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Case report

Atypical language localization in right temporal lobe epilepsy: An fMRI case report

Layla Gould [a,*], Adam Wu [a], Jose F. Tellez-Zenteno [b], Josh Neudorf [c], Shaylyn Kress [c], Katherine Gibb [c], Chelsea Ekstrand [c], Hamid Dabirzadeh [d], Syed Uzair Ahmed [a], Ron Borowsky [c]

[a] Department of Surgery, Division of Neurosurgery, Royal University Hospital, 103 Hospital Drive, Saskatoon, SK, S7N 0W8, Canada
[b] Department of Medicine, Division of Neurology, Royal University Hospital, 103 Hospital Drive, Saskatoon, SK, S7N 0W8, Canada
[c] Department of Psychology, University of Saskatchewan, 9 Campus Drive, Saskatoon, SK S7N 5A5, Canada
[d] Department of Medical Imaging, Royal University Hospital, 103 Hospital Drive, Saskatoon, SK S7N 0W8, Canada

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ABSTRACT

We report a 41- year-old, left-handed patient with drug-resistant right temporal lobe epilepsy (TLE). Presurgical fMRI was conducted to examine whether the patient had language functioning in the right hemisphere given that left-handedness is associated with a higher prevalence of right hemisphere dominance for language. The fMRI results revealed bilateral activation in Broca's and Wernicke's areas and activation of eloquent cortex near the region of planned resection in the right temporal lobe. Due to right temporal language-related activation, the patient underwent an awake right-sided temporal lobectomy with intraoperative language mapping. Intraoperative direct cortical stimulation (DCS) was conducted in the regions corresponding to the fMRI activation, and the patient showed language abnormalities, such as paraphasic errors, and speech arrest. The decision was made to abort the planned anterior temporal lobe procedure, and the patient instead underwent a selective amygdalohippocampectomy via the Sylvian fissure at a later date. Post-operatively the patient was seizure-free with no neurological deficits. Taken together, the results support previous findings of right hemisphere language activation in left-handed individuals, and should be considered in cases in which presurgical localization is conducted for left-hand dominant patients undergoing neurosurgical procedures.

1. Introduction

Temporal lobe epilepsy (TLE) is the most common form of focal epilepsy. In patients who do not achieve adequate seizure control with antiseizure medication, surgery has become an effective and widely used treatment worldwide. Anterior temporal lobectomy (ATL) involves removing a portion of the anterior temporal lobe along with the amygdala and hippocampus, and leads to a significant reduction of seizures or complete seizure control in about 70% to 80% of cases [1–3]. Selective amygdalohippocampectomy (SAH) without resection of the temporal lobe has been favored by some experts, but multiple studies have consistently displayed lower rates of seizure freedom than ATL (see [4] for review). In both cases, cognitive processes such as language and memory can be affected if surgery is performed on the language-reliant hemisphere. As such, language localization is of critical importance for presurgical evaluation prior to surgery in order to avoid the development of post-operative cognitive deficits.

While the left hemisphere is typically considered dominant for language function (approximately 90% to 95% of the population; [5,6]), a higher proportion of atypical (i.e., right or bilateral) language dominance is encountered in patients with epilepsy compared to healthy controls [7–10]. Atypical language representation in right-handed patients with epilepsy ranges from approximately 20% to 33% according to Wada and fMRI studies [9,11–14], yet the presence or absence of atypical language patterns may vary depending on differing patient characteristics [8,15,16], such as handedness [9,13,14]. In healthy controls, atypical language lateralization is more prevalent in left-handers than in right-

* Correspondence to: L. Gould, Department of Surgery, University of Saskatchewan, SK S7N 5A5, Canada.
E-mail addresses: layla.gould@usask.ca (L. Gould), ron.borowsky@usask.ca (R. Borowsky).

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handers [6,17,18]. In left-handed patients with epilepsy, the likelihood of atypical language dominance may be even greater [8], with studies suggesting a range of 30–70% show atypical language representation [13,19,20]. Due to the heterogeneity of epilepsy, language localization is of critical importance for evaluation prior to surgery in order to avoid the development of post-operative cognitive deficits [8,15].

There are a number of techniques available for localizing language, including the Wada test [21–24], electrical stimulation mapping (ESM) [25,26], electrocorticography (ECoG) [25–28], and fMRI [24,26,29,30]. Although the Wada test has historically been a prevalent localization strategy, its invasiveness and other limitations [24,30] have led to more clinicians opting to use the other techniques, with ESM being considered the gold standard by some in recent years [e.g. [26]]. In particular, many contemporary studies have investigated the use of ECoG to precisely observe real time activation in the language areas of the brain [26]. ECoG has high concordance with the other measures of laterality, including its counterpart ESM, as well as fMRI [25,26]. However, ESM and ECoG are both invasive processes, requiring the surgical placement of an electrode grid to either stimulate regions or measure activation. Although ECoG has less potential for complications compared to ESM (measuring activation will not accidently induce seizures in the patient) [26], fMRI is appealing as a non-invasive localization alternative. Several studies have shown that functional magnetic resonance imaging (fMRI) offers a non-invasive and reliable tool for mapping eloquent cortex in patients prior to brain surgery [31–38], and specifically, for evaluating language localization in patients with TLE prior to surgery [21,22,27]. fMRI activation has been correlated with preoperative performance on neuropsychological language assessments (with the degree of left laterality being negatively correlated with performance in LTLE patients and positively correlated with performance in RTLE patients) [29], and numerous studies have tested the concordance of fMRI with the other lateralisation techniques with great success (see [21,24] for reviews; see also [22,25,26]). For these reasons, fMRI has been recommended in the AAN guideline as a preliminary lateralisation test to complement the other, more invasive techniques [24]. Moreover, it has been shown that the risk of postsurgical language and memory deficits are directly related to the presurgical lateralization of language function, and that presurgical fMRI mapping leads to fewer post-operative deficits [39].

The goal of the present case report is to evaluate the evidence for the possibility of right hemisphere language activation in this left-handed right TLE patient, and discuss the value of fMRI of language tasks for presurgical planning in epilepsy cases. Moreover, the case report highlights how fMRI findings can alter surgical strategy and how intraoperative brain mapping validated these findings, which ultimately led to a successful outcome.

2. Case report

We report a 41-year-old, left-handed male with drug-resistant right TLE. The patient was otherwise healthy with no significant past medical history. The patient had seizures since the age of three, but the seizures were infrequent for many years until he reached the age of 31 years of age when they became intractable. He had focal impaired awareness seizures, but also with secondary generalization. He had falls from the seizures resulting in soft tissue injuries as a result. His PET and MRI scans did not reveal any clear anatomical abnormalities in the right temporal lobe. A multidisciplinary epilepsy team review, including input from neurosurgeons and neurologists, determined that the patient was a candidate for a right temporal lobectomy with intraoperative electroencephalography (EEG) monitoring. A functional MRI scan prior to surgery was requested, as the patient was left-handed and thus had a higher likelihood to be right hemisphere dominant for language compared to right-handed people [6]. A Wada test was not performed as our center decided to forgo Wada testing given less invasive alternatives (i.e., fMRI and intraoperative neurophysiology) are available to our patients and thus preferred over the Wada test. The patient's consent was obtained and the scan was performed in compliance with the Declaration of Helsinki (2008) and the relevant laws and institutional guidelines, and was approved by the University of Saskatchewan Research Ethics Board. Before surgery, he was talking lamotrigine 200 mg and phenytoin 200 mg orally once per day. He failed to respond in the past to topiramate, clonazepam, levetiracetam and phenobarbital.

2.1. Seizure semiology

The patient had focal impaired awareness seizures and focal to bilateral tonic-clonic seizures. He would have speech arrest in 50% of the seizures, then lose contact with people and the environment, ‘space out’ and not move for 30 s, followed by post-ictal confusion. He had also the same onset for his focal to bilateral tonic-clonic seizures.

3. Materials and methods

3.1. fMRI protocol

All imaging was conducted using a 3 Tesla Siemens AG (Erlangen, Germany) Skyra scanner. The anatomical scans were whole-brain T1-weighted echo-planar images, and the functional tasks were T2*-weighted EPI scans. The patient responded vocally during the regular, periodic gap in the image acquisition.

3.2. Stimuli and fMRI tasks

The patient performed four reading-aloud tasks, which included exception word reading (e.g., ‘yacht’, which force whole-word lexical reading), picture naming, the ‘how’ task (i.e., a semantic generation task that asks how you would interact with an object [33,40–42] , and semantic questions (e.g., “what do you use to shave?”. These tasks were performed in separate runs, each had a duration of 3 min and 12 s.

3.3. fMRI analyses

All preprocessing and statistical analyses for functional images were performed using Brain Voyager QX (*www.brainvoyager.com*). Functional images were preprocessed and corrected for slice scan time acquisition, 3D motion correction, and temporal filtering with a high-pass filter to remove frequencies less than two cycles/time course. Lower-level analyses of the contrast between task versus rest for each condition (i.e., word reading, picture naming, semantic questions, and how task) were then performed using a sinusoidal double-gamma hemodynamic response function convolution. Linear correlations were carried out and the images were statisically thresholded using clusters determined by a (corrected) cluster significance threshold of $p < .05$. The thresholds for the tasks were word reading, $r = 0.59$, picture naming, $r = 0.65$, semantic questions, $r = 0.61$, and how task, $r = 0.59$, and differ due to different visible image artifacts between tasks. The centroids and number of voxels of activation clusters for each task were located, and the total number of voxels of these clusters was calculated for the left (L) and right (R) hemispheres, which were used to calculate the laterality index (LI) as $(R - L) / (R + L)$. The LI values fall between -1 and 1, with negative values indicating left dominance, positive values indicating right dominance, and values close to 0 indicating bilateral activation.

4. fMRI results

The conjunction of word reading, picture naming, and how task revealed consistent fMRI activation in left Broca's area (Fig. 1a) and right

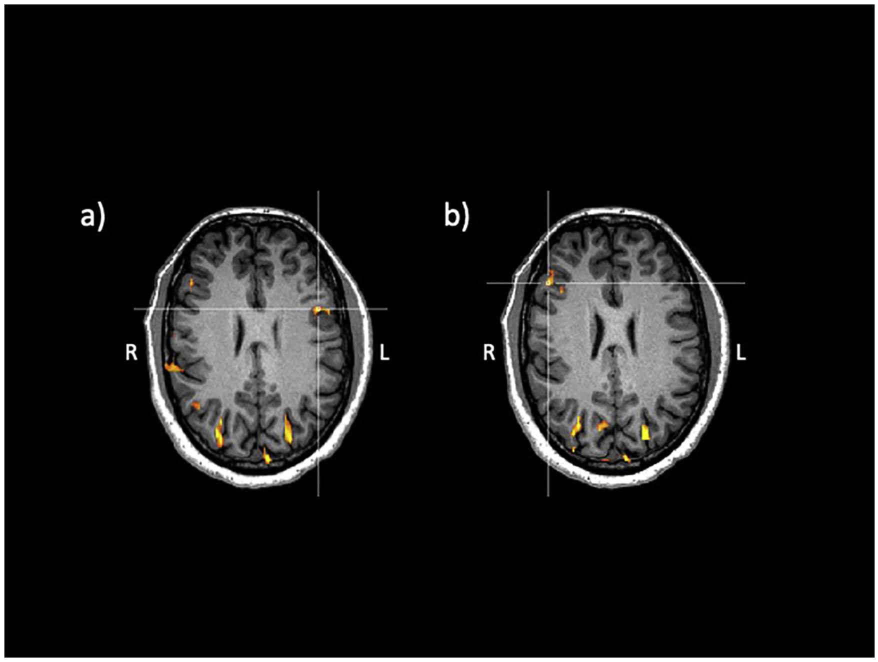

Fig. 1. a) Conjunction map for word reading, picture naming, and how task with crosshairs indicating the region that all three tasks activated in Broca's area, b) Conjunction map for word reading, picture naming, and how task with crosshairs indicating the region that all three tasks activated Broca's area homolog. Each cluster represents an area of fMRI activation, with the color representing the strength of the fMRI response (e.g., yellow areas showing the greatest activity compared to baseline).

hemisphere Broca's homolog (Fig. 1b). Additionally, the word reading task showed activation in left Wernicke's area and right hemisphere Wernicke's homolog (see Fig. 2a and b for bilateral Broca's and Fig. 2c and d for bilateral Wernicke's areas). The conjunction of word reading and picture naming tasks also revealed activation in the right temporal pole (Fig. 3a), and the questions task activated the right hippocampus (Fig. 3b), which were all in the region of planned resection. The laterality index (LI) results also reveal bilateral activation for each of the language tasks given that the values are all close to 0 (spatial coordinates of the centroids for the activation maps and the LI for each task are shown in Table 4; Appendix). Taken together, these findings suggested that the patient has bilateral activation for language processing. Additionally, the fact that there are larger swaths of activation in the right hemisphere and that there are regions of activation in the right hemisphere but not the left for some of the language tasks, indicates

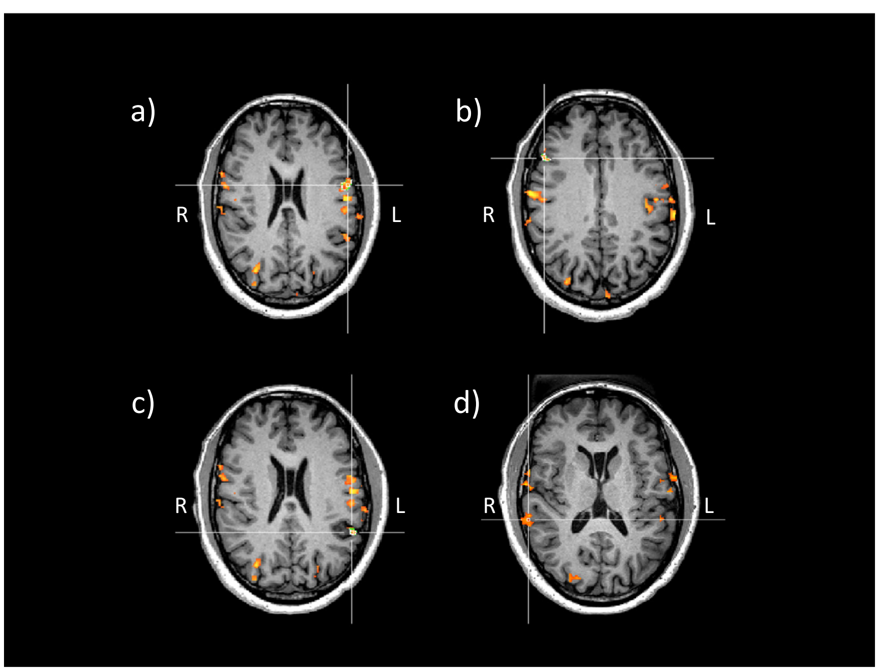

Fig. 2. a) Activation for word reading with crosshairs indicating Broca's area, b) Activation for word reading with crosshairs indicating Broca's area homolog, c) Activation for word reading with crosshairs indicating Wernicke's area, d) Activation for word reading with crosshairs indicating Wernicke's area homolog.

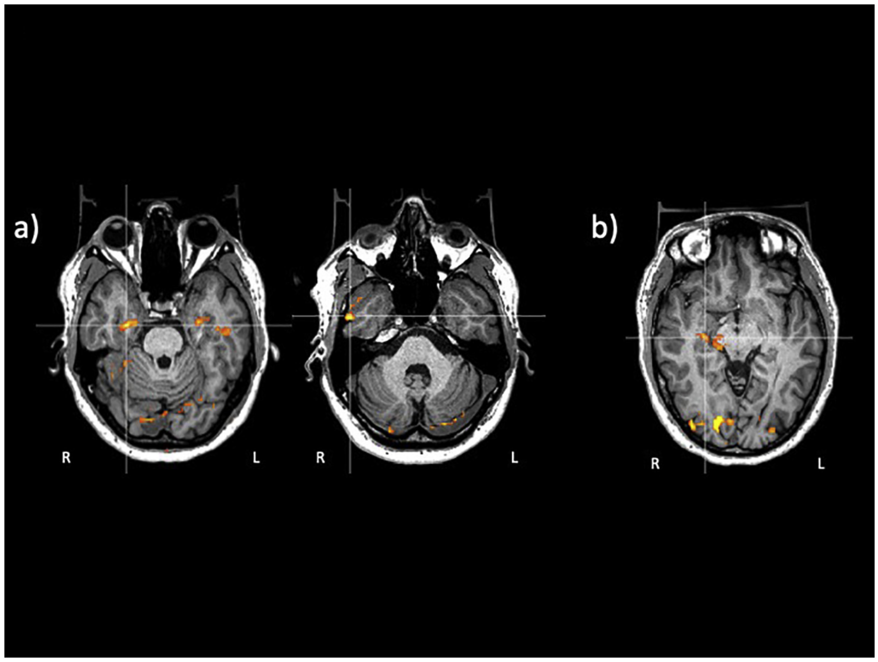

Fig. 3. a) Conjunction map for word reading and picture naming with crosshairs indicating regions of activation in the right temporal lobe in the planned area of resection, b) Activation for semantic questions in the right temporal lobe near the planned area of resection.

that the patient may have significant right hemisphere involvement for language.

5. Surgical procedure

Due to right temporal language activation, the patient was consented to an awake right-sided temporal lobectomy with intraoperative speech/language mapping, and intraoperative EEG monitoring. The fMRI activation for the word reading, picture naming, and semantic questions (i.e., tasks that showed activation near the resection) were loaded onto the Stealth neuronavigation system (Medtronic, Inc., U.S.A.), which was then used to map out the temporal lobe. A standard temporal lobe approach using a modified pterional craniotomy was performed. After exposure of the temporal lobe surface, the intraoperative EEG team placed a 1-through-8 lead over the surface of the temporal lobe and speech/language was mapped using an Ojemann stimulator (Integra LifeSciences, USA). Beginning with 2 milliamps of stimulation , the functional team visually presented pictures with the use of an iPad, using the same pictures that were presented to the patient during fMRI. The patient had originally performed moderately well at 2 milliamps of stimulation. Once this was increased to 4 milliamps, the patient exhibited increased word association abnormalities intraoperatively, including paraphasic errors (e.g., for a picture of a comb the patient answered "hair"), and complete speech arrest. Following testing at 4 milliamps, it was concluded that there was no safe operative corridor to approach the targeted area of lobectomy without potentially putting speech/language-related function at risk. The decision was made to abort the planned ATL procedure and pursue further methods of targeting the lesion.

A discussion was held with the patient and family to change the operative plan to SAH, with the decreased likelihood of seizure freedom. Consent was obtained, and the patient returned to the operating room approximately a month later. The transsylvian approach [43], was employed. Sylvian fissure dissection was carried out and the carotid cistern opened. The MCA branches were then isolated from the carotid terminus into the Sylvian fissure, and using anatomical landmarks and neuronavigation, a small incision was placed in the piriform cortex above the amygdala. Parts of the amygdala were then removed using an ultrasonic aspirator, keeping the underlying arachnoid membrane intact. The temporal horn was entered and a cotton pledglet was placed at the entrance. The anterior and posterior parts of the hippocampus were removed via suction-aspiration, and the draining vein was coagulated and cut. Tissue samples were sent to the pathology lab, and closure was obtained in usual fashion. The patient had transient drowsiness on emergence, which had resolved by the morning after surgery. There were no speech/language deficits, and neurocognition was preserved. Two months post-surgery the patient was seizure-free with no cognitive deficits.

6. Discussion

The present case report illustrates the usefulness of fMRI in preoperative mapping of eloquent cortex in a left-handed individual with epilepsy. Utility was shown in the assessment of language lateralization and localization for standard resective epilepsy surgery to guide the optimal surgical approach and prevent postoperative speech/language deficits as recommended in the AAN guideline [24]. In addition to aiding global lateralization, the fMRI tasks also localized particular language regions, such as left and right Broca's area and Wernicke's area (Figs. 1 & 2). There was also fMRI activation in the right temporal lobe for word reading, picture naming, and semantic questions, which was in the region of planned resection (Fig. 3). These findings support those observed by several studies documenting the ability of fMRI to localize language in patients with epilepsy [see 21, 24 for reviews; 22, 26]. Importantly, the fMRI findings in this case altered the surgical strategy and were confirmed using DCS, and ultimately led to a successful outcome.

In this case, the team suspected that the patient may have right hemisphere involvement for language based on his left-handedness and the fact that he lost speech during his seizures 50% of the time. The fMRI results revealed bilateral activation for language, and showed that there was activation of eloquent cortex near the region of planned resection in the right temporal lobe. An fMRI study by Mazoyer et al. revealed that healthy left-handed individuals showed more frequent atypical language lateralization than in right handers [6]. Lastly, Allendorfer et al. showed that 18 of their 73 atypical/left-handed participants showed either symmetric or right hemisphere dominance for the fMRI language task [17]. The results of this case thus indicate agreement with previous studies showing patients with atypical dominance more likely to have atypical handedness (in left-handed patients and those with mixed dominance).

One critical issue in fMRI is that it can indicate regions that are *involved* in a particular cognitive process (e.g., language tasks), but it does not indicate whether that particular region is *critical* (i.e., necessary) to that cognitive process [21]. Thus, in the present study the findings of bihemispheric activation presurgically for the language tasks does not specify whether either side could mediate language functions independently, or if both hemispheres were necessary. ECoG is able to localize language with high degrees of spatial and temporal resolution [25–28] but also is unable to determine necessity, while Wada and ESM are able to determine necessity but have their own limitations due to risk of complications [21,23,24,26]. In the present study, the necessity of the regions found in the fMRI language tasks were confirmed using DCS during the awake craniotomy, highlighting fMRI's successful role as a non-invasive technique for language lateralization prior to conducting more invasive localization strategies [e.g., DCS; 24].

7. Conclusions

In summary, the present report demonstrates that fMRI of linguistic tasks is a useful clinical tool for presurgical language localization. In this case, functional MRI of language tasks revealed right hemisphere language involvement in a left-handed right TLE patient resulting in DCS-verified language regions requiring the surgical plan to be altered thereby leading to a successful outcome. We recommend considering fMRI as a presurgical guide in cases involving DCS in cases such as the one reported here (i.e., left handed, right TLE cases) and potentially for ambidextrous individuals.

Ethical statement

The patient's consent was obtained and the scan was performed in compliance with the Declaration of Helsinki (2008) and the relevant laws and institutional guidelines, and was approved by the University of Saskatchewan Research Ethics Board.

Declarations of interest

None.

Appendix A

Table 1
Table 1Activation coordinates for words. Laterality Index (Number of Voxels) (R - L)/(R + L) = −0.068.

Hemi-sphere	x	y	z	Voxels	Hemi-sphere	x	y	z	Voxels
L	23.44	−70.66	48.46	148	R	88.8	18.35	33.99	765
L	1.91	−50.76	61.54	508	R	89.25	−11.45	49.04	110
L	5.72	−59.44	36.42	193	R	83.28	10.07	49.66	582
L	6.08	−74.47	23.29	336	R	88.98	−2.38	40.38	128
L	4.9	−45.08	21.65	152	R	82.11	30.56	62.14	119
L	−10.64	0.87	50.59	271	R	79.31	−39.68	19.77	154
L	−25.19	3.49	40.32	3777	R	75.49	41.79	49.27	185
L	−21.67	−25	41.41	187	R	70.64	−25.64	2	166
L	−22.8	36.49	18.6	279	R	66.69	−36.34	61.15	344
					R	63.19	−23.77	79.74	155
					R	58.3	−40.55	71.98	174
					R	55.45	−61.15	41.28	1729
					R	59.91	−22.3	1.78	113
					R	53.23	−77.75	26.08	201
					R	45.2	−47.86	64.66	185
Total				5851	Total				5110

Table 2
Table 2Activation coordinates for pictures. Laterality Index (Number of Voxels) (R - L)/(R + L) = −0.088.

Hemi-sphere	x	y	z	Voxels	Hemi-sphere	x	y	z	Voxels
L	14.01	−68.47	14.33	5180	R	92.84	14.9	26.76	104
L	2.08	−50.26	61.15	884	R	87.54	−11.89	47.52	261
L	6.98	−57.54	41.85	763	R	86.01	11.96	50.25	135
L	5.7	−32.52	2.4	142	R	86.36	25.31	58.41	129
L	−5.75	−34.25	54.6	216	R	77.09	35.12	66.55	257
L	−4.6	−32.08	−2.59	255	R	74.35	−49.14	14.71	112
L	−13.84	29.27	49.6	302	R	66.49	−37.36	57.32	905
L	−17.26	13.8	67.37	256	R	75.67	44.13	47.3	108
L	−12.87	50.35	56.76	126	R	70.7	−22.32	10.82	115
L	−28.36	−15.22	36.16	224	R	63.6	−38.03	71.77	392
					R	67.15	−24.19	60.58	317
					R	68.39	24.63	53.48	157
					R	58.67	−23.44	3.44	770
					R	55.72	−66.19	32.33	811

(continued on next page)

Table 3
Table 3Activation coordinates for the semantic questions task. Laterality Index (Number of Voxels) (R - L)/(R + L) = 0.162.

Hemi-sphere	x	y	z	Voxels	Hemi-sphere	x	y	z	Voxels
L	27.39	−62.94	54.63	885	R	89.79	−11.77	47.25	171
L	4.93	−50.18	60.1	853	R	87.4	21.64	39.01	184
L	8.41	40.87	77.9	266	R	82.82	9.94	49.95	311
L	10.51	−18.7	−18.57	172	R	84.19	23.88	57.18	144
L	5.29	−57.08	39	583	R	83.46	13.36	−7.06	165
L	−9.58	12.26	74.5	964	R	71.41	−36.39	47.92	229
L	−1.51	25.04	77.04	107	R	73.09	−20.16	7.56	158
L	−11.78	28.56	48.52	134	R	73.17	−22.61	65.7	100
L	−19.88	23.13	62.45	190	R	66.19	−36.99	60.61	526
L	−25.01	11.57	39.43	702	R	67.43	23.33	53.52	172
L	−17.25	18.63	39.29	150	R	51.71	−53.93	53.17	3390
L	−16.34	31.01	−6.08	113	R	49.45	−1.47	15.37	567
L	−19.62	−27.85	41.57	123	R	55.76	−40.94	71.62	140
L	−24.95	23.54	45.43	243	R	53.17	−75.31	30.04	459
					R	40.26	29.55	90.15	894
Total				5485	Total				7610

Table 4
Table 4Activation coordinates for the how task. Laterality Index (Number of Voxels) (R - L)/(R + L) = −0.046.

Hemi-sphere	x	y	z	Voxels	Hemi-sphere	x	y	z	Voxels
L	11.35	−52.17	64.49	318	R	87.01	−13.14	46.53	174
L	6.91	−58.25	42.26	538	R	80.36	32.05	63.62	101
L	1.77	42.73	30.68	379	R	70.18	22.06	53.52	524
L	−7.54	−36.52	55.78	102	R	75.02	48.65	47.24	341
L	−3.69	−49.95	57.47	370	R	68.15	−29.49	58.74	514
L	−4.57	−31.68	−2.03	127	R	67.84	−22.32	75.95	146
L	−10.83	56.45	36.47	178	R	59.13	−56.44	58.18	348
L	−17	26.67	47.35	912	R	62.16	−37.91	57.13	208
L	−16.59	48.45	46.07	126	R	56.32	−54.85	44.48	219
L	−17.66	−14.53	31.06	174	R	45.89	−47.28	62.5	298
L	−19.84	23.36	60.04	107	R	37.87	39.89	52.2	162
L	−25.68	−5.52	37.8	252	R	34.7	25.36	75.96	115
					R	34.46	43.32	63.7	115
Total				3583	Total				3265

Table 2 (*continued*)

Hemi-sphere	x	y	z	Voxels	Hemi-sphere	x	y	z	Voxels
					R	48.33	−48.1	63.68	1119
					R	56.6	−55.23	43.77	565
					R	39.22	29.3	89.9	627
					R	36.95	−76.64	33.54	119
Total				8348	Total				7003

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