas.0905267106. [PubMed: 19620724]

Smith SM, Miller KL, Salimi-Khorshidi G, Webster M, Beckmann CF, Nichols TE, Woolrich MW. Network modelling methods for FMRI. Neuroimage. 2011; 54(2):875–891. DOI: 10.1016/j.neuroimage.2010.08.063 [PubMed: 20817103]

Song XW, Dong ZY, Long XY, Li SF, Zuo XN, Zhu CZ, Zang YF. REST: a toolkit for resting-state functional magnetic resonance imaging data processing. PLoS One. 2011; 6(9):e25031.doi: 10.1371/journal.pone.0025031 [PubMed: 21949842]

Stark RE, McGregor KK. Follow-up study of a right- and a left-hemispherectomized child: implications for localization and impairment of language in children. Brain Lang. 1997; 60(2): 222–242. DOI: 10.1006/brln.1997.1800 [PubMed: 9344478]

Tie Y, Rigolo L, Norton IH, Huang RY, Wu W, Orringer D, Golby AJ. Defining language networks from resting-state fMRI for surgical planning— a feasibility study. Hum BrainMapp. 2014; 35(3): 1018–1030. DOI: 10.1002/hbm.22231

Tomasi D, Volkow ND. Resting functional connectivity of language networks: characterization and reproducibility. Mol Psychiatry. 2012; 17(8):841–854. DOI: 10.1038/mp.2011.177 [PubMed: 22212597]

van den Heuvel MP, Hulshoff Pol HE. Exploring the brain network: a review on resting-state fMRI functional connectivity. Eur Neuropsychopharmacol. 2010; 20(8):519–534. DOI: 10.1016/j.euroneuro.2010.03.008 [PubMed: 20471808]

Voets NL, Adcock JE, Flitney DE, Behrens TE, Hart Y, Stacey R, Matthews PM. Distinct right frontal lobe activation in language processing following left hemisphere injury. Brain. 2006; 129(Pt 3): 754–766. DOI: 10.1093/brain/awh679 [PubMed: 16280351]

Woodcock, RW. Woodcock Reading Mastery Tests – III. Circle Pines, MN: American Guidance Service; 2011.

Yan CG, Wang XD, Zuo XN, Zang YF. DPABI: Data Processing & Analysis for (Resting-State) Brain Imaging. Neuroinformatics. 2016; 14(3):339–351. DOI: 10.1007/s12021-016-9299-4 [PubMed: 27075850]

Yarkoni T, Poldrack RA, Nichols TE, Van Essen DC, Wager TD. Large-scale automated synthesis of human functional neuroimaging data. Nat Methods. 2011; 8(8):665–670. [PubMed: 21706013]

Zhang J, Mei S, Liu Q, Liu W, Chen H, Xia H, Li Y. fMRI and DTI assessment of patients undergoing radical epilepsy surgery. Epilepsy Res. 2013; 104(3):253–263. DOI: 10.1016/j.eplepsyres.2012.10.015 [PubMed: 23340329]

Zhu L, Fan Y, Zou Q, Wang J, Gao JH, Niu Z. Temporal reliability and lateralization of the resting-state language network. PLoS One. 2014; 9(1):e85880.doi: 10.1371/journal.pone.0085880 [PubMed: 24475058]

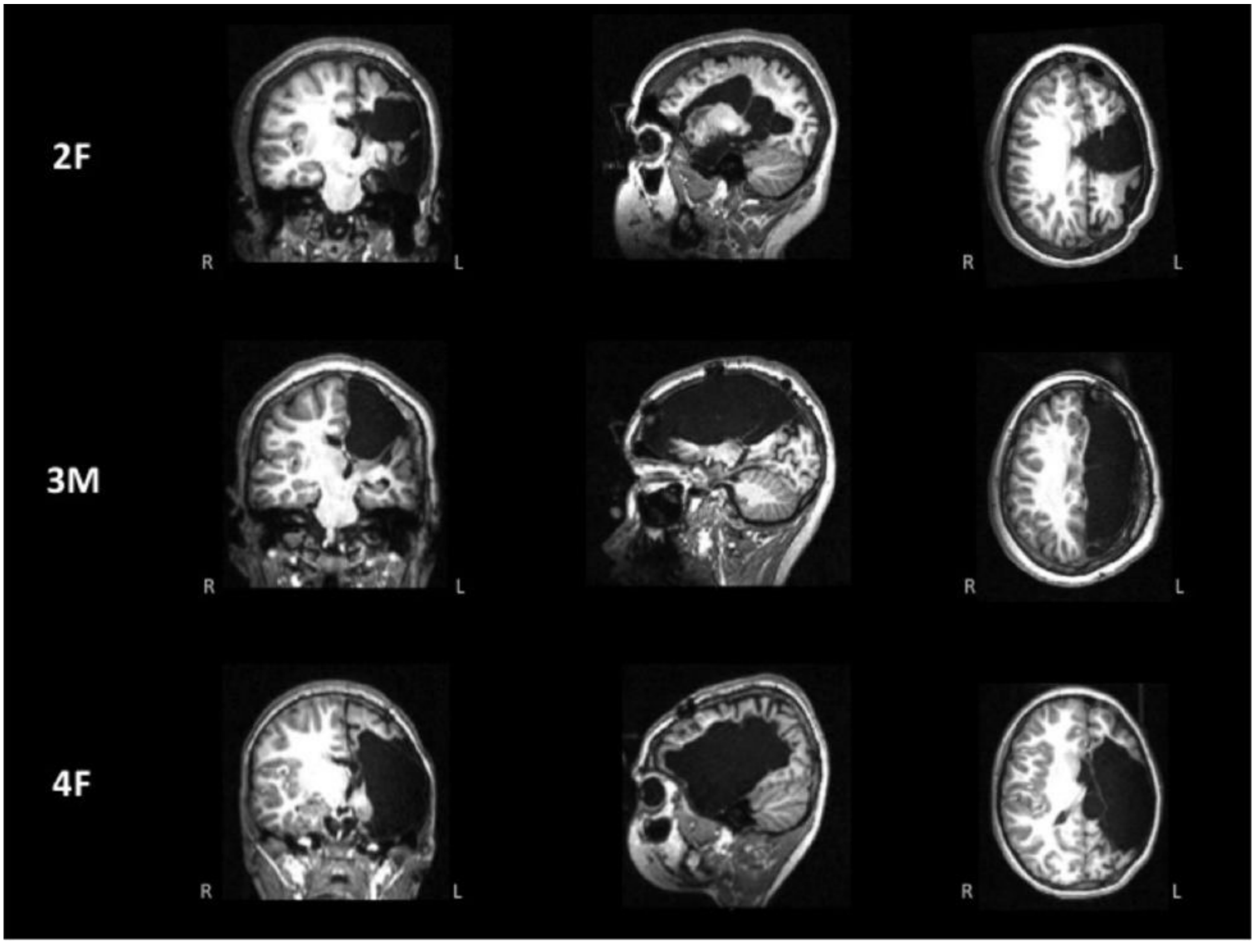

Figure 1.

High resolution structural MRI from three of the four examined patients with left hemispherectomy. All underwent peri-insular functional hemispherectomy (i.e., hemispherotomy); connections to the remaining hemisphere were completely severed (Cook et al., 2004).

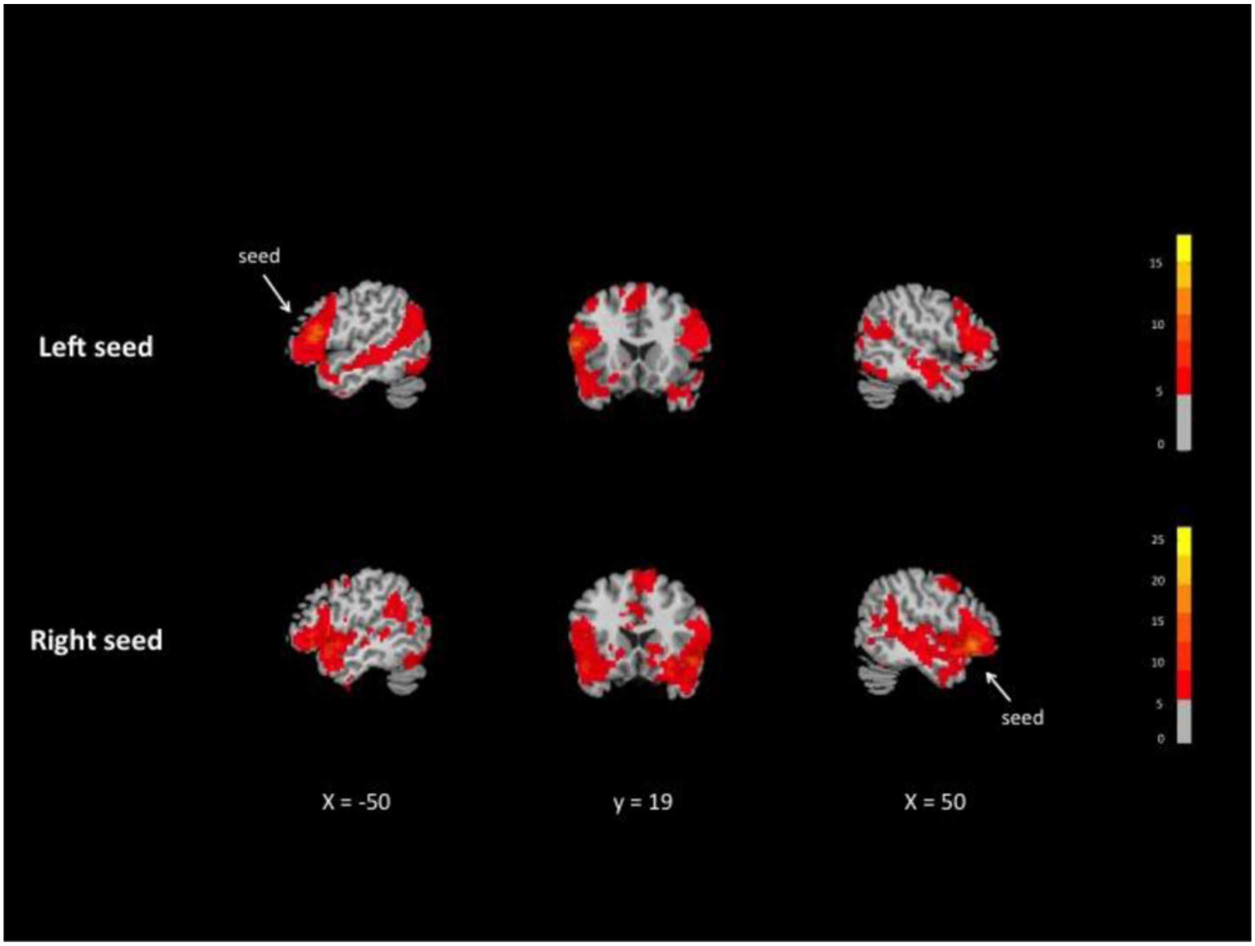

Figure 2.

Intrinsic connectivity networks in neurotypical individuals obtained by placing ROIs in the left IFG (−53 20 15) and the right IFG (50 28 −10) (Gaussian random field corrected, *p*-value = .0001).

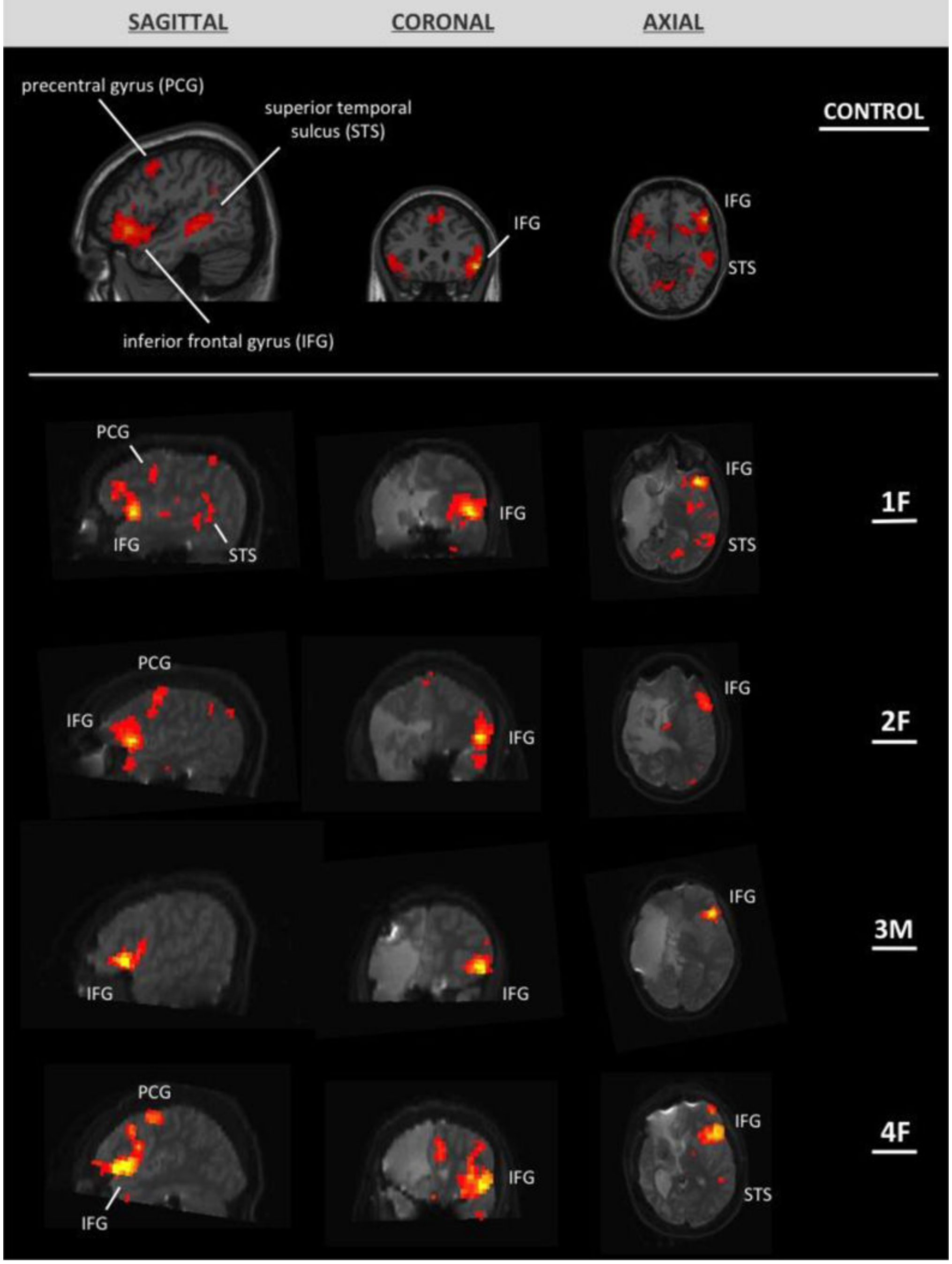

Figure 3.

Functional connectivity maps for neurotypical control group and four individual patients with left hemispherectomy, with seed placed in the right pars orbitalis. IFG – inferior frontal gyrus, PMC – premotor cortex, STS – superior temporal sulcus.

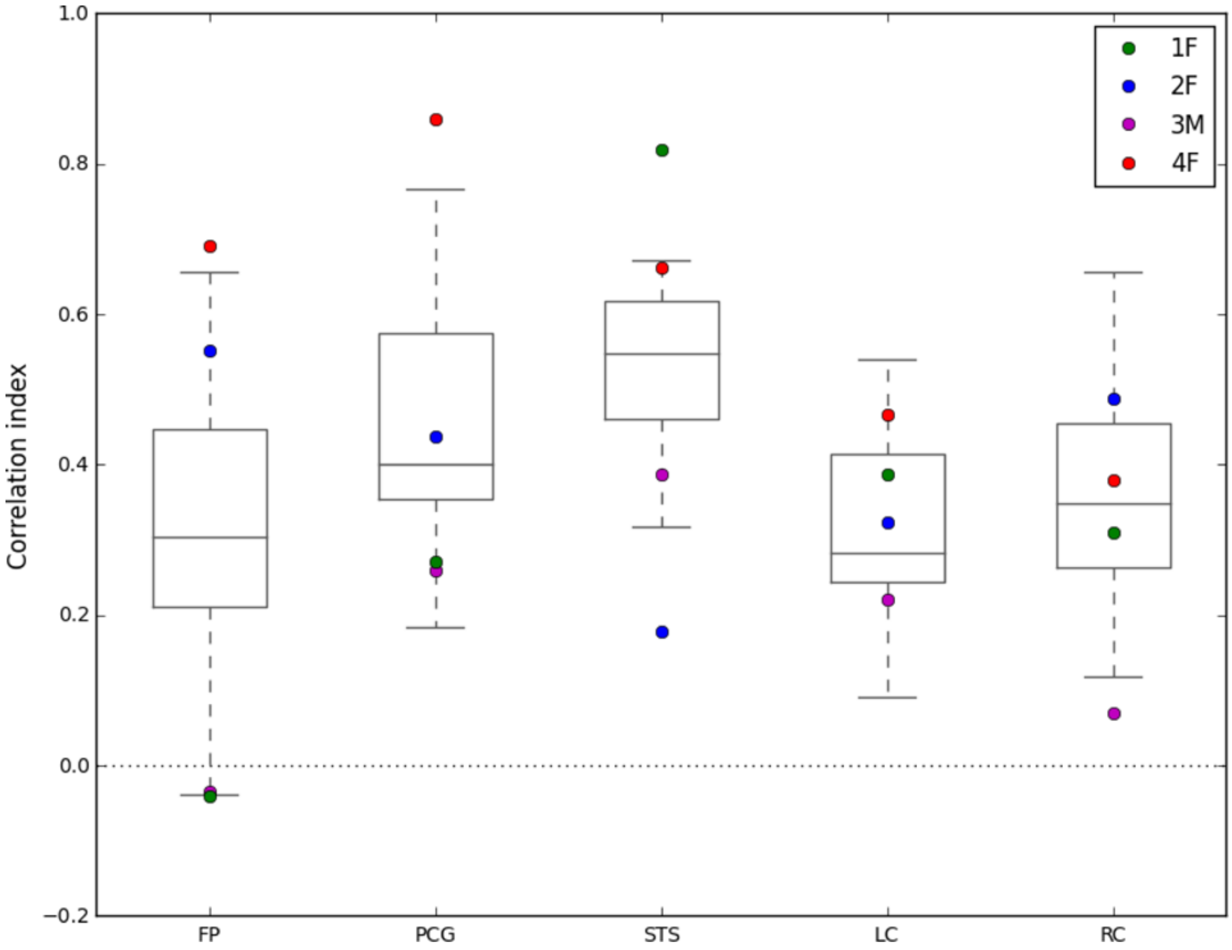

Figure 4.

Strength of correlation between the seed in inferior frontal gyrus and seeds placed in the major nodes of the right hemisphere language ICN. “Correlation index” stands for Pearson’s R. Boxplots represent the control data (top and bottom lines indicate the range of scores, the box represents the interquartile range, and the midline represents the median), while dots show the scores of participants after hemispherectomy. FP – right frontal pole, PCG – right precentral gyrus, STS – right superior temporal sulcus, LC - left cerebellum, RC - right cerebellum.

Table 1

Clinical variables and language proficiency of hemispherectomy patients

	Age at testing, years	Age at surgery, years	Age at seizure onset, years	Receptive vocabulary PPVT*	WRMT**	
					Reading Words	Comprehension
1F	21	9	8	100	95	103
2F	16	11	4	89	86	91
3M	13	11	9	94	73	65
4F	11	2	Birth	78	56	73

-Standard Scores 100 ± SD 15

[*] Peabody Picture Vocabulary Test (Dunn & Dunn, 2007)

[**] Woodcock Reading Mastery Test – III (Woodcock, 2011)

Table 2

List of clusters that compose the intrinsic connectivity network obtained by placing ROIs either in the left IFG (−53 20 15) or the right IFG (50 28–10) in neurotypical controls. Subcortical structures are italicized.

Cluster	**Peak MNI coordinate (seed in left IFG)**	**Peak MNI coordinate (seed in right IFG)**
Left IFG	−54 21 15	−51 12 9
Right IFG	57 27 15	48 27 −6
Left superior temporal sulcus	−60 −39 −3	−64 −39 3
Right superior temporal sulcus	54 −12 −12	51 −39 3
Left precentral gyrus	−42 9 48	−42 6 48
Right precentral gyrus	42 6 51	45 6 45
Left angular gyrus	−60 −57 9	−57 −54 24
Right angular gyrus	60 −63 15	63 −45 24
Left temporal pole	−39 24 −24	−51 12 −15
Right temporal pole	33 21 −27	54 15 −13
Right frontal pole	18 57 −21	18 57 −18
Right superior frontal gyrus	3 54 39	3 42 45
Left basal ganglia	*−15 9 6*	*−12 12 3*
Right basal ganglia	*12 0 12*	*9 6 3*
Left cerebellum	*−24 −87 −27*	*−18 −72 −36*
Right cerebellum	*24 −75 −18*	*12 −81 −30*

Table 3

Activation clusters for each hemispherectomy patient, compared to a group result for neurotypical controls.

	pars triangularis	*pars opercularis*	*precentral gyrus*	*superior temporal sulcus*	*left cerebellum*	*right cerebellum*	*Novel regions*
1F	x		x	x		x	SPL
2F	x	x	x	x	x	x	SPL
3M	x	x					–
4F	x	x	x	x	x	x	SPL, PostCG

SPL – superior parietal lobule, PostCG – postcentral gyrus

Table 4

Regions of high and low correlation with the seed in right inferior frontal gyrus in participants with hemispherectomy. The ROI is listed in the table if its functional connectivity score lies outside the interquartile range of scores for control participants; the region is marked with an asterisk if its connectivity score lies outside the observed range of the control group scores.

Participant	High correlation indices	Low correlation indices
1F	STS *	FP, PCG
2F	FP, RC	STS *
3M	–	FP, PCG, STS, LC, RC *
4F	FP *, PCG *, STS, LC	–

*outside the normal range

FP – right frontal pole, PCG – right precentral gyrus, STS – right superior temporal sulcus, LC - left cerebellum, RC - right cerebellum