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Case Report

Functional MRI reveals an interhemispheric dissociation of frontal and temporal language regions in a patient with focal epilepsy

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Abstract

We report the case of a patient with frontal lobe epilepsy in whom the Wada test failed to lateralize representation of language (fluent speech was observed after amobarbital injection on both the right and left side). Functional magnetic resonance imaging (fMRI) during a lexical processing task revealed an atypical organization of language represented by an interhemispheric dissociation of language regions with a right frontal dominance and a left temporal dominance. Consistent with the fMRI results, the patient's ability to name pictures was not reliably impaired by electrocortical stimulation (ECS) of left frontal cortex. The findings from Wada, fMRI, and ECS were confirmed by a lack of language impairment after left frontal lobectomy for seizures. This case illustrates that fMRI can precisely map cortical language networks in epileptic patients and that fMRI may be used to help interpret laterality results provided by the Wada procedure.

Keywords: Functional magnetic resonance imaging assessment of language; Wada testing; Electrocortical stimulation; Epilepsy

1. Introduction

Left focal epilepsy affecting language regions may be associated with a cerebral reorganization of language networks [1] yielding an atypical lateralization of language (e.g., a right dominant or bilateral representation). Although language regions are most often situated in the same hemisphere, in some epileptic patients, an interhemispheric dissociation of frontal regions (e.g., Broca's area) and temporoparietal regions (e.g., Wernicke's area) can occur [2]. We report here the case of a patient with frontal lobe epilepsy in whom an fMRI lexical processing task revealed an interhemispheric dissociation between a region predominantly in right frontal cortex and a region predominantly in left temporal cortex. The Wada test, the electrocortical stimulation (ECS) of left frontal cortex, and the patient's postsurgical language outcome were in agreement with the fMRI results.

2. Case report

The patient, D.C., is a 30-year-old man with onset of seizures at age 4. He was diagnosed at age 9 with epilepsy, and three types of seizures were reported: (a) petit mal seizures with transient decrease of awareness; (b) complex partial seizures with behavior arrest, staring, and posturing; and (c) generalized tonic–clonic seizures. In 1998, an MRI examination revealed a left frontal tumor (ganglioglioma) within the superior and middle

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frontal gyrus. EEG showed lateral frontal interictal spikes. He underwent surgery in 1998 to remove the tumor (see the tumor cavity denoted by the red arrow in Fig. 1), with only temporary cessation of seizures.

Evaluation for a second surgery was performed in 2002 for medically intractable seizures. D.C. was left-handed by handedness assessment [3] without any history of familial sinistrality. Neurological assessment was normal with the exception of a constructional apraxia. Neuropsychological assessment using the WAIS-III indicated a low verbal IQ of 76 and a low performance IQ of 80. In general, the patient's performance on the different subtests of the Wechsler Memory Scale was also low (e.g., Working Memory Index = 79, General Memory Index = 81, Immediate Memory Index = 82), which may have been due in part to noticeable deficits in the patient's ability to sustain attention and to maintain task goals. After surgery to place left frontal and left interhemispheric grid electrodes, electrocorticography revealed that the epileptogenic zone was located within the premotor cortex in the superior and middle frontal gyrus (adjacent to the previous resection). A second resection was performed, with motor cortex (as determined by cortical stimulation) as the posterior boundary and inferior frontal gyrus as the inferior border. There was no noticeable change in D.C.'s language function after surgery based on clinical, bedside evaluation (although subtle changes cannot be excluded because the patient is yet to have postoperative neuropsychological testing and has had medication changes). Importantly, the absence of difficulty in the early postoperative period would be unlikely if he had undergone resection of the posterior frontal lobe on the dominant side.

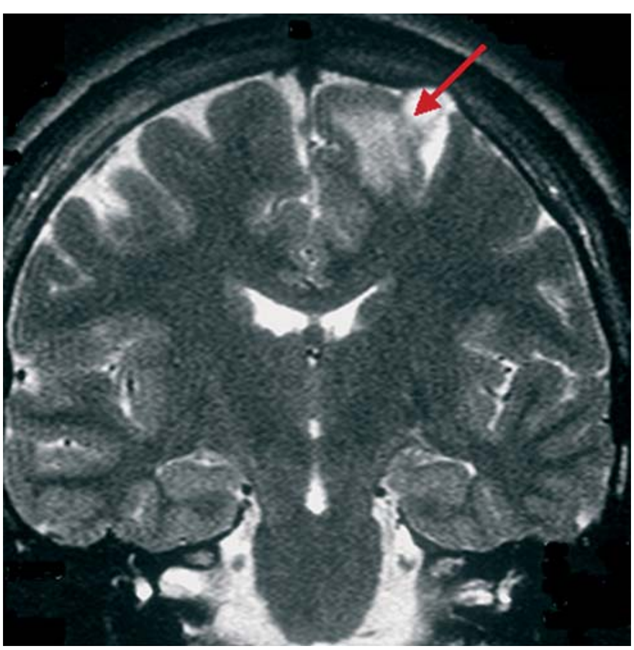

Fig. 1. MR (T_2 weighted) coronal slice obtained before the first surgery (1998) in D.C. The image is presented in radiological convention (i.e., the left hemisphere is on the right side of the image). The tumor cavity (ganglioglioma), situated within the left superior and middle frontal gyrus, is indicated by the red arrow. After tumor resection, the seizures recurred. Invasive monitoring for resection of the seizure focus was performed in 2002. A larger region situated within the middle frontal gyrus was removed (with motor cortex as the posterior boundary and inferior frontal gyrus as the inferior border).

3. Method and results

Prior to his second surgery, D.C.'s language function was mapped using three different techniques: Wada test, fMRI, and ECS.

3.1. Wada test

The Wada test consisted of language evaluation after injection of 150 mg of amobarbital, first into the left internal carotid artery and second into the right internal carotid artery. A complete contralateral arm drop was achieved after injection of each hemisphere. However, D.C. spoke fluently after injection of each hemisphere. Reading and memory were also assessed during the Wada test and determined to be unimpaired. Therefore, the Wada results indicated that either hemisphere could sustain his baseline level of speech.

3.2. fMRI examination

One month before his second surgery, D.C. underwent an fMRI examination. A lexical processing task was used in which 16-item lists of words were presented visually [4]. In this task, words were related either by meaning (e.g., *bed*, *rest*, *awake*) or by sound (e.g., *dog*, *frog*, *log*). At the beginning of each set of meaningfully related words, a "meaning" cue was presented to instruct the patient to attend to the meaning relations

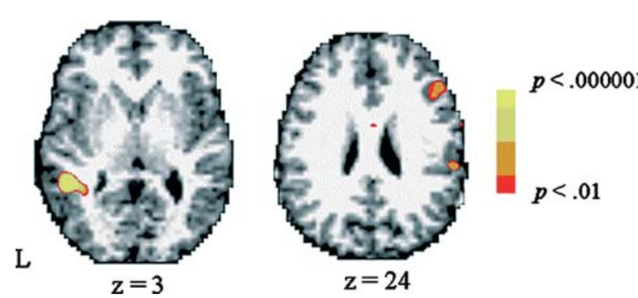

Fig. 2. Representative functional maps obtained by using fMRI in D.C. when comparing lexical processing (i.e., meaning and rhyme processing combined) with fixation. The images are presented in neurological convention (i.e., the left hemisphere is on the left side of the image). Significant activation ($P < 0.01$, $z \geqslant 2.58$; uncorrected z map, positives only displayed) was obtained within left middle temporal cortex and within right inferior frontal cortex.

among words. At the beginning of each set of phonologically related words, a "rhyme" cue was presented to instruct the patient to attend to the sound relations among words (with special emphasis on pronunciations). This task was selected because direct, statistical comparisons of meaning and rhyme processing have been shown to elicit robust activation in inferior frontal (e.g., BA 47, 47/11, 44/45, 6/44) and middle temporal (BA 22/21) regions in healthy young adults (aged 18–32). Furthermore, this dissociation of meaning and rhyme processing has been observed with this fMRI language protocol in both group averages and, more importantly for clinical purposes, in individual subjects. Additional detail about this protocol can be obtained by referring to McDermott et al. [4].

A blocked design (alternating task and control periods) was used during eight functional scans. During task periods (12.5 seconds each), semantic and phonological lists (randomly ordered) were presented (12 lists/functional scan, 96 lists/examination, 48 phonological and 48 semantic lists). Words were displayed one at a time for 560 milliseconds with a 50-millisecond interstimulus interval. During control periods (12.5 seconds each), a fixation crosshair (e.g., +) was shown, and the patient was asked to look at it. fMRI scans were obtained on a 1.5-T Siemens Vision System (Erlangen, Germany). Structural images were acquired using a high-resolution T1-weighted sagittal sequence. Functional images were collected with an echo-planar asymmetric spin-echo sequence. In each functional run, 128 sets of 16 contiguous, 8-mm-thick axial images (TR = 2500 milliseconds, 3.75×3.75-mm in-plane resolution) were acquired parallel to the anterior–posterior commissure plane. To detect task-correlated activation, the functional data were analyzed using an implementation of the general linear model.

Statistical comparisons were performed using random effect *t* tests. As shown in Fig. 2, there was significant ($P < 0.01$, $z \geqslant 2.58$) right-lateralized activity in the inferior frontal region and significant left-lateralized activity in the middle temporal regions during lexical processing. Hence, according to the fMRI results, D.C.'s language function was predominantly right-lateralized in inferior frontal cortex, whereas his language function was predominantly left-lateralized in middle temporal cortex.

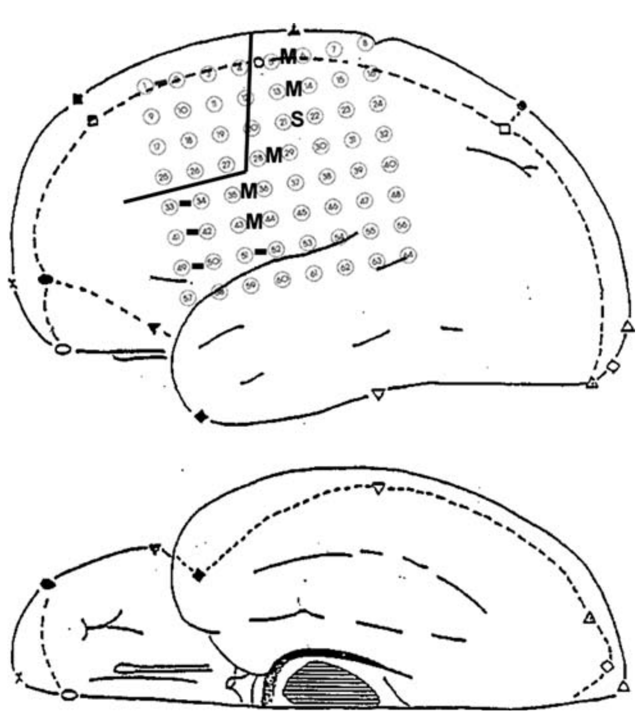

Fig. 3. Schematic representation of 8×8-cm electrode array placed over the left frontal convexity. The solid lines represent the posterior and inferior boundaries of the resection of epileptic foci. Electrode pairs where stimulation evoked motor (M) or sensory (S) changes are indicated. Electrodes where stimulation resulted in no change in language function are indicated by small rectangles. Electrodes superior to these electrodes showed frequent interictal discharges and could not be stimulated because of the likelihood of evoking seizures. After an extensive frontal lobectomy, with margins indicated, D.C. had no postoperative changes in speech, which is unusual for such a resection in the dominant frontal lobe.

3.3. Electrocortical stimulation

Subdural grids (8×8-cm arrays) were placed on the patient's left frontal lobe, and bipolar stimulation at variable amplitude (below the afterdischarge threshold) was delivered through the Ojemann Cortical Stimulator (OCS-1, Radionics Co., Burlington, MA, USA). Pictures of objects (40 total, each picture presented for 4 seconds) were presented one at a time on a laptop computer and the patient was instructed to name each picture before it was removed from the computer screen. All objects were readily namable based on standard aphasia scales (e.g., *baby*, *car*, *plane*). During some trials, stimulation of the cortex was applied. D.C. did not produce reliable errors (e.g., speech arrest or paraphasias) in picture naming with stimulation for any of the leads over inferior frontal gyrus (see Fig. 3). Overall, D.C.'s picture naming performance was poor (53% correct).

4. Discussion

The results of D.C.'s Wada test were intriguing because no speech arrest was observed. Possible explanations for this finding are that (1) the dose of the amobarbital may have been too low for inducing speech arrest, and/or (2) the patient had habituated to amobarbital as a result of his treatment. However, it is difficult to reconcile this "null effect" interpretation of the Wada results with the observation that D.C.'s arm dropped after contralateral hemisphere anesthesia, as the dose of amobarbital would have to be sufficient to produce an arm drop for the patient but insufficient to induce speech arrest. In this light, the results of D.C.'s Wada test suggest potential bilateral organization of expressive language. Hence, as noted above, whatever hemisphere was injected, D.C. continued to speak fluently. Consistent with this interpretation, the fMRI lexical processing task yielded an interhemispheric dissociation between a language region activated predominantly in right inferior frontal cortex and one activated predominantly in left middle temporal cortex.

McDermott et al. [4] found (a) greater involvement of temporal regions (BA 22/21) for semantic than phonological processing in healthy young adults and (b) dissociated different frontal regions subserving semantic (BA 47/11 and BA 44/45) and phonological (BA 6/44) processing. Using the same fMRI lexical processing task, D.C. produced a pattern of results different from those of the young adults in the McDermott et al. study. Specifically, semantic and phonological lists were equally likely to recruit temporal as well as frontal regions during lexical processing (i.e., direct comparisons of semantic and phonological lists at a statistical threshold of $P < 0.01$ did not yield a reliable dissociation in either frontal or temporal cortex). Given D.C.'s poor vocabulary knowledge and difficulty maintaining task goals, it is possible that he did not discriminate between the meaning and rhyme lists used in this fMRI protocol as effectively as the healthy young adults tested in the McDermott et al. study. This could have minimized the likelihood of identifying frontal and temporal language regions preferentially involved in semantic or phonological processing. Even so, the *combined* meaning and rhyme fMRI results shown in Fig. 2 yielded converging evidence with other clinical language assessments for patient D.C. including Wada (which indicated a bilateral organization of speech and reading) and cortical stimulation (which revealed null effects of stimulation in left frontal cortex during picture naming).

Early lesions may be more associated with right hemispheric involvement because the developing brain has an increased potential for functional reorganization [5]. D.C. was about 4 when he first presented with seizures. Moreover, D.C. was left-handed. In conjunction with the fMRI results shown in Fig. 2, these observations suggest that D.C.'s underlying language networks may have shifted (at least in part) to the right hemisphere along with his motor function [1]. Furthermore, D.C.'s atypical organization of language may be due not only to the lesion situated in his left frontal lobe but also to the initial surgery performed to remove his tumor. That is, the initial surgery on the left frontal regions may have unmasked or disinhibited corresponding right frontal regions, allowing these right frontal regions to become dominant for language, paralleling findings observed in poststroke recovery [6]. It is also possible that D.C.'s language organization in frontal cortex was bilateral early in development and, hence, less likely to be influenced by either progressive (e.g., a longstanding left frontal mass) or sudden (e.g., left frontal surgery) changes to left frontal cortex.

An important, related question raised from this case is how language dominance should be quantified using fMRI. The majority of imaging studies calculate global lateralization indices based on all of the activation detected within a given hemisphere [7]. Consistent with other observations in the literature [8,9], the present case suggests that although language dominance is a relative concept, it may be more accurate to quantify language region by region rather than strictly by hemisphere. In this light, it is noteworthy that ECS findings in some individuals demonstrate only temporal or frontal language sites on the side of surgery [10].

In conclusion, this case illustrates that (1) fMRI may be a useful, complementary method to Wada testing and cortical stimulation when mapping language networks in epileptic and/or brain tumor patients who may be at risk for language impairment, and (2) lateralization for frontal and temporal language regions may not be concordant. Interhemispheric dissociations as revealed by fMRI may offer a potential explanation for inconclusive Wada tests in patients like D.C. where, despite motor effects, language is not disrupted on either side.

Acknowledgments

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