Clinical commentary

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Wada testing and fMRI in a polyglot evaluated for epilepsy surgery

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ABSTRACT – Despite advancements in the neurophysiology of language and presurgical evaluation for epilepsy surgery, there is a paucity of information in the literature regarding presurgical evaluation of multilingual patients. We present a case of a 52-year-old right-handed woman with refractory epilepsy who was fluent in six languages and underwent subsequent trilingual presurgical evaluation which included neuropsychological testing, Wada testing, functional magnetic resonance imaging (fMRI), and electrocortical stimulation. These studies suggested a seizure focus in the left temporal lobe and language localization that was predominantly right-hemispheric; she subsequently underwent left temporal laser interstitial thermal therapy without clinical disturbance in language function while remaining seizure-free. A multidisciplinary effort was integral in providing an optimal outcome for this patient.

Key words: language, brain, function, Wada, fMRI, epilepsy, seizures, drug-resistant, polyglot

As epilepsy surgery continues to be increasingly utilized for the treatment of drug-resistant epilepsy, studies assessing presurgical language function have become routine (Baxendale and Thompson, 2010; Guerrini *et al.*, 2013). The earliest scientific writings regarding neural circuitry in patients who speak more than one language can be found in cases of bilingual aphasia reported in the late nineteenth century, some thirty years after Broca first described "*perte de la parole*" (loss of speech) (Lorch, 2007). Although the literature on presurgical evaluation, language localization, and the neural circuitry of language physiology has expanded exponentially over the past two decades, a paucity of information exists regarding the variables that must be considered when evaluating multilingual patients for possible surgical intervention (Fernandez-Coello *et al.*, 2017). Herein, we present a case of a polyglot woman, fluent in six languages, who was evaluated for epilepsy surgery with

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neuropsychiatric evaluation, functional neuroimaging, and language mapping with electrocortical stimulation, which provided valuable information for subsequent successful epilepsy surgery. We report right superior temporal gyrus localization as the source for several languages in a right-handed polyglot with left temporal epilepsy and bilateral language function with right hemispheric predominance. Additionally, we review the neurophysiology of language in the polyglot brain as it impacts surgical treatment of people at risk of significant post-operative language deficits.

Case study

A 52-year-old, right-handed, Caucasian female with a history of migraine, generalized anxiety disorder, and attention-deficit disorder was seen in the epilepsy clinic for further evaluation of uncontrolled seizures. Her seizures began at the age of 13 and manifested as episodes of staring that subsequently recurred on a monthly basis. Her seizures became resistant to anti-seizure medication, with unsuccessful trials of carbamazepine, valproic acid, lamotrigine, topiramate, and levetiracetam. Risk factors for epilepsy included "low oxygen at birth" and a prolonged high fever at the age of one; a lumbar puncture at that time did not reveal evidence of meningoencephalitis. Her medications at the time of evaluation included levetiracetam at 1,250 mg BID, carbamazepine extended-release at 400 mg BID, and topiramate at 50 mg BID. She described her seizures as beginning with an aura of a "quick scene", similar to *déjà vu* followed by staring, impaired consciousness, chewing, and bilateral stiffness without asymmetry for 30-60 seconds with post-ictal state. She was still experiencing seizures on a monthly basis which were disabling enough to cause her to seek a surgical evaluation.

She was born in the United States but moved to Switzerland at the age of seven, where she was subsequently raised. She is able to speak six languages which include German, English, Spanish, Italian, French, and Swiss-German, an Alemannic dialect spoken in the German-speaking part of Switzerland which is distinct from German with its own grammar. Her first acquired languages were Swiss-German (which she considers to be her first language), English (which she learned from ages two to five), and German (which she began to learn around the age of seven). These languages were reinforced during childhood prior to seizure onset. She began learning French, Italian, and Spanish at ages 13, 16, and 18, respectively. At the age of 20, she began to relearn English, which she had not spoken since age five. She reports her language competency for Swiss-German, English, Spanish, and German as ILR-5 (*Interagency Language Roundtable* scale, a standardized method of grading language proficiency, which ranges from lowest proficiency at ILR-0 to highest at ILR-5), equivalent to native language proficiency[1]. She rates her French proficiency as ILR-3 ("professional working proficiency") and Italian as ILR-2 ("limited working proficiency"). She had the equivalent of 14 years of education and completed three years of college education.

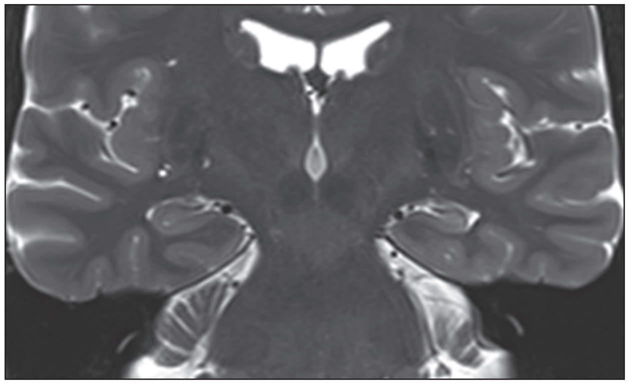

Figure 1. Coronal turbo-spin-echo T2-weighted MRI sequence revealing left mesial temporal sclerosis with atrophy and gliotic change.

Her neurologic examination was unremarkable. Initial standard electroencephalogram (EEG) revealed occasional independent bitemporal delta and theta slowing with intermittent left temporal sharp waves. Magnetic resonance imaging (MRI) revealed prominent left mesial temporal sclerosis (MTS) with gliotic changes and significant atrophy (*figure 1*). Neuropsychological studies performed in English revealed intact language comprehension, spelling, and repetition, however, naming ability and speeded word generation were impaired. She also demonstrated learning and memory inefficiencies that were greater for verbal information, as well as relative slowing of right-hand manual dexterity. A battery of neuropsychological tests were administered, including the Montreal Cognitive Assessment (MoCA); Wechsler Adult Intelligence Scale (WAIS-IV); subtests of the Wide Range Achievement Test (WRAT-IV); Boston Naming Test (BNT); subtests of Boston Diagnostic Aphasia Examination (BDAE-3) and Delis-Kaplan Executive Function Scales (D-KEFS); Incomplete Letters; Rey-Osterrieth Complex Figure(Rey-O); California Verbal Learning Test (CVLT-II); subtests of the Wechsler Memory Scale (WMS-IV); Grooved Pegs; Frontal Assessment Battery; and Beck Depression Inventory (BDI-II) in accordance with a pre-established presurgical evaluation (Greenway *et al.*, 2017). Her multilingualism was considered a potential contributing factor to the observed

[1] *Interagency Language Roundtable*. 2011. http://www.govtilr.org (consulted on 21 November 2019).

language-based difficulties, however, the overall neuropsychological profile was suggestive of acquired temporal and frontal lobe dysfunction, greater in the left hemisphere.

During video-EEG monitoring, six seizures were noted with oral automatisms, left manual automatisms, and right upper extremity dystonic posturing that was semiologically consistent with left temporal lobe origin. Electrographically, four of the six seizures were left temporal at onset with two seizures of right temporal onset, however, both right temporal onset seizures had semiology suggesting left temporal onset, which raised the question of false lateralization.

She underwent Wada testing in English. On baseline evaluation, she incorrectly named two of eight presented objects, calling a corkscrew a "screwdriver" and a spool of thread a "yarn". Baseline memory for objects was intact with 8/8 target hits and 0/16 false-positive identifications. During Wada testing, initial injection of sodium methohexital into the left internal carotid artery (ICA) with initial injection of 3 mg followed by 2 mg resulted in brief speech arrest and then correct naming of 6/8 target objects. Memory testing following recovery from the injection was intact, with 7/8 correct target hits and 0/16 false-positive identifications. Following injection of 3 mg of sodium methohexital into the right ICA, initial global aphasia was documented as she was unable to spontaneously produce the names of the first six objects presented, although she was later able to repeat some of the names when provided by the examiner. She provided partial responses to the final two objects presented during the naming portion of the procedure ("rubber" for rubber band and "paste" for toothpaste). Memory assessment suggested impaired encoding of information during the injection, with 2/8 correct target hits and 0/16 false-positive responses. This is in comparison to injection of sodium methohexital into the left ICA, during which she was still able to name 6/8 objects and recall 7/8 objects. EEG confirmed respective unilateral hemispheric slowing during periods of testing. These overall findings support right hemisphere memory dominance. Bilateral language representation was also apparent during each injection with impaired comprehension and fluent expression, but function was relatively preserved in the right hemisphere compared to the left.

Functional MRI was then performed with language paradigms in German, English, and French, which revealed receptive language localized primarily to the right hemisphere along the banks of the superior temporal gyrus (Szaflarski *et al*,. 2017). English and German were represented exclusively in the right hemisphere at the inferior frontal gyrus and superior temporal sulcus while French had bilateral representation with right-hemispheric predominance. No significant activation of subcortical structures was seen (*figure 2*). The language fMRI was obtained with blood oxygenation-level dependent signal separately with English, French and German silent reading comprehension tasks using a standard block design. Additional tasks with similar results (not shown) included semantic decision and silent word generation as parts of our standard language fMRI protocol. The acceptable head motion threshold was less than 0.5 mm in all three axes. The data was processed on MRIx fMRI software and the activation maps were generated using false discovery rate (FDR) with a p value threshold of 0.001. As suggested during Wada testing, motor language had bilateral representation.

Given the possibility of false lateralization of recorded focal seizures during scalp-based video-EEG monitoring, bitemporal depth electrodes were placed for lateralization of seizure foci during intracranial video-EEG seizure monitoring. Over the course of five days, positive and negative spikes and sharp waves were noted in the temporal depths bilaterally. Nine seizures were captured and were confirmed to originate from the left temporal lobe, which supported the notion of previously suspected false lateralization on scalp EEG recordings. Subsequently, direct electrical stimulation was performed. Anterior and posterior portions of the temporal lobes were stimulated with increasing bipolar electrical current up to 6.5 milliamperes (mA) at 50 Hz and 200-microsecond pulse duration. The maximum charge density was maintained at less than 30 $\mu C/cm^2$/100 grams of tissue. During this time, reading, comprehension and naming was tested in English, Spanish, and German. Stimulation of the posterior right temporal lobe with a current of 3 mA resulted in subtle paraphasic errors, language hesitancy, and naming errors. This was consistent with previous fMRI testing which suggested the right superior temporal gyrus to be integral to language function.

Shortly thereafter, the patient underwent left mesial temporal laser interstitial thermal therapy (LITT) ablation of the amygdalohippocampal complex without complications. No language deficits were noted post-operatively. After six months of follow-up, she remained seizure-free, no specific memory concerns were noted, and the neurologic examination was unremarkable. Given these considerations, formal neuropsychological testing was declined at the patient's request following epilepsy surgery given her successful outcome. After 13 months of follow-up via telephone, the patient did note subjective short-term memory difficulties but reported continued seizure freedom and no language deficits in any of her six languages.

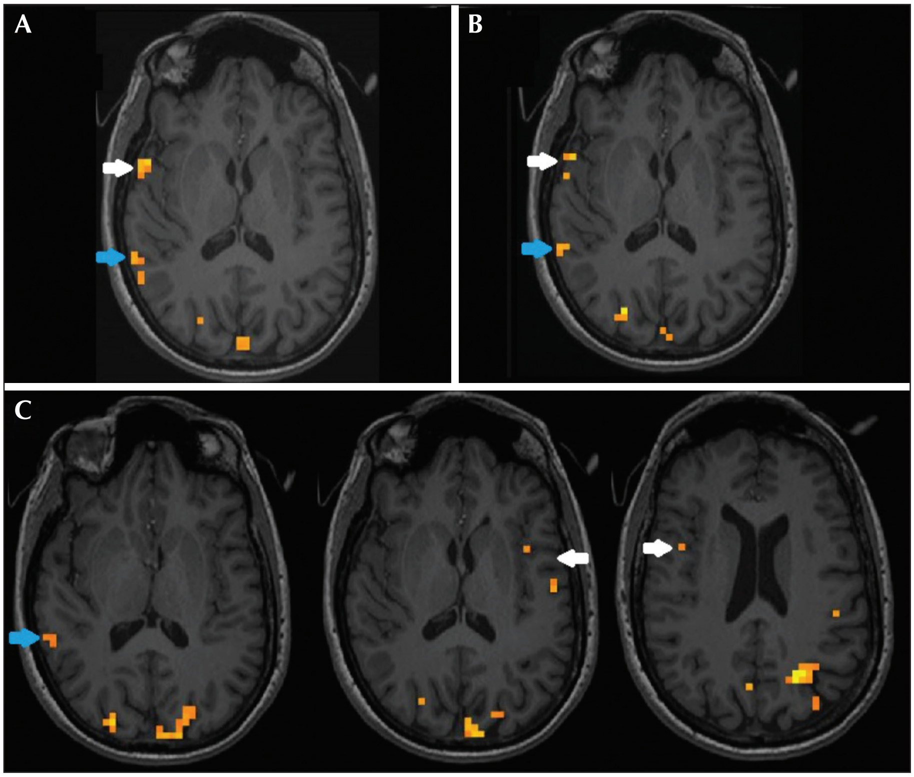

Figure 2. fMRI activation maps for reading comprehension tasks in English (A), German (B), and French (C). With all three paradigms, there is right-sided BOLD activation in the right superior temporal sulcus (blue arrows), consistent with right-hemispheric dominance. Inferior frontal gyri activation (white arrows) is seen in the right hemisphere only for English (A) and German (B) but in both hemispheres for French (C).

Discussion

Despite a large body of research investigating bilingual language control (Hull and Vaid, 2007), a paucity of research on polyglot language control exists (Hervais-Adelman *et al.*, 2018; Abutalebi *et al.*, 2013; Hervais-Adelman *et al.*, 2015; Kong *et al.*, 2014). Current research, based on clinicopathologic correlation and functional MRI findings, suggests that a complex fronto-subcortical-cerebellar network governs multilingual language production with substantial involvement by the caudate and putamen (Hervais-Adelman *et al.*, 2015). The fMRI evaluation in our patient did not reveal activation of subcortical structures during the assigned tasks, but this is likely due to the higher threshold setting that was used for the clinical protocol for language localization rather than lower thresholds used for purely research bases. In addition to the fMRI studies investigating polyglot language control, frontal lobe pathology has been associated with pathologic language switching in a trilingual patient (Kong *et al.*, 2014), and a case of cerebellar infarction resulting in polyglot aphasia of six non-dominant languages suggests that the left cerebellar hemisphere also plays a role in polyglot language (Marien *et al.*, 2017). In the case presented, Wada testing, functional brain MRI and direct electrocortical stimulation were concordant in demonstrating a major role of the right superior temporal gyrus in language control in our right-handed patient who is fluent in six languages.

The localization of language becomes extremely important clinically when evaluating patients for possible epilepsy surgery. A study of 445 patients (number of languages spoken unspecified) with epilepsy undergoing bilateral Wada testing at Cleveland Clinic revealed that approximately 16% of patients did have bilateral language representation with 78% and 6% left-hemisphere and right-hemisphere dominant, respectively (Moddel *et al.*, 2009). Language function is typically seen with left hemisphere predominance, especially in a right-handed individual. However, approximately 4% of right-handed patients demonstrate right-hemispheric dominance (Moddel *et al.*, 2009). Of note, considering our patient, right-handed individuals with left-sided lesions did not differ from those without lesions in terms of language laterality. Furthermore, left hippocampal sclerosis in right-handed patients was still greatly associated with left hemisphere laterality (in 55 of 69 cases, or 79.7%) (Moddel *et al.*, 2009). We recognize that due to neuroplasticity, reorganization of language function may occur in children. The age at which reorganization of language localization ceases has traditionally been the age of six, although rarely language reorganization has been reported in children aged 7-14 years as well (Hertz-Pannier *et al.*, 2002). In our patient, significant reorganization from the dominant hemisphere to the non-dominant hemisphere was unexpected given the age of seizure onset at 13 years. Additionally, serial acquisition of six languages occurred over adolescence and adulthood. While some degree of neuroplasticity could be present, the likelihood of complete re-lateralization in a right-handed person without atypical language representation is unexpected.

There is extremely scant data regarding language predominance in multilingual individuals undergoing evaluation for epilepsy surgery and outcomes (Guerrini *et al.*, 2013; Polczynska *et al.*, 2017). However, a 2017 presurgical evaluation study of language laterality among *bilingual* patients undergoing surgery for either epilepsy, tumor, or arteriovenous malformation revealed that early bilingualism is associated with greater bihemispheric language representation than healthy controls (Polczynska *et al.*, 2017). Laterality of the language was influenced by age at acquisition of non-native languages as well as the duration and extent of intracranial pathology such as hippocampal sclerosis or tumor that could lead to language reorganization to the non-dominant side. Supporting these findings, our patient had right-predominant language representation with a history of early childhood language acquisition, and the presence of likely long-standing left MTS supports the finding of bilateral language representation. Compared to bilingualism, multilingualism is associated with additional factors that can complicate language localization and evaluation including additional neuronal networks potentially involved with different languages, variable levels of language proficiency, and a larger span of time over which languages are acquired. Bello *et al.* reported seven right-handed multilingual patients with left frontal gliomas who underwent intraoperative language localization, demonstrating left-hemispheric language involvement (Bellow et al., 2006). Interestingly, in contrast to our findings, the first acquired language was found to localize to distinct cortical sites with additional languages in a different, common site, or multiple distinct sites. In another report, Fernandez-Coello *et al.* reported 13 right-handed multilingual patients undergoing awake brain mapping (11 for tumor resection) and reported perisylvian left hemisphere frontoparietotemporal language localization with the specific finding that earlier acquired language had greater cortical representation than languages acquired later (Fernandez-Coello *et al.*, 2017). All but one of the patients were found to have an area in the brain at which electrocortical stimulation produced speech arrest in all languages, and four of these were at the left superior temporal gyrus. This single localization for multiple languages is similar to the present study. However, in our patient, mesial temporal sclerosis -more typical of drug-resistant focal epilepsy- lies in contrast to the prior studies involving gliomas, indicative of adult-onset brain injury. This unique pathology reported in a polyglot may be responsible for a right-sided shift in language function as opposed to the expected localization (variable or residing in the left superior temporal gyrus). The finding by Fernandez-Coello *et al.*, that earlier acquired languages had greater cortical representation, does seem to conflict with the results of our fMRI results, which demonstrated bilateral activation for French, which was reported to be a relatively lower proficiency and later-acquired language compared to English and German. This discrepancy may be explained by the fact that fMRI may overestimate cortical language areas when required tasks are difficult or when the patient is using a language in which they are less proficient (Fernandez-Coello *et al.*, 2017).

With the relative paucity of literature regarding language laterality and functional neuroanatomy of multilingualism, selecting a surgical approach with the lowest neuropsychological complication is important. Data does exist suggesting that less invasive options such as LITT (the approach used for this patient) have similar efficacy in reducing seizures when compared to traditional anterotemporal lobectomies with less neuropsychological adverse effects (Grewal *et al.*, 2019). Despite the reports of reduced complications, some decline in verbal memory has been commonly reported following LITT, more commonly when the dominant hemisphere is targeted (Grewal *et al.*, 2018). Additionally, a recent study examining 26 patients undergoing LITT for mesial temporal sclerosis (over 50% of whom were Spanish-speaking) reported a significantly reduced incidence of post-operative language or verbal memory decline compared to previously reported complication rates of anterior temporal lobectomies (Bermudez *et al.*, 2019).

We recognize possible limitations to interpreting the results. The use of topiramate has the potential to cause speech and language dysfunction. However, these deficits were not clinically apparent in our patient. In addition, topiramate is unlikely to affect language lateralization/localization as opposed to production. Also, each of the patient's six languages was not systematically tested during testing paradigms. Developing fMRI protocols for low frequency languages and coordinating multiple simultaneous interpreters represents a pragmatic challenge and incurs a theoretical safety risk to patients by prolonging procedure time. Therefore, the predictability of compromising individual language use and proficiency of untested languages should be discussed with patients prior to surgical management in the event of unexpected language localization. Nevertheless, previous reports of multilinguals suggest overlapping localization for languages acquired later in life (Fernandez-Coello *et al.*, 2017). Although our patient declined formal neuropsychometric testing following surgery and reported no deficits in any of her six languages, there were subjective short-term memory difficulties reported at 13 months of follow-up via telephone. Given the relatively infrequent but known possibility of adverse cognitive events following LITT, our patient indeed may have had objective decline on formal neuropsychometric testing if performed (Bermudez *et al.*, 2019). Finally, given our report of a single multilingual patient who was evaluated for epilepsy surgery after acquisition of all languages, our findings may not be generalizable to other patients with similar language profiles.

Conclusion

The existing literature regarding presurgical evaluation of multilingual individuals is extremely scarce. Our multilingual right-handed patient with bilateral language representation and right-hemisphere predominance underwent successful epilepsy surgery using LITT for symptomatic drug-resistant left temporal lobe epilepsy without post-operative language deficits. Concordant presurgical evaluation with neuropsychometric testing, Wada testing, fMRI, and direct electrocortical stimulation verified language function for subsequent decision-making regarding epilepsy surgery (Szaflarski *et al.*, 2017). This case illustrates the unique nature of this population and the importance of multidisciplinary presurgical evaluation for multiple languages. We recommend utilizing multiple lines of evidence in polyglots to obtain concordance when localizing language function to guide surgical planning in patients with drug-resistant focal epilepsy. □

Disclosures.
None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) At what age is reorganization of language localization traditionally thought to cease?

A. At one year
B. At three years
C. At six years
D. At 14 years
E. At 21 years

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".