Title

Role of the Wada test and functional magnetic resonance imaging in preoperative mapping of language and memory: two atypical cases

Journal

Neurocase, 21(6)

ISSN

1355-4794

Authors

Połczyńska, MM
Benjamin, CFA
Moseley, BD
et al.

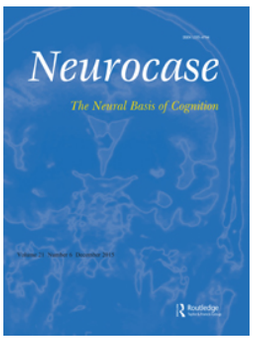
Publication Date

2015-11-02

DOI

10.1080/13554794.2014.977300

Peer reviewed



Routledge
Taylor & Francis Group

Neurocase
The Neural Basis of Cognition

ISSN: 1355-4794 (Print) 1465-3656 (Online) Journal homepage: http://www.tandfonline.com/loi/nncs20

Role of the Wada test and functional magnetic resonance imaging in preoperative mapping of language and memory: two atypical cases

Monika M. Połczyńska, Christopher F.A. Benjamin, Brian D. Moseley, Patricia Walshaw, Dawn Eliashiv, Celia Vigil, Michael Jones & Susan Y. Bookheimer

To cite this article: Monika M. Połczyńska, Christopher F.A. Benjamin, Brian D. Moseley, Patricia Walshaw, Dawn Eliashiv, Celia Vigil, Michael Jones & Susan Y. Bookheimer (2015) Role of the Wada test and functional magnetic resonance imaging in preoperative mapping of language and memory: two atypical cases, Neurocase, 21:6, 707-720, DOI: 10.1080/13554794.2014.977300

To link to this article: http://dx.doi.org/10.1080/13554794.2014.977300

Neurocase, 2015
Vol. 21, No. 6, 707–720, http://dx.doi.org/10.1080/13554794.2014.977300

Role of the Wada test and functional magnetic resonance imaging in preoperative mapping of language and memory: two atypical cases

Monika M. Połczyńska[a,b]*, Christopher F.A. Benjamin[a], Brian D. Moseley[c], Patricia Walshaw[a], Dawn Eliashiv[d], Celia Vigil[a], Michael Jones[a] and Susan Y. Bookheimer[a]

[a]*Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, CA, USA;* [b]*Faculty of English, Adam Mickiewicz University, Poznań, Poland;* [c]*Department of Neurology and Rehabilitation Medicine, University of Cincinnati, Cincinnati, OH, USA;* [d]*Department of Neurology, University of California, Los Angeles, CA, USA*

(*Received 14 April 2014; accepted 10 October 2014*)

The Wada test is an invasive procedure used to determine cerebral memory and language dominance as well as risk of cognitive deficits following neurosurgery. However, the potential risks of Wada testing have led some to consider foregoing Wada testing in candidates for resective epilepsy surgery with right hemispheric seizure onset. We present two atypical cases in which the Wada test showed unexpected memory and language lateralization. These cases underscore the importance of functional magnetic resonance in which imaging and Wada examination in right-handed individuals even when the lesion would not suggest atypical language representation.

Keywords: language; memory; Wada; fMRI; epilepsy

Resection of the zone of epileptogenesis is potentially curative in patients with refractory temporal lobe epilepsy (TLE) (Quirico-Santos et al., 2013). Since removal of cortex essential to language or memory function may result in aphasia or amnesia (Hader et al., 2013) and therefore contraindicate surgery, lateralization of memory and language dominance is an essential goal in epilepsy surgical planning.

Individuals with epilepsy have a higher rate of atypical language representation than the healthy population (Dijkstra & Ferrier, 2013). Predictors of atypical language dominance include left-handedness (Janszky et al., 2003), early age of onset for brain pathology (Korman et al., 2010), lesion location (Helmstaedter, Kurthen, Linke, & Elger, 1997), epileptic activity (Hamberger & Cole, 2011), and pathology such as hippocampal sclerosis (Rathore, George, Kesavadas, Sankara Sarma, & Radhakrishnan, 2009). Between 20% and 33% of all patients with TLE (including right-handed individuals) have bilateral or right hemispheric language representation (Berl et al., 2014; Janecek, Swanson, Sabsevitz, Hammeke, Raghavan, Rozman, et al. 2013; Springer et al., 1999; Thivard et al., 2005).

Wada testing is an invasive procedure that characterizes postsurgical risk to both memory (e.g., Paolicchi, 2008) and language function (Whitman, Morrison, Becske, Barr, & Carlson, 2012). Here, the ability of the healthy hemisphere to encode material for memory and support language is evaluated during anesthetization of the pathological hemisphere. Use of the Wada test is declining due to the attendant risk of complications, such as cerebrovascular events (1.3%; Willinsky et al., 2003). While over 95% of epilepsy surgery centers in the world used the Wada procedure in 1993 (Rausch et al., 1993), this rate has progressively declined with functional magnetic resonance imaging (fMRI) replacing Wada testing for language lateralization (Baxendale, Thompson, & Duncan, 2008; Binder, 2011). Some authors have argued that in patients who are right-handed, have solid verbal memory, and right temporal lesions, the Wada is likely unnecessary (Kemp, Wilkinson, Caswell, Reynders, & Baker, 2008).

We present two subjects with epilepsy who would typically be considered good candidates for surgery who, per the above criteria, may have foregone a Wada procedure. However, Wada tests that were performed revealed atypical language and memory dominance in both subjects. These cases demonstrate the importance of Wada testing, even in individuals who are right-handed and whose lesion does not suggest functional reorganization.

Case reports

Subject 1

Subject 1 was a 32-year-old right-handed male with a 10-year history of medically refractory focal dyscognitive seizures with occasional secondary generalization. He continued to have one to two seizures monthly while on multiple anti-seizure medications (AEDs). Brain MRI without and with contrast showed an oval, nonenhancing lesion in the body of the right hippocampus measuring 12 × 9 × 9 mm (Figure 1). Fluorodeoxyglucose positron emission tomography (FDG-PET) revealed decreased metabolic activity

*Corresponding author. Email: plmonik@wa.amu.edu.pl

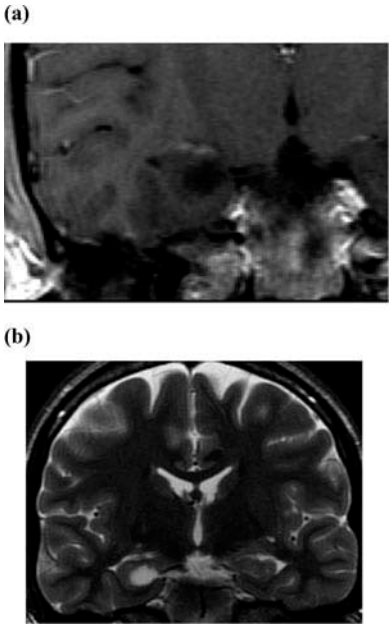


Figure 1. MRIs showing a nonenhancing lesion in the body of the right hippocampus in Subject 1: (a) T1-weighted MRI, the lesion had low signal; (b) T2-weighted MRI the lesion had high signal intensity.

over the right hippocampal lesion. During prolonged video electroencephalography (EEG) monitoring, 20 seizures were captured, with an aura of a strange, indescribable feeling, followed by behavior arrest, staring, and oral automatisms. Three of these secondarily generalized, with initial head and eye deviation to the left. Scalp EEG localized 17/20 seizures to the right temporal region, while ictal onsets in three seizures were left temporal. On separate intracranial EEG monitoring with bitemporal depth electrodes, all 14 captured seizures emanated from the right mesial temporal contacts (Figure 2). On neuropsychological testing, his overall level of functioning fell within the low average range (Table 1). Select language measures were clearly impaired (Animal fluency and Boston Naming Task, 1st percentile). Verbal memory was below expectation; while recall was low average to average on measures of passage and list learning (Wechsler Memory Scale-III [WMS-III] Logical Memory; California Verbal Learning Task-IIA [CVLT-IIA]), on a measure of mesial temporal forms of memory (WMS-III Verbal Paired Associates), initial recall was impaired (1st percentile) though he could retain the bulk of what was learned at delay (low average range). Nonverbal memory was relatively better than verbal memory with only minor difficulties in complex figure recall and initial learning and recognition of simple figures.

Subject 2

Subject 2 was a 33-year-old left-handed male. Family history of ambidexterity/left-handedness (mother) was also noted. The patient had a history of hypercoagulation. He had neonatal seizures of unknown semiology followed by stereotypic focal dyscognitive seizures. These were treated with Dilantin from age 3. He suffered his first generalized tonic clonic seizure when taken off AEDs at age 7 though was then seizure free until age 18. From this time, he had ongoing focal dyscognitive seizures with occasional secondary generalization. Stereotypic seizures at the time of presentation were 2–3 day clusters of 3–4 focal onset seizures daily, typically separated by 9–14 seizure-free days. MRI showed an old basal ganglia injury with compensatory dilation and irregularity of the left lateral ventricular body and mild cerebral atrophy. The left hippocampus and amygdala were smaller and relatively hyperintense (T2/FLAIR) suggesting left mesial temporal sclerosis (MTS) (Figure 3(a)–(c)). PET indicated mild to moderate left anterior temporal hypometabolism and left basal ganglia and thalamic hypometabolism (Figure 3(d) and (e)). During prolonged video EEG monitoring, the patient experienced seven focal onset seizures, three of which secondarily generalized. EEG localized to the left anterior temporal region in all cases.

Initial neuropsychological assessment (Table 1) reported evidence of difficulties in working memory and attention to detail and worse verbal than nonverbal functioning. The patient complained of slowed speech, word-finding problems, and memory difficulties. Formal assessment, however, documented average to superior intellectual function consistent with education with "no evidence for a language disorder." While circumlocution was noted qualitatively, confrontation naming was high average. Semantic fluency was high average. Memory function was a strength: verbal memory was generally superior; visuospatial memory, average. Executive-type memory deficits (recognition poorer than recall) were apparent on occasion. Surgical work-up was halted after the patient suffered a right thalamic stroke during Wada testing.

Due to an increase in seizure frequency, however, the patient requested reconsideration for surgical candidacy. Post-Wada MRI showed an area of encephalomalacia in the left caudate body, near the caudothalamic groove, extending into the posterior left putamen and a lacunar infarct in the right thalamus and the anterior pons. Evidence of left MTS persisted. Updated FDG-PET continued to reveal left anterior temporal and thalamic hypometabolism. Repeat prolonged video EEG captured seven focal dyscognitive seizures. These consisted of an aura of increased sensory sensitivity and nausea, then behavioral arrest, repetitive chewing, and repetitive left finger pointing and shushing movements. Two of these seizures secondarily generalized, with head and eye version to the right upon generalization. Scalp EEG identified a left temporal onset (Figure 4). Cognitive functioning remained within the high average range (Table 1). Language function remained generally unremarkable with measures

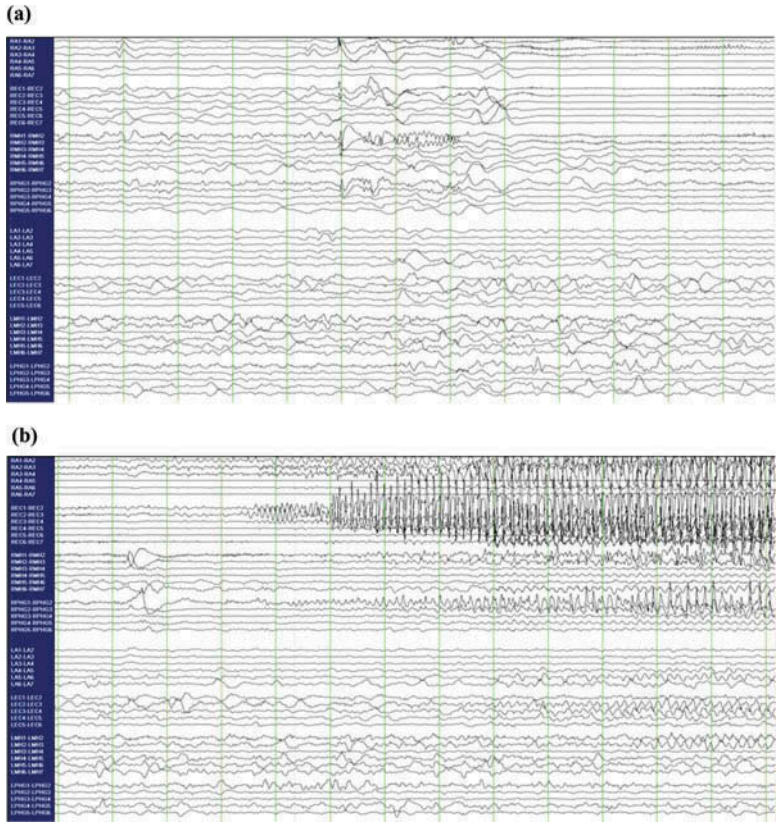


Figure 2. Intracranial EEG of Subject 1: (a) Although scalp EEG suggested the patient had seizures arising independently from the right greater than left temporal regions, bilateral depth electrode recordings revealed seizures arising exclusively from the right mesial temporal lobe. Onset was characterized by a broad spike in the mesial contacts of all right-sided electrodes, followed by focal paroxysmal fast activity (PFA) in the mesial right amygdala (RA) contacts. (b) The PFA quickly spread to the right entorhinal cortex (REC) and right middle hippocampus (RMH) electrodes, followed by the development of spike wave activity in the mesial right-sided contacts. Key: RA – right amygdala; REC – right entorhinal cortex; RMH – right middle hippocampus; RPHG – right parahipppocampal gyrus; LA – left amygdala; LEC – left entorhinal cortex; LMH – left middle hippocampus; LPHG – left parahipppocampal gyrus; contact 1 most mesial, contact.

consistently average to high average, though phonemic and semantic fluency were considered to have declined. Verbal memory remained impressive. Nonverbal memory was considered to have declined (measures being low average–average; previously average–high average). Of note, performance on a measure of complex nonverbal memory was depressed secondary to poor organization consistent with his previously observed executive memory deficits.

Postoperatively, this patient received a targeted cognitive assessment. Results of this limited assessment indicated either no change or improvement in overall verbal and nonverbal intellectual function and verbal memory remained well above normative expectations.

Procedure

Both patients underwent Wada testing and language fMRI utilizing established methodology described later (Bookheimer, 2007; Sharan, Ooi, Langfitt, & Sperling, 2011).

Data acquisition and analysis

fMRI tasks

Our subjects completed three language fMRI tasks engaging the language network with stimuli from different modalities. (1) In *object naming with action generation*, patients silently named objects displayed on screen and generated a related action verb (e.g., Rutten, Ramsey, van Rijen, Noordmans, & van Veelen, 2002). (2) In *auditory responsive naming*, patients named auditorily described objects (e.g., "color of snow"). (3) In *reading responsive naming*, patients named objects in response to written cues (e.g., "tall pink bird") (e.g., Gaillard et al., 2004). Stimuli were presented in alternating 10 s blocks of task/rest.

Table 1. Neuropsychological test data for cases.

	Subject 1	Presurgery	Subject 2	Pre-surgery, prestroke	Subject 2	Presurgery, poststroke	Subject 2	Postsurgery
	Percentile	Rating	Percentile	Rating	Percentile	Rating	Percentile	Rating
Language								
Vocabulary (WAIS-III/III/IV)	37	Average	98	Superior	84	High avg.	84	High avg.
Similarities (WAIS-III/III/IV)	25	Average	75	Average	75	Average	91	High avg.
Letter fluency (FAS/DKEFS/DKEFS/FAS/FAS)	34	Average	63	Average	25	Average	54	Average
Category fluency (animals/DKEFS/DKEFS/animals)	1	Ex. low	90	High avg.	50	Average	66	Average
Boston Naming Task	1	Ex. low	77	High avg.	38	Average	66	Average
Woodcock–Johnson III Word Attack	–	–	41	Average	75	Average	–	–
Visuospatial								
Block Design (WAIS-III/III/IV/IV)	25	Average	75	Average	75	Average	91	High avg.
Picture Completion (WAIS-III)	25	Average	–	–	–	–	–	–
Object Assembly (WAIS-III)	–	–	50	Average	–	–	–	–
Matrix Reasoning (WAIS-IV/IV)	–	–	–	–	84	High avg.	91	High avg.
Verbal Memory								
Logical Memory (WMS-III/III/IV/IV)								
Immediate	25	Average	95	Superior	98	V. superior	95	Superior
Delayed	9	Low avg.	95	Superior	95	Superior	91	High avg.
Recognition	–	–	29/30	Raw score	>75	High avg.	>75	High avg.
Verbal Paired Associates (WMS-R/III/IV)								
Immediate	<1	Ex. low	91	High avg.	37	Average	–	–
Delayed	19	Low avg.	84	High avg.	75	Average	–	–
Recognition	–	–	24/24	Raw score	>75	High avg.		
List Learning (CVLT-IIA/II/II/RAVLT)								
Trial 1	31	Average	–	–	31	Average	>99	V. superior
Trial 5	69	Average	–	–	69	Average	91	High avg.
Interference trial	16	Low avg.	50	Average	69	Average	54	Average
Short delay recall	69	Average	84	High avg.	69	Average	90	High avg.
Short delay cued recall	50	Average	50	Average	69	Average	–	–
Long delay recall	50	Average	84	High avg.	69	Average	81	High avg.
Long delay cued recall	31	Average	50	Average	50	Average	–	–
Recognition hits	7	Borderline	69	Average	50	Average	82	High avg.
Recognition false positives	Raw = 0	–	50	Average	50	Average	–	–

(*continued*)

Table 1. (*Continued*).

	Subject 1	Presurgery	Subject 2	Pre-surgery, prestroke	Subject 2	Presurgery, poststroke	Subject 2	Postsurgery
	Percentile	Rating	Percentile	Rating	Percentile	Rating	Percentile	Rating
Nonverbal Memory								
Brief Visual Memory Task-Revised								
Trial 1	18	Low avg.	92	Superior	54	Average	–	–
Trial 2	–	–	88	High avg.	38	Average	–	–
Trial 3	34	Average	82	High avg.	14	Low avg.	–	–
Total recall	21	Low avg.	92	Superior	34	Average	–	–
Delayed recall	43	Average	84	High avg.	24	Low avg.	–	–
Recognition hits	5	Borderline	>16	WNL	>16	WNL	–	–
Recognition false positives	Raw = 0	–	–	–	–	–	–	–
Rey Complex Figure Task								
Copy	>16	WNL	27	Average	<1	Ex. low	–	–
3’	27	Average	–	–	31	Average	–	–
30’	14	Low avg.	44	Average	14	Low avg.	–	–
Recognition	–	–	<1	Ex. low	86	High avg.	–	–
Visual Reproduction (WMS-R/III/IV)								
Immediate	90	High avg.	98	Superior	75	Average	–	–
Delayed	89	High avg.	75	High avg.	37	Average	–	–
Recognition	2/4	Raw score	84	High avg.	51–75	Avg. to high avg.	–	–

Note: WNL = within normal limits.

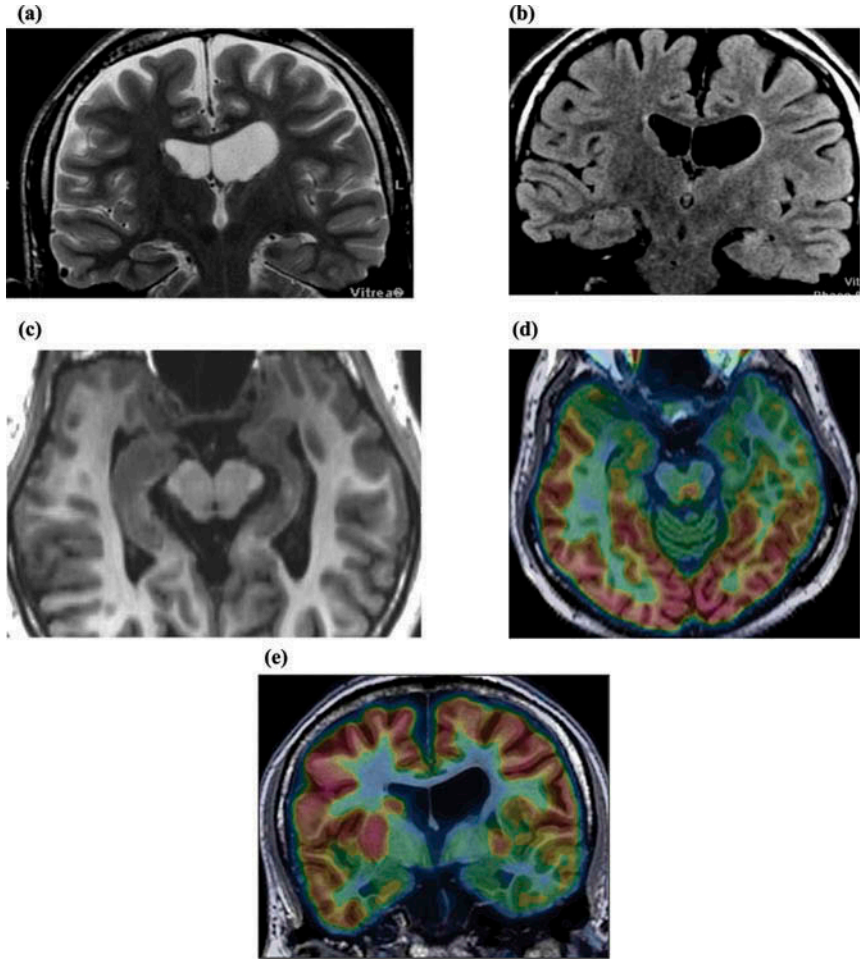


Figure 3. Poststroke brain imaging of Subject 2: (a) T2-weighed MRI showing a smaller left hippocampus and amygdala suggesting left mesial temporal sclerosis, (b) T2 FLAIR-weighted MRI showing increased signal within the smaller left hippocampus and amygdala suggestive of left MTS, (c) T1 MRI demonstrating the smaller left hippocampal structures, (d) axial PET indicated mild to moderate left anterior temporal hypometabolism and hypometabolism in the left basal ganglia and thalamus, (e) coronal PET showing left anterior temporal hypometabolism. The color scale on the PET images goes from green and blue to bright red and yellow. The colors are interpreted qualitatively to look for signal loss.

Memory fMRI also included three tasks. (1) In a *picture novelty*, novel and repeated images of interior scenes and landscapes alternated in 30-s blocks. This task activates posterior parahippocampus, fusiform gyrus, and posterior hippocampus (Binder, Bellgowan, Hammeke, Possing, & Frost, 2005). (2) In *face–name association*, seven novel face–name pairs were presented in 30-s blocks with encoding, rest and recall conditions. In recall, participants recalled the name in response to a face cue. This task engages bilateral hippocampus and parahippocampal gyrus (Zeineh, Engel, Thompson, & Bookheimer, 2003). (3) In *face–place association*, patients are familiarized with images of famous people and places pre-fMRI. During the task, participants then encode novel associations between these people/places and when cued with one item (e.g., face) attempt to recall the other (e.g., place).

Image acquisition

MRI was performed using a 3T Siemens Allegra MRI scanner with a 12-channel head coil. EPI sequences included 28-slice volumes where TR = 2500; TE = 35 ms; voxel size = 3.1 × 3.1 × 3 mm; flip angle = 90º; field of view = 200 mm. Anatomical localization was completed with a 1.5 mm in-plane resolution matched bandwidth spin echo EPI sequence (TR = 4000 ms; TE = 35 ms; 3 mm slices; flip angle = 8°; matrix size 128 × 128).

fMRI data analysis was completed using custom software. Data were smoothed (kernel size = 2 mm) then compared with predicted blood flow at each voxel using Pearson's correlation coefficient. Images were thresholded by clinicians (SB, PW) who have completed well over 1000 clinical fMRI scans between them. Each task's correlation map was thresholded at .2 (corresponding to $p = .05$), and the

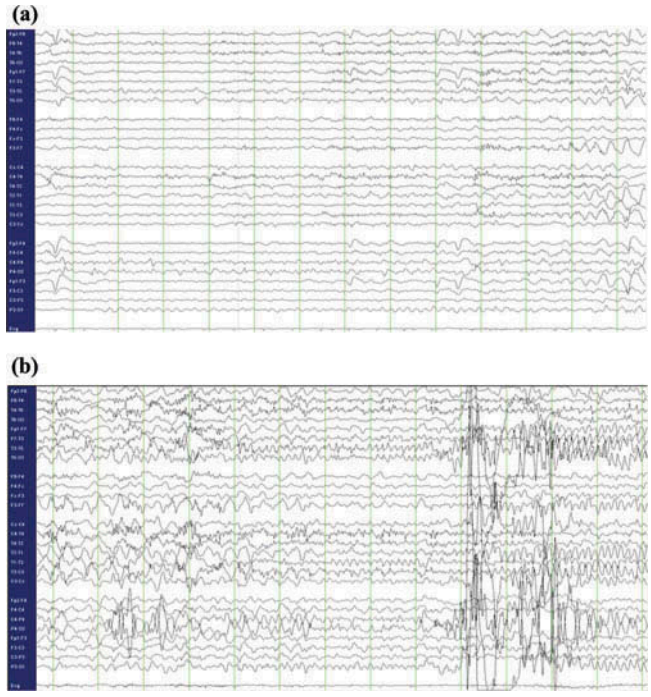


Figure 4. Scalp EEG of Subject 2: (a) At the onset of a focal dyscognitive seizure, rhythmic slowing can be observed over the left hemisphere. However, the slowing has maximum phase reversal over the left temporal (T1) head region. (b) The slowing evolved into rhythmic 6–7 Hz epileptiform discharges with maximum amplitude noted over the left temporal head region. Key: Fp – frontopolar; F – frontal; T – temporal; O – occipital; C – central; P – parietal; Z – midline electrode. Electrodes with odd numbers are left-sided. Electrodes with even numbers are right-sided. The larger the number, the further that electrode is from the midline.

three maps were then combined using conjunctive analysis, where only activation at .2 threshold on all three scans is retained. The resulting activation map includes only primary language areas with significance of activation at $p < .000125$. Laterality indices were then calculated (L − R/L + R), such that −1 = right while +1 = left (Binder et al., 1996).

Wada protocol

Briefly, using a standardized protocol (Engel, 2013), after angiogram confirmed catheter placement, 125 mg sodium amytal was injected into the internal carotid artery in a bolus of 10 cc of saline while the patient began counting. When the contralateral arm became flaccid (strength 0/5) and EEG indicated anesthetization, the encoding phase began. Here, the patients were presented with six visual objects (e.g., *spoon*) and two verbal commands (e.g., *stick out your tongue*) to remember. This evaluated language and memory for the items is later tested to determine dominance. We then waited until patients could reply to basic questions (e.g., *Where are you right now?*) before completing the recovery phase. Here, strength and EEG were monitored and language was tested more extensively using tasks requiring comprehension of complex ideation and syntax as well as auditory responsive naming and phrase repetition. Upon full recovery (12–15 min postinjection), free and cued recall and then recognition memory (forced recognition paradigm; four choices) were evaluated. Language and recall scores varied from 0 to 8 items (6 objects, 2 commands) unless the patient was aphasic, when the verbal commands were omitted from the recollection total (0–6).

Results

Subject 1

fMRI

Subject 1's language fMRI revealed some bilateral representation for language, with relatively greater activation in right basal temporal, right posterior temporal cortex (Wernicke's area) and right Broca's areas, as well as supplementary motor area (SMA) observed to the right of the midline (Figure 5; Laterality Index = −0.24). At the same time, there were strong activations in the left superior (parietal) aspect of the Wernicke's area.

In the memory fMRI, we observed left parahippocampal activations in the face–place task and primarily right anterior hippocampal activations for face–name encoding with minimal left activations (Figure 6). Approximately one third of the memory fMRI acquisitions were discarded due to excessive movement.

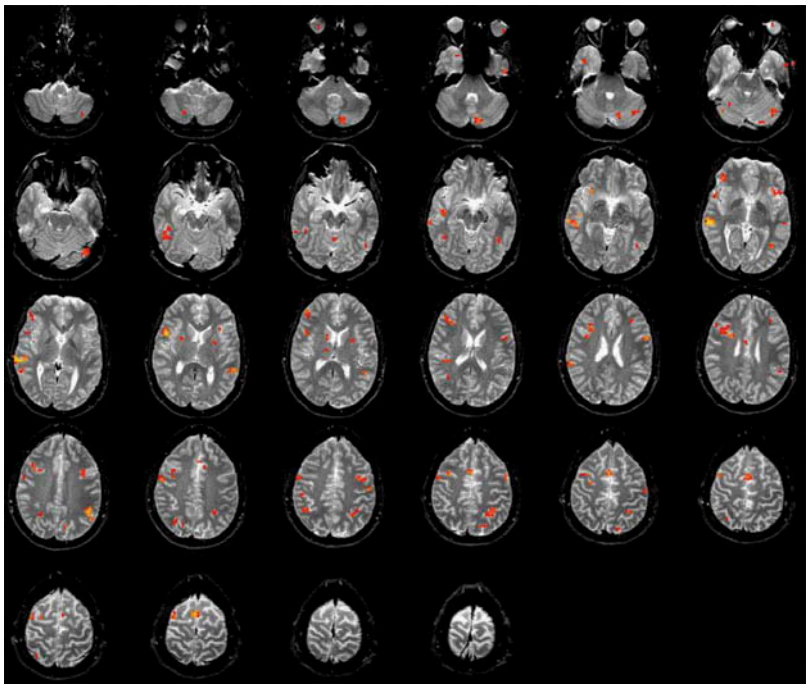


Figure 5. Language fMRI of Subject 1. Greater activation in right basal temporal, right Wernicke's area and right Broca's areas, as well as SMA to the right of the midline. Strong activations are seen in the superior aspect of the left Wernicke's area. [To view this figure in color, please see the online version of this Journal.]

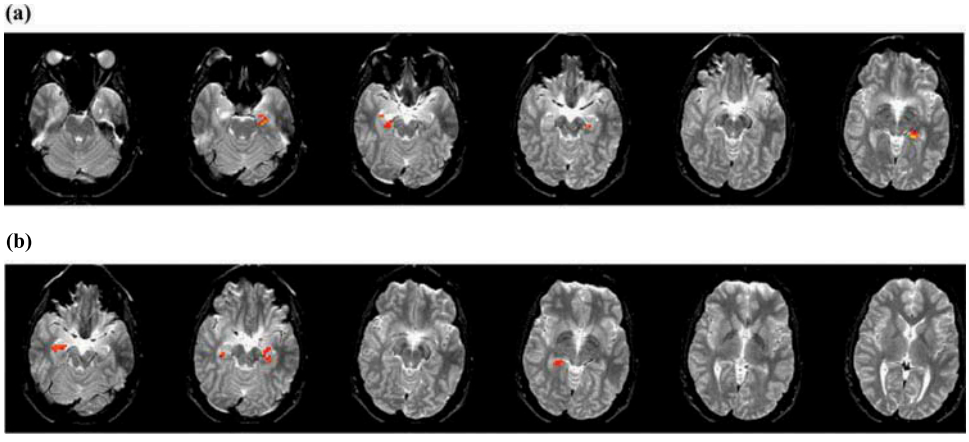


Figure 6. Memory fMRI of Subject 1. (a) Face–name association, (b) face–place association. [To view this figure in color, please see the online version of this Journal.]

Wada

Subject 1 underwent two bilateral Wada procedures indicating right hemisphere (RH) language and memory dominance (see Table 2). During the first procedure (2012; 112.5 mg amytal), the patient had posterior communicating artery (PCA) filling with a visual field cut and was somewhat obtunded. Results indicated RH dominance for language and memory (100% recall) with the left hemisphere (LH) alone supporting poor memory (25% correct with self-reported "guess"; no reported episodic memory) and limited language (aphasic errors in expressive language; subsequent recall of one verbal item). Due to a PCA/field cut in the first procedure, the Wada procedure was repeated (2013; 90 mg amytal). The test again showed RH dominance for language with evidence for minimal left expressive and receptive language as the patient continued to vocalize and state one object name during the right injection and was able to perform the verbal

Table 2. Summary of Wada test results.

	Language		Memory	
Subject	LH (RH injection)	RH (LH injection)	LH (RH injection)	RH (LH injection)
Subject 1				
Wada 1 (%)	0	87.5	25	100
Wada 2 (%)	37.5	100	16.7	75
Subject 2				
Wada 1 (%)	0	100	100	0
Wada 2 (%)	–	100	–	100
Wada 3 (%)	–	100	–	100

Note: For Subject 2 Wada tests 2 and 3 only included a left hemisphere injection.

commands. Memory results indicated right memory dominance with 16.7% recall with a RH injection and 75% recall with a LH injection.

Clinical determination

Due to a high risk of cognitive function loss, Subject 1 did not undergo surgery.

Subject 2

fMRI

In the language fMRI examination, Subject 2 showed primarily RH language activation with some atypical features (Figure 7; Laterality Index = −0.39). Broca's area (both the orbital portion and Brodmann's area 44/45) and Wernicke's area (the inferior and parietal aspects) were in the RH. SMA was right of the midline. There was some bilateral frontal lobe activation, but the pattern clearly indicated RH dominance. The basal temporal region was not well visualized.

The memory fMRI test indicated no anterior hippocampal activation. There was bilateral activity in the posterior hippocampal-parahippocampal region for the picture novelty task (Figure 8(a)). Selecting for both the hippocampus and parahippocampal gyrus, we could see strong bilateral parahippocampal gyrus activation, but with minimal hippocampal activation, consistent with parahippocampal place area activation (Epstein, Harris, Stanley, & Kanwisher, 1999) but not in hippocampus proper. The

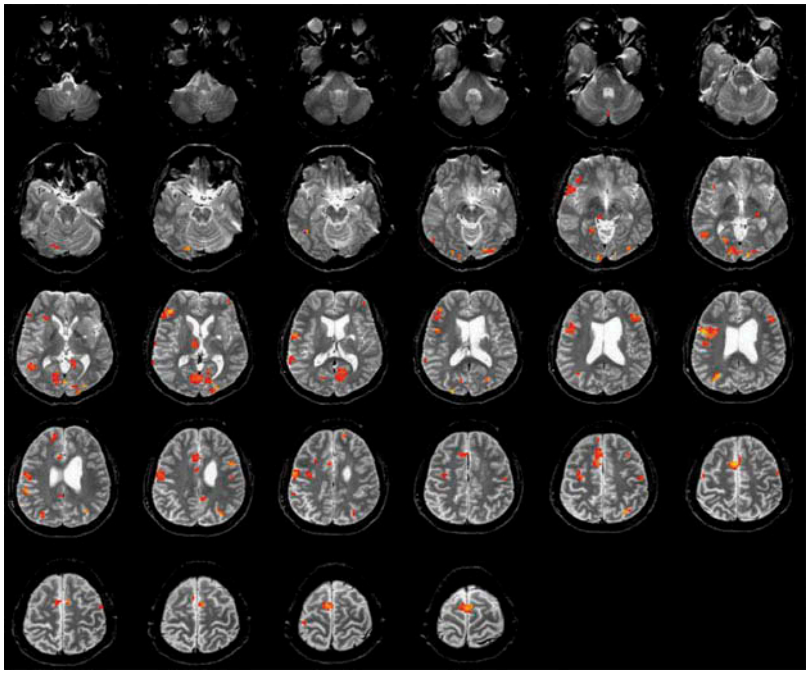


Figure 7. Language fMRI of Subject 2. Primarily RH language activation with some atypical features. [To view this figure in color, please see the online version of this Journal.]

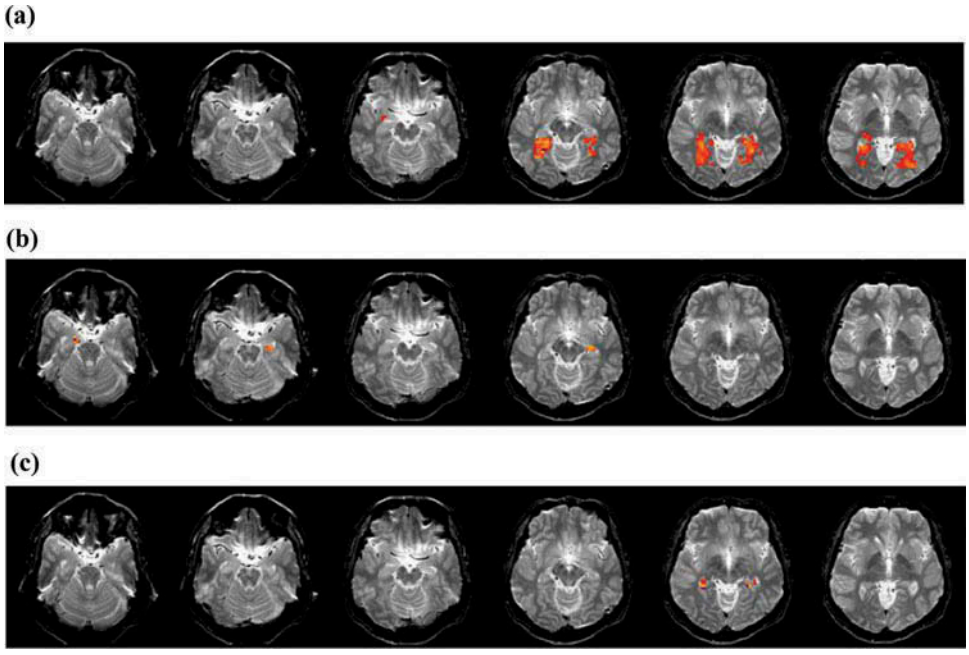


Figure 8. Memory fMRI of Subject 2: (a) picture novelty, (b) face–name association, (c) face–place association. [To view this figure in color, please see the online version of this Journal.]

face–name association task showed activation in the left anterior and mid-hippocampal region. There was a very small area of activation near the right amygdala-hippocampal border, but the LH clearly dominated (Figure 8(b)). In the face–place task, there was activation in the left anterior hippocampus; minimal right mesial temporal activation was observed, with some activation just posterior to the hippocampus in the parahippocampal gyrus. There was bilateral activation in the posterior hippocampus (Figure 8(c)). In sum, the fMRI exam showed strong LH memory and weak RH memory.

Wada

A series of three Wada tests revealed RH language dominance and bilateral memory support (Table 2). Wada in 2006 (left and right injections, 125 mg amytal) found RH language dominance and LH memory dominance (0% recall after left injection; 100% after right injection; recall performed at 10 min postinjection). The angiogram revealed anterior communicating artery (ACA) cross-filling. The second Wada was completed at a lower dose and with a longer recovery period (12 min) (one left injection, 100 mg). The test indicated RH language and 100% memory recall. Given the divergent memory results and concern that full anesthetization may not have occurred in the second procedure, a third and final Wada was performed with a slightly higher dose and a longer recovery period (12 min) (one left injection, 110 mg), which again found RH language and memory (100% recall). We believe that reason for discrepant results between the first and the subsequent two Wadas was that with bilateral ACA filling the patient was unable to retrieve information until the frontal lobes were completely clear of the amytal. During recall, he was verbal, alert, and oriented. Yet, based on careful examination of his motor recovery pattern using fine motor coordination rather than gross strength, he appeared to be still anesthetized until a full 12 min postinjection and was likely still anesthetized on the prior exam in which he was given less time to recover. Given sufficient time to clear the amytal, Subject 2 was able to retrieve and recognize encoded material on the subsequent Wada tests.

Clinical determination

The patient was considered a good surgical candidate and proceeded with surgery.

Discussion

In this report, we described two patients with medically refractory epilepsy who had atypical language and memory dominance. Subject 1 was right-handed with a right temporal lesion and well-established right temporal lobe seizure onset. The radiologic features of this lesion were consistent with either a dysembryoplastic neuroepithelial tumor or low-grade glioma. Neuropsychological assessment was suggestive of atypical lateralization, and both fMRI and Wada testing indicated RH language

dominance. fMRI showed a predominantly RH language representation and bilateral memory function. Wada testing revealed RH dominance for language and memory. Thus, the patient's language and memory dominance patterns were unexpected; with a right temporal lobe lesion and seizure onset, and right-handedness, he would have been considered a good candidate to skip the Wada and proceed to surgery. While such cases are very uncommon, this patient's data indicate the potential risk for postoperative deficits without memory and language mapping. Subject 2 had a lifelong history of left-handedness, developed seizures at an early age, and had a left hippocampal lesion (probable MTS). Neuropsychological data were less definitively lateralizing, though suggested typical lateralization (weakness in some verbal skills). Functional MRI also revealed primarily RH language dominance with less marked but considerable LH activation and, in contrast, largely LH memory function. Wada testing showed RH language and 100% memory recall with a left injection. In this case, had we used only the noninvasive fMRI we would have incorrectly concluded the patient was not a surgical candidate. The relationship between language and memory dominance in left-handers is not known; the paucity of cases with comprehensive testing, both invasive and noninvasive, among those with atypical laterality suggests a continued need for invasive testing.

Early onset left TLE is associated with a higher likelihood of RH representation of memory (both visual and verbal) compared with late onset TLE (Kim & Yi, 1997). Further, the degree of lateralization for language is lower with supplementary involvement of the RH (Cousin, Baciu, Pichat, Kahane, & Le Bas, 2008). Subject 2 had seizures from birth and both his language and memory may have reorganized to the RH. Individuals with lesions in the LH have a higher probability of developing atypical language than patients with pathology in the RH (Berl et al., 2005), especially if the focus is in the left temporal lobe (Duke et al., 2012). If Subject's 2 left hippocampal sclerosis originated early in his childhood, it may have further contributed to atypical lateralization of language (Dijkstra & Ferrier, 2013). Patients with atypical (both RH-dominant or bilateral) language patterns achieve better scores on neurological testing than patients with typical language patterns, suggesting reorganization can be compensatory (Thivard et al., 2005). Subject 2, whose language was represented predominantly in the RH, had language scores within the high average range on neuropsychological evaluation, which would be unexpected if he had language in the LH. The testing also revealed not only intact but impressive verbal memory function. The patient's small right thalamic stroke caused some motor decline, along with a global cognitive decline, in particular, a decrease in nonverbal memory, which is in agreement with electrophysiological studies (Johnson & Ojemann, 2000). Subject 2 had a history of hypercoagulation, which had been overlooked by the anesthesiologist. In retrospect, this was probably a preventable problem. The stroke, however, did not seem to have affected the results of the Wada test. As such, Subject 2 achieved a 100% RH dominance score for memory on Wada. This case therefore illustrates the importance of specific factors (e.g., early onset epilepsy, familial left-handedness, lesion in the LH) in predicting atypical lateralization of cognition. In contrast, Subject 1, who was right-handed, maintained his atypical RH memory dominance despite a large right hippocampal lesion. His neuropsychological testing revealed impairment of language-dominant memory function. This patient is particularly unique and is most likely a rare example of an individual with right brain language and memory before his first seizure at age 22. It appears that he had congenital RH language despite being right-handed. Cunningham, Morris, Drea, and Kroll (2008) also reported two epileptic patients with RH seizure focus, RH language, and no history of left-handedness in the family. Such cases while rare reinforce the importance of careful clinical evaluation including invasive testing even when the probability or RH language is low. In this case, aggressive surgery could easily have caused significant cognitive impairment. A focused resection based on these tests made a negative outcome unlikely.

These cases, and the first case in particular, highlight the critical role played by neuropsychological assessment in epilepsy evaluation. In the absence of clinical fMRI or Wada testing, in the first case, neuropsychological assessment was the sole indicator of atypical representation and possible severe postoperative impairment. Specifically, in the context of his overall lower average function, there was indication that his RH pathology and seizures were cooccurring with relative impairment of verbal functions. Memory performance also suggested relative impairment of dominant verbal rather than nondominant nonverbal memory on commonly used clinical measures. Subject 2's neuropsychological results emphasize the importance of preoperative Wada and fMRI mapping. Here, neuropsychological data were less definitively lateralizing in the context of his LH pathology. His complaint of word-finding difficulties did suggest verbal (dominant) impairment, as did his relatively poor performance on measures of naming and category fluency. Importantly, however, memory performance was more consistent with nondominant impairment. Critically here, on a postoperative screen, verbal intellectual function and verbal memory skills were essentially unchanged or improved relative to preoperative performance.

The Wada test is used to predict postsurgical memory and determine language dominance in patients with epilepsy who are candidates for resective surgery (Sharan et al., 2011). However, there has been an increasing

trend worldwide to forgo the procedure due to its costly nature (Baxendale et al., 2008) and complications (Wang, Peters, de Ribaupierre, & Mirsattari, 2012). Based on a sample of 74 patients who underwent Wada testing, Loddenkemper, Morris, and Möddel (2008) reported that the procedure is associated with up to 10.9% of minor and major complications. The complications included encephalopathy (7.2%), seizures (1.2%), strokes (0.6%), transient ischemic attacks (0.6%), localized hemorrhage at the site of catheter insertion (0.6%), carotid artery dissections (0.4%), allergic reaction to contrast (0.3%), infection (0.1%), and bleeding from the site of catheter insertion (0.1%). Subject 2 is interesting because he indicates both the risks of the Wada procedure and the benefits of it.

The most commonly reported alternative method is fMRI (Arora et al., 2009; Sharan et al., 2011). Bauer, Reitsma, Houweling, Ferrier, and Ramsey (2013) found that fMRI is a reliable mapping tool in case of strong left-lateralized language. However, the authors observed only 51% agreement between fMRI and the Wada test in individuals with atypical language lateralization. They argue that the Wada test is warranted when fMRI does not show clear left-lateralization. Drane et al. (2012) carried out a study in which they analyzed the Wada tests and intraoperative language mapping procedures involving the RH. The authors concluded that the Wada test is a valid measure for identifying RH language with no false lateralization found in intraoperative language mapping. Thus, a positive Wada result may be 100% sensitive for detecting RH language. Cunningham et al. (2008) recommend performing the Wada test in all epilepsy surgery candidates (right- and left-handed) in order to minimize the risk of severe postoperative language decline. They claim that despite being relatively uncommon, right brain language may be more frequent than complications occurring from cerebral angiography. The main problem with using language fMRI in resection planning is that activation is typically more extensive than primary language areas, which may falsely identify other areas as potentially eloquent, especially if the task does not have perceptual control task. At the same time, areas that are not active may be resected due to lack of sensitivity of the particular fMRI protocol, resulting in iatrogenic cognitive impairments (Binder, 2011). fMRI mapping of memory function carries an additional risk of signal dropout in the hippocampal area due to macroscopic field inhomogeneity (Fransson, Merboldt, Ingvar, Petersson, & Frahm, 2001), especially when longer echo time is employed (Milian et al., 2013). fMRI maps can also be distorted by motion which tends to progress during the study from patient exhaustion (Kim, Angthong, Jeon, & Semelka, 2014). Furthermore, the reliability of fMRI in the vicinity of cerebral lesions may limit its use in presurgical mapping. fMRI analysis of individuals with fMRI-critical lesions (e.g., mass defects, severe atrophy) shows lower lateralization indices and fMRI results that are more often discordant with the Wada test than patients without lesions (Wellmer et al., 2009). fMRI lateralization results may depend on types of tasks used as well as their controls (Lee et al., 2008) and they can be discordant in regard to language localization (Arora et al., 2009; Lee et al., 2008). Janecek, Swanson, Sabsevitz, Hammeke, Raghavan, Mueller, et al. (2013) recently reported that fMRI was better than Wada test for predicting outcome in cases where there was a strong discrepancy in language results. Yet, there is still a lot to be learned about both fMRI and Wada as well as the most consistent protocols to evaluate hemispheric dominance of cognitive functions. fMRI memory paradigms currently used are still work in progress. They may not be fully reliable and they need future refinement for improved accuracy. While fMRI is helpful in surgical planning (Kapsalakis et al., 2012) and it may predict outcome on a group level after anterior temporal lobectomy, we do not know the optimal set of fMRI memory paradigms, in particular, for cases in who there may be atypical memory dominance or in who there may be a dissociation between memory and language. Thus, Wada test is still necessary to identify rare cases with atypical dominance of cognitive functions.

Our interpretation of these cases has limitations. We do not have pediatric imaging of either of our cases, hence we cannot confirm that Subject's 2 MTS was developmental. As respective epilepsy surgery was not pursued in Subject 2, we do not have pathology as to determine whether he had a long-standing developmental lesion or a more recent finding. Another limitation is that we do not have a post-operative neuropsychological evaluation of Subject 1 to validate that we were correct with our Wada findings. Further, we did not include behavioral monitoring for our fMRI tasks, which might have impacted task involvement and accuracy. However, after many years of study, we established that in terms of activation it is better to conduct a generation task in which the patient internally generates their responses than a recognition or a verbal response task. We verify subject involvement and accuracy by (1) testing the patient neuropsychologically, (2) asking them immediately after each fMRI task if they had any problems with it, and (3) examining primary visual and auditory activations to ensure that the patient was actively engaged in the task. Another caveat in the study is that we used rest as the contrast task for all the fMRI tasks. The choice of a contrast task remains a controversy. We operated on a conservative assumption that while there are certainly language processes taking place at rest, by reducing the length of periods of rest, as well as using multiple rest periods, language activation becomes stronger (Bookheimer, 2007). We did not employ a perceptual control task because it relies on a pure insertion model with the expectation that it will control for perceptual aspects perfectly, when in fact that is not necessarily the

case. Unless there is perceptual identity, there will be no perfect control. Further, if there is perceptual identity, there are also implicit language processes that take place. We have used the conjunction procedure to eliminate the perceptual control problem.

In summary, the presented cases underscore the importance of both the Wada test and fMRI in epilepsy surgery planning. This is true even in right-handed individuals, when the lesion would not suggest reorganization, or when there are no behavioral signs of language dominance to indicate the Wada is necessary. Without such data, it is difficult to counsel patients on the true risk of postoperative memory and language deficits. Such counseling allows patients to make more informed decisions and prevent potential complications that may be seen as more harmful than the epileptic seizures themselves. While cases of very atypical organization, such as the cases reported here, are rare, we would argue that the primary purpose of these invasive procedures is to identify the rare cases who are at greatest risk for unexpected postoperative cognitive decline.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This research was funded by the Polish Ministry of Science and Higher Education, grant # 608/MOB/2011/0 (Investigator MP) and partially funded by a National Academy of Neuropsychology Award grant (2014).

References

Arora, J., Pugh, K., Westerveld, M., Spencer, S., Spencer, D. D., & Todd Constable, R. (2009). Language lateralization in epilepsy patients: FMRI validated with the Wada procedure. *Epilepsia*, *50*, 2225–2241. doi:10.1111/j.1528-1167.2009.02136.x

Bauer, P., Reitsma, J., Houweling, B., Ferrier, C., & Ramsey, N. (2013). Can fMRI safely replace the Wada test for preoperative assessment of language lateralisation? A meta-analysis and systematic review. *Journal of Neurology, Neurosurgery, & Psychiatry*, *85*, 581–588. doi:10.1136/jnnp-2013-305659

Baxendale, S., Thompson, P. J., & Duncan, J. S. (2008). The role of the Wada test in the surgical treatment of temporal lobe epilepsy: An international survey. *Epilepsia*, *49*, 715–720. doi:10.1111/j.1528-1167.2007.01515_1.x

Berl, M. M., Balsamo, L. M., Xu, B., Moore, E. N., Weinstein, S. L., Conry, J. A., … Gaillard, W. D. (2005). Seizure focus affects regional language networks assessed by fMRI. *Neurology*, *65*, 1604–1611. doi:10.1212/01.wnl.0000184502.06647.28

Berl, M. M., Zimmaro, L. A., Khan, O. I., Dustin, I., Ritzl, E., Duke, E. S., … Gaillard, W. D. (2014). Characterization of atypical language activation patterns in focal epilepsy. *Annals of Neurology*, *75*, 33–42. doi:10.1002/ana.24015

Binder, J. R. (2011). Functional MRI is a valid noninvasive alternative to Wada testing. *Epilepsy & Behavior*, *20*, 214–222. doi:10.1016/j.yebeh.2010.08.004

Binder, J. R., Bellgowan, P. S. F., Hammeke, T. A., Possing, E. T., & Frost, J. A. (2005). A comparison of two FMRI protocols for eliciting hippocampal activation. *Epilepsia*, *46*, 1061–1070. doi:10.1111/j.1528-1167.2005.62004.x

Binder, J. R., Swanson, S. J., Hammeke, T. A., Morris, G. L., Mueller, W. M., Fischer, M., … Haughton, V. M. (1996). Determination of language dominance using functional MRI: A comparison with the Wada test. *Neurology*, *46*, 978–984. doi:10.1212/WNL.46.4.978

Bookheimer, S. (2007). Pre-surgical language mapping with functional magnetic resonance imaging. *Neuropsychology Review*, *17*, 145–155. doi:10.1007/s11065-007-9026-x

Cousin, E., Baciu, M., Pichat, C., Kahane, P., & Le Bas, J.-F. (2008). Functional MRI evidence for language plasticity in adult epileptic patients: Preliminary results. *Neuropsychiatric Disease and Treatment*, *4*, 235–246.

Cunningham, J., Morris, G., Drea, L., & Kroll, J. (2008). Unexpected right hemisphere language representation identified by the intracarotid amobarbital procedure in right-handed epilepsy surgery candidates. *Epilepsy & Behavior*, *13*, 139–143. doi:10.1016/j.yebeh.2008.02.019

Dijkstra, K. K., & Ferrier, C. H. (2013). Patterns and predictors of atypical language representation in epilepsy. *Journal of Neurology, Neurosurgery, and Psychiatry*, *84*, 379–385. doi:10.1136/jnnp-2012-303141

Drane, D. L., Roraback-Carson, J., Hebb, A. O., Hersonskey, T., Lucas, T., Ojemann, G. A., … Ojemann, J. G. (2012). Cortical stimulation mapping and Wada results demonstrate a normal variant of right hemisphere language organization. *Epilepsia*, *53*, 1790–1798. doi:10.1111/j.1528-1167.2012.03573.x

Duke, E. S., Tesfaye, M., Berl, M. M., Walker, J. E., Ritzl, E. K., Fasano, R. E., … Gaillard, W. D. (2012). The effect of seizure focus on regional language processing areas. *Epilepsia*, *53*, 1044–1050. doi:10.1111/j.1528-1167.2012.03490.x

Engel, J. (2013). *Seizures and epilepsy*. New York, NY: Oxford University Press.

Epstein, R., Harris, A., Stanley, D., & Kanwisher, N. (1999). The parahippocampal place area: Recognition, navigation, or encoding? *Neuron*, *23*, 115–125. doi:10.1016/S0896-6273(00)80758-8

Fransson, P., Merboldt, K.-D., Ingvar, M., Petersson, K. M., & Frahm, J. (2001). Functional MRI with reduced susceptibility artifact: High-resolution mapping of episodic memory encoding. *Neuroreport*, *12*, 1415–1420. doi:10.1097/00001756-200105250-00024

Gaillard, W. D., Balsamo, L., Xu, B., McKinney, C., Papero, P. H., Weinstein, S., … Theodore, W. H. (2004). fMRI language task panel improves determination of language dominance. *Neurology*, *63*, 1403–1408. doi:10.1212/01.WNL.0000141852.65175.A7

Hader, W. J., Tellez-Zenteno, J., Metcalfe, A., Hernandez-Ronquillo, L., Wiebe, S., Kwon, C.-S., & Jette, N. (2013). Complications of epilepsy surgery – A systematic review of focal surgical resections and invasive EEG monitoring. *Epilepsia*, *54*, 840–847. doi:10.1111/epi.12161

Hamberger, M. J., & Cole, J. (2011). Language organization and reorganization in epilepsy. *Neuropsychology Review*, *21*, 240–251. doi:10.1007/s11065-011-9180-z

Helmstaedter, C., Kurthen, M., Linke, D. B., & Elger, C. E. (1997). Patterns of language dominance in focal left and right hemisphere epilepsies: Relation to MRI findings, EEG, sex, and age at onset of epilepsy. *Brain and Cognition*, *33*, 135–150. doi:10.1006/brcg.1997.0888

Janecek, J. K., Swanson, S. J., Sabsevitz, D. S., Hammeke, T. A., Raghavan, M., Rozman, M. E., & Binder, J. R. (2013).

Language lateralization by fMRI and Wada testing in 229 patients with epilepsy: Rates and predictors of discordance. *Epilepsia*, *54*, 314–322. doi:10.1111/epi.12068

Janecek, J. K., Swanson, S. J., Sabsevitz, D. S., Hammeke, T. A., Raghavan, M., Mueller, W., & Binder, J. R. (2013). Naming outcome prediction in patients with discordant Wada and fMRI language lateralization. *Epilepsy and Behavior*, *27*, 399–403. doi:10.1016/j.yebeh.2013.02.030

Janszky, J., Jokeit, H., Heinemann, D., Schulz, R., Woermann, F. G., & Ebner, A. (2003). Epileptic activity influences the speech organization in medial temporal lobe epilepsy. *Brain*, *126*, 2043–2051. doi:10.1093/brain/awg193

Johnson, M. D., & Ojemann, G. A. (2000). The role of the human thalamus in language and memory: Evidence from electrophysiological studies. *Brain and Cognition*, *42*, 218–230. doi:10.1006/brcg.1999.1101

Kapsalakis, I., Kapsalaki, E., Gotsis, E., Verganelakis, D., Toulas, P., Hadjigeorgiou, G., & Fountas, K. (2012). Preoperative evaluation with FMRI of patients with intracranial gliomas. *Radiology Research and Practice*, *2012*, 17 pp. doi:10.1155/2012/727810

Kemp, S., Wilkinson, K., Caswell, H., Reynders, H., & Baker, G. (2008). The base rate of Wada test failure. *Epilepsy & Behavior*, *13*, 630–633. doi:10.1016/j.yebeh.2008.07.013

Kim, B. S., Angthong, W., Jeon, Y.-H., & Semelka, R. C. (2014). Body MR imaging: Fast, efficient, and comprehensive. *Radiologic Clinics of North America*, *52*, 623–636. doi:10.1016/j.rcl.2014.02.007

Kim, H., & Yi, S. (1997). The effect of early versus late onset of temporal lobe epilepsy on hemispheric memory laterality: An intracarotid amobarbital procedure study. *Journal of Korean Medical Science*, *12*, 559–563. doi:10.3346/jkms.1997.12.6.559

Korman, B., Bernal, B., Duchowny, M., Jayakar, P., Altman, N., Garaycoa, G., … Rey, G. (2010). Atypical propositional language organization in prenatal and early-acquired temporal lobe lesions. *Journal of Child Neurology*, *25*, 985–993. doi:10.1177/0883073809357242

Lee, D., Swanson, S. J., Sabsevitz, D. S., Hammeke, T. A., Scott Winstanley, F., Possing, E. T., & Binder, J. R. (2008). Functional MRI and Wada studies in patients with interhemispheric dissociation of language functions. *Epilepsy & Behavior*, *13*, 350–356. doi:10.1016/j.yebeh.2008.04.010

Loddenkemper, T., Morris, H. H., & Möddel, G. (2008). Complications during the Wada test. *Epilepsy and Behavior*, *13*, 551–553. doi:10.1016/j.yebeh.2008.05.014

Milian, M., Zeltner, L., Klamer, S., Klose, U., Rona, S., & Erb, M. (2013). BOLD signal in memory paradigms in hippocampal region depends on echo time. *Journal of Magnetic Resonance Imaging*, *37*, 1064–1071. doi:10.1002/jmri.23888

Paolicchi, J. M. (2008). Is the Wada test still relevant? Yes. *Archives of Neurology*, *65*, 838–840. doi:10.1001/archneur.65.6.838

Quirico-Santos, T., Meira, I. D., Gomes, A. C., Pereira, V. C., Pinto, M., Monteiro, M., … Alves-Leon, S. V. (2013). Resection of the epileptogenic lesion abolishes seizures and reduces inflammatory cytokines of patients with temporal lobe epilepsy. *Journal of Neuroimmunology*, *254*, 125–130. doi:10.1016/j.jneuroim.2012.08.004

Rathore, C., George, A., Kesavadas, C., Sankara Sarma, P., & Radhakrishnan, K. (2009). Extent of initial injury determines language lateralization in mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS). *Epilepsia*, *50*, 2249–2255. doi:10.1111/j.1528-1167.2009.02300.x

Rausch, R., Silfvenius, H., Weiser, H., Dodrill, C., Meador, K., & Jones-Gotman, M. (1993). Intra-arterial amobarbital procedures. In J. Engel Jr. (Ed.), *Surgical treatment of the epilepsies* (2nd ed., pp. 341–357). New York, NY: Raven Press.

Rutten, G. J. M., Ramsey, N. F., van Rijen, P. C., Noordmans, H. J., & van Veelen, C. W. M. (2002). Development of a functional magnetic resonance imaging protocol for intraoperative localization of critical temporoparietal language areas. *Annals of Neurology*, *51*, 350–360. doi:10.1002/ana.10117

Sharan, A., Ooi, Y. C., Langfitt, J., & Sperling, M. R. (2011). Intracarotid amobarbital procedure for epilepsy surgery. *Epilepsy & Behavior*, *20*, 209–213. doi:10.1016/j.yebeh.2010.11.013

Springer, J. A., Binder, J. R., Hammeke, T. A., Swanson, S. J., Frost, J. A., Bellgowan, P. S. F., & Mueller, W. M. (1999). Language dominance in neurologically normal and epilepsy subjects: A functional MRI study. *Brain*, *122*, 2033–2046. doi:10.1093/brain/122.11.2033

Thivard, L., Hombrouck, J., Tézenas du Montcel, S., Delmaire, C., Cohen, L., Samson, S., & Lehéricy, S. (2005). Productive and perceptive language reorganization in temporal lobe epilepsy. *NeuroImage*, *24*, 841–851. doi:10.1016/j.neuroimage.2004.10.001

Wang, A., Peters, T., de Ribaupierre, S., & Mirsattari, S. (2012). Functional magnetic resonance imaging for language mapping in temporal lobe epilepsy. *Epilepsy Research and Treatment*, *2012*, 8 pp. doi:10.1155/2012/198183

Wellmer, J., Weber, B., Urbach, H., Reul, J., Fernandez, G., & Elger, C. E. (2009). Cerebral lesions can impair fMRI-based language lateralization. *Epilepsia*, *50*, 2213–2224. doi:10.1111/j.1528-1167.2009.02102.x

Whitman, L. A., Morrison, C. E., Becske, T., Barr, W. B., & Carlson, C. (2012). The intracarotid amobarbital procedure: When is it worth repeating? *Epilepsia*, *53*, 721–727. doi:10.1111/j.1528-1167.2011.03399.x

Willinsky, R. A., Taylor, S. M., TerBrugge, K., Farb, R. I., Tomlinson, G., & Montanera, W. (2003). Neurologic complications of cerebral angiography: Prospective analysis of 2,899 procedures and review of the literature. *Radiology*, *227*, 522–528. doi:10.1148/radiol.2272012071

Zeineh, M., Engel, S., Thompson, P., & Bookheimer, S. (2003). Dynamics of the hippocampus during encoding and retrieval of face-name pairs. *Science*, *299*, 577–580. doi:10.1126/science.1077775