Is fMRI Ready to Replace IAP? Wait, Wait,…We Are Not There Yet!

Commentary on: Lesser, RP. Can fMRI Substitute for the Wada Test?
Epilepsy Curr. **2003;3(6):210–211.**
doi:10.1046/j.1535-7597.2003.03613.x. PMID: 15346156

In 2002, the authors of the editorial "Is it time to replace the Wada test?" indicated that "we are almost there" and that functional magnetic resonance imaging (fMRI) will be ready to fully replace the intracarotid amobarbital procedure (IAP) when "a paradigm or battery of fMRI paradigms can be validated for identification of language regions that should be excluded from excision, and for prediction of postoperative memory function."[1] An *Epilepsy Currents* commentary expressed similar hope in 2003.[2] Unfortunately, almost 20 years later, we are not there yet…

Substantial progress has been made since 2002 including several publications that have evaluated the concordance between fMRI activations and IAP deactivations and the fMRI's ability to predict the cognitive outcomes after temporal lobectomy for seizure control. However, before we discuss this research, we need to understand the potential advantages, disadvantages, and fallacies of IAP.

For many decades, an invasive IAP provided information about hemispheric lateralization of language that neurologists and neurosurgeons learned to depend on when making surgical decisions. Later, methods were developed and added to utilize IAP for memory lateralization. However, IAP fails to provide any information about function localization within the temporal or frontal lobes which is of primary importance for tailored surgical resections. Further, its ability to predict post-surgical memory outcome has been questioned.[3] Intracarotid amobarbital procedure's validity depends on demonstrating relatively symmetric and separate blood supplies to each hemisphere and patient compliance with the testing. In addition to its function lateralizing value, some have used IAP to provide information regarding seizure onset lateralization[4] or to predict epilepsy surgery outcome.[5] However, in patients with epilepsy, the angiographic procedure required for IAP and the injection of the anesthetic medication carry a combined complication rate of up to $\sim 11\%$.[6] Intracarotid amobarbital procedure has also been reported to be falsely lateralizing and be subject to variable effects of anesthesia, rates of amobarbital or methohexital injection and distribution, patient cooperation, and significant variation in testing methods between centers. In recent years, a decline in the proportion of patients receiving IAP in Europe and some US epilepsy centers during the presurgical evaluation has been reported with the above and other factors frequently listed as the main reasons.[7,8]

The issues identified above combined with the developments in the neuroimaging field have resulted in advancement of other techniques for the presurgical evaluation of language and memory localization—single-photon emission computed tomography (SPECT), positron emission tomography (PET), near infrared spectroscopy and imaging (NIRS), magnetoencephalography (MEG), transcranial magnetic stimulation (TMS), intraoperative mapping, and fMRI. However, fMRI is of major clinical and practical importance because of its widespread availability, perceived safety, and a relatively low cost when used for clinical and research purposes. Further, the use of fMRI in presurgical evaluation of epilepsy patients has been popularized by initial reports of high correlation between the fMRI activation and IAP for language lateralization[9] and the reports of its ability to predict naming memory deficits after temporal lobectomy.[10] Later studies have shown that while fMRI of language and IAP were both predictive of postsurgical verbal memory decline, fMRI predicted additional variance in outcomes while IAP did not.[11] In parallel, studies compared various fMRI tasks among each other and in combination for their ability to lateralize language functions and correlate them with IAP.[12,13] These and other studies were recently included in a meta-analysis that derived pooled estimates of the positive and negative predictive values of the fMRI using IAP as the standard reference.[14] However, considering the fallacies of IAP mentioned above, using it as a standard reference may be problematic in and by itself. Nevertheless, the meta-analysis has shown that 81% of patients were correctly classified as having left or right language dominance or mixed language representation; agreement was 94% for typical language lateralization and 51% for atypical language lateralization. Of further interest may be that the predictions were not significantly different between the receptive or expressive language fMRI tasks. However, questions of using fMRI in patients with atypical language lateralization remain.[15]

Intracarotid amobarbital procedure has also been used for memory lateralization. However, as raised by the *Epilepsy Currents* editorial from 2003, the initial development of fMRI memory tasks has been lacking compared to the language tasks.[2] Early fMRI studies in people with epilepsy using tasks such as mental navigation, verbal or nonverbal encoding, and naming have shown that the medial temporal structures activate bilaterally, that there likely is a shift of activation to the unaffected hemisphere,[16-18] and that there is a correlation between presurgical neuropsychological memory testing and fMRI lateralization of memory encoding.[19] However, in recent years, visual or verbal memory encoding tasks tried to fill this void.[20-22] In one of the latest studies, preoperative auditory naming, picture naming, and verbal fluency fMRI paradigms were correlated with postoperative naming decline.[23] In patients with left temporal lobe epilepsy, activation of the left posterior inferior temporal gyrus during auditory naming and activation of left fusiform gyrus during picture naming were related to greater postoperative naming decline. In the multivariate regression model, presurgical activation laterality indices were the best individual predictors of naming decline with >90% positive predictive value for picture naming, 58.3% for auditory naming, and no effect for verbal fluency indicating that auditory and picture naming fMRI may be clinically applicable to predicting postoperative naming decline after left temporal lobe resection.

In 2017, the American Academy of Neurology (AAN) published the first guideline summary that addressed the use of fMRI in the presurgical evaluation of patients with epilepsy.[24] The authors of the guideline put forth several level B and level C recommendations regarding the use of fMRI in place of IAP for lateralization of language and/or memory functions and for prediction of postsurgical language and verbal memory outcomes. However, the guideline also identified several gaps concerning the use of fMRI in this setting and made several recommendations regarding future research. The unknowns and the recommendations for research included conduct of studies comparing fMRI and IAP with regard to their ability to predict language and memory outcomes in patients receiving various treatments, including thermoablation versus resection, studies comparing various language and memory fMRI paradigms in their agreement with IAP and their ability to predict respective outcomes, replication studies using the same tasks across multiple centers and imaging platforms, studies targeting pediatric populations, and studies evaluating how resection of fMRI activated tissue relates to outcomes. Since then, quality research has started addressing these issues—the above mentioned study compared 3 fMRI paradigms with memory outcomes[23] and another study retrospectively evaluated the issue of activated tissue resection.[25,26] A recently completed multicenter prospective and blinded study evaluated a novel story versus math fMRI task[27] for the purpose of predicting postsurgical verbal memory outcomes and its results are expected soon.

The progress in the last few years since the publication of the AAN guideline suggests that task fMRI may soon be able to reliably replace IAP in patients undergoing presurgical evaluation. However, we cannot forget that in addition to the task fMRI, new data collection and analysis methods are being developed. For example, one of the first functional connectivity and postsurgical outcome studies indicated that verbal memory task-related connectivity between hippocampus and cortical areas was higher in those who subsequently had worse verbal learning outcomes after surgical resection.[28] This and other connectivity studies, including resting state functional connectivity,[29,30] may further change the landscape of epilepsy presurgical evaluation in the future. However, we need to remain cognizant that while fMRI is noninvasive, is relatively inexpensive, and easy to implement and use, it has its own drawback: The available data are typically from small studies limited to a single center with center-specific fMRI tasks with very few multicenter studies being reported; studies are limited to highly cooperative temporal lobe epilepsy adult patients and very few relate to patients with lesions or extra-temporal lobe epilepsy; results may be analysis method and threshold dependent,[31] repeatability outside of the frontal areas has not been tested extensively and has been questioned,[2,32,33] and finally, the ability of fMRI to predict global amnesia has not been assessed to date.[24] We also need to remember that not all patients will be able to undergo fMRI—The ability to cooperate is important and dependent on the age of the patient and their cognitive status, and the presence of epilepsy-related (eg, VNS, RNS, DBS) and other hardware will preclude patients from receiving fMRI. Finally, some patients will fail fMRI or the results will be unexpected and will need verification—in these patients, the current standards—IAP and direct cortical mapping—will remain the mainstay of epilepsy presurgical evaluation.

By Jerzy P. Szaflarski
University of Alabama at Birmingham, USA

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