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Electrical Wada for Pre-Surgical Memory Testing - A Case Report

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Summary

We report a case study of a surgical candidate, a 51 year-old woman with left temporal lobe epilepsy, who failed a left injection intracarotid amobarbital procedure (e.g, Wada test) scoring 0 of 8 items. This raised concerns for postoperative memory decline. However, the patient was uninterested in a neuromodulatory approach and wished to be reconsidered for surgery. A stereotactic laser amygdalohippocampotomy (SLAH) was considered, encouraging the need for an alternative test for evaluating risk for memory decline. We developed a novel approach to testing memory during stimulation of a depth electrode implanted in the hippocampus, i.e., an *electric Wada*. During multiple stimulation trials across a range of amplitudes the patient scored up to 8 of 8 items, which suggested strong contralateral memory support. The surgical team proceeded with a radiofrequency ablation and a subsequent SLAH. The patient remains seizure-free at 12 months post SLAH with no evidence of verbal or visuospatial memory decline on a post-surgical neuropsychological battery. We believe that this case study provides a proof of concept of the feasibility and possible utility of an electric version of the Wada procedure. Future studies are needed to develop an optimal paradigm and to validate this approach.

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Introduction

Neurosurgical intervention is a first-line treatment for patients with refractory temporal lobe epilepsy (TLE)[1]. However, proceeding with surgery remains a complex decision for patients and clinicians, with risk of postoperative memory decline a major concern. After anterior temporal lobectomy (ATL), memory significantly declines in up to 60% of patients (1). Minimally-invasive surgical procedures, such as stereotactic laser amygdalohippocampotomy (SLAH), spares more of the temporal lobe resulting in a decreased risk to memory at a group level (2); however, as MTL structures are usually still targeted, risk is not completely mitigated. Reliable methods for assessing the risk of post-operative memory decline in individual patients remains a critical issue in decision-making.

The intracarotid amobarbital procedure (IAP), also known as Wada test, is often used preoperatively in North America (3) to determine risk of post-surgical memory impairment via the delivery of a briefly-acting barbiturate to one hemisphere at a time, via the internal carotid artery (ICA; 4). This transient impairment attempts to simulate the permanent effects of ablation or resection on post-operative brain function during memory testing (ICA-IAP). Particularly when employing newer minimally invasive surgical approaches, false-positives on the ICA-IAP (i.e., overestimating memory decline) risk keeping patients from life-improving treatment. Here we present the case of a patient who failed an ICA-IAP, presenting the risk of post-operative memory impairment. However, the patient's performance on memory testing carried out using electrical stimulation, through an implanted depth electrode along the long axis of the hippocampus, provided support for proceeding with surgery with successful memory and seizure outcomes post-surgically.

Case Report

A 51-year-old left-handed Hispanic woman with a history of febrile seizures presented with a 36-year history of intractable epilepsy, with near-daily focal seizures treated with lacosamide and lamotrigine, having failed prior appropriate trials of antiseizure medications. Her seizure semiology consisted of an aura of an epigastric rising sensation followed by behavioral arrest, staring, then manual and oral automatisms with rare progression to generalized convulsions. Scalp EEG revealed left anterior temporal epileptiform discharges and one seizure with left anterior temporal rhythmic theta activity at onset. MRI demonstrated unilateral left mesial temporal sclerosis (Figure 1A) and PET-CT showed hypometabolism broadly in the left temporal region. Neuropsychological testing, completed in Spanish, was consistent with general memory impairment (Table 1), which included impaired visual memory scores and impaired to mildly impaired verbal memory scores. Nonetheless, we were concerned for memory and functional declines following a destructive procedure involving the left temporal lobe and therefore performed ICA-IAP, with 0 of 8 items recalled with left injection. EEG during the ICA-IAP (Figure 1B) revealed lateralized, left hemispheric delta/theta slowing, maximal over the left centro-temporal region. Examination of the vasculature (Figure 1C) showed that the patient had a robust 'fetal' left posterior communicating artery; thus the left ICA injection of barbiturate likely affected not only the left ICA territory (including the hippocampal head and amygdala), but also the body and tail of the hippocampus. Radiographically, cross-filling of the contralateral

side was not present. Taken together, these data suggested that the ICA-IAP was valid. A posterior cerebral artery IAP was also attempted, but she was unable to tolerate this procedure due to physical discomfort and agitation, leaving no standard clinical method to clear the patient's medial temporal structures for surgery.

The patient was offered, and declined, a neuromodulatory therapeutic approach; rather she and her family pressed for a destructive surgical procedure. The clinical team considered a SLAH (i.e., a more spatially selective surgery) but the cognitive impact of this procedure in the setting of a failed ICA-IAP is unknown. We proposed the use of a neurostimulation-based memory test using a typical Wada test procedure, henceforth referred to as an 'electric-Wada'. Similar to the use of electrical stimulation mapping to assess risk of post-operative language impairment, we employed this model to test the contribution of the to-be-ablated hippocampal formation to memory. The patient's left hippocampus was implanted for the purposes of the electric-Wada using a single depth electrode along a longitudinal occipito-temporal trajectory with 10 contacts (Adtech RD10RSPO3X000; 8 contacts within the hippocampus; Figure 1D).

For the electric-Wada, we replicated the ICA-IAP memory procedure used at Emory University (4), but instead of a barbiturate injection, we simultaneously stimulated across the most anterior 8 electrode contacts, while the patient completed a memory test. A charge-balanced biphasic waveform was used with the anterior 8 contacts stimulated as four simultaneous adjacent bipolar pairs. This arrangement was chosen in preference to a monopolar reference, since a separate intracranial or extracranial location might have produced a risk of independent stimulation, pain, or distracting sensations. Stimulation parameters were similar to those that patients had tolerated well in prior studies and which have been shown to consistently disrupt memory (5,6).

As this was an exploratory clinical approach, we tested the patient's memory on more than one occasion using different levels of current. For each test, the patient was shown 8 individual real objects that she was told to remember (encoding phase). After approximately 15 minutes we tested the patient's recognition memory. Each electric-Wada test used a different set of objects. On the first day of testing (D1) we stimulated at 5 mA at 100 Hz with a pulse width of 500 μs; given that current was distributed to four pairs of contacts, the current was approximately 1.3 mA per contact pair (at this pulse width the safety limit of 30 $\mu C/cm^2$/phase is about 4 mA per pair). The patient's electric-Wada performance was normal, with 8 out of 8 items recognized, vastly superior to her ICA-IAP performance. We next attempted a higher amplitude charge (~2.5 mA per contact) with other stimulation parameters unchanged. During this procedure, the patient had a typical focal seizure with impaired awareness. We allowed the patient to recover for more than 30 minutes, and then attempted the procedure once more at an amplitude of ~2 mA. With these parameters, the patient produced a 6/8 item recognition score with no false positives. Two days later (D3), we continuously stimulated throughout the morning and afternoon at ~1.3 mA during which a final electric-Wada was performed. The patient again passed with a score of 8/8 object recognition with 1 false positive error. According to the patient and family, there were no reports of cognitive or functional problems experienced by the patient during this prolonged period of stimulation.

Based on this performance, as an additional safety measure, the epilepsy surgery team elected to perform a radiofrequency ablation (RFA) on D4 using the contacts of the implanted depth electrode, with the plan to follow with a SLAH if there was no impact on memory, assuming seizures remained uncontrolled. On D5, one day post-RFA, the patient was reassessed. The patient performed equivalently or better than her pre-surgical baseline on the Rey Auditory Verbal Learning Test with a normal learning score and low average recall of words after a delay (most of her scores had been impaired on this test at baseline). The patient's seizures recurred approximately 3 months post-RFA, as expected given the small lesions and extant literature (7). Therefore, left SLAH was performed 5 months post-RFA (Figure 1E). She has now been seizure-free for 12 months following the SLAH, and underwent a thorough neuropsychological battery at the 7-month post-SLAH time point (Table 1). The patient's performance was generally equivalent or significantly better than her baseline performance. Her mood also improved on a self-report measure from severely depressed to mildly depressed (Beck Depression Inventory declined from 51 to 13).

Discussion

Risk for cognitive decline poses a barrier to the expansion of surgery in epilepsy treatment, with the number of epilepsy surgeries remaining stagnant despite an increasing pre-surgical volume of patients (8). Surgery can be more cost effective than medical management (9), may be protective against progressive brain atrophy in temporal lobe epilepsy (10), and in many patients is associated with improved quality of life and functional outcomes (11). Here we report the case of a patient who would not have proceeded to surgery based on her memory performance during an ICA-IAP; however, when tested with an electric-Wada, she was cleared for surgery, with a favorable seizure and cognitive outcome. The extant research on the ICA-IAP evaluation has been in the context of larger open resection surgical procedures (e.g., ATL), rather than more selective approaches (e.g., SLAH) in which the anatomical region affected by the injection is mismatched to subsequent destructive procedures. Therefore, developing and validating techniques to more precisely estimate risk for memory decline following highly targeted surgeries (12) could make a considerable impact on clinical care.

There is currently no consensus regarding how to best predict post-surgical cognitive outcomes. In 1993, 85% of centers worldwide reported using the IAP for nearly every patient; however, by 2008 these numbers had decreased significantly (3). The decreasing use of the ICA-IAP test is due in part to concerns over its low ability to predict memory decline (13). Nevertheless, the ICA-IAP procedure usage remains higher in North America (3), particularly in cases where there is generalized dysfunction or discordant neuropsychological findings, which may indicate an increased risk of a poor memory outcome. Alternatives include cognitive mapping via fMRI (14), but fMRI provides only an indirect measure of regions involved in a cognitive process, not a measure of the necessity of any one region (15). We have found that operating on patients who have failed IAPs can lead to impaired functional outcomes when results have been ignored due to other extenuating circumstances considered in the risk-benefit matrix (e.g., high risk of SUDEP; 16). Features of this case, such as the presence of both visual and verbal memory deficits, suggested the potential for a pattern of bilateral hippocampal dysfunction and in the presence of a failed

ICA-IAP called into question the reserve capacity of the contralateral hippocampus. These complexities highlight the potential for an electric Wada to help more fully characterize this risk at a single-patient level as part of a move toward precision medicine (17).

Utilizing neurostimulation to simulate post-surgical neural function will require advances in our understanding of how neurostimulation affects the brain. Depending on various factors, brain stimulation has been shown to both facilitate (18) and disrupt memory (6). This heterogeneity of outcomes may be one reason stimulation has not yet been translated for clinical use in testing cognition. The key question is *what stimulation parameters and protocols are needed to achieve the highest spatial precision, reliably disrupt memory, and maintain safety for the patient*? Parallel literatures explore the spread of stimulation-evoked activity in the brain (19), the effects of neurostimulation on more focal neural activity (5), and the safety of stimulation parameters (20). A critical consideration for patient safety is that stimulation in certain frequencies (e.g. 50Hz) or with too large an amplitude may elicit seizures, as occurred with our patient. Ideally, a multi-channel stimulator and continuous recording from the same contacts should be used to better titrate stimulation. A single electrode approach may not be best, with the potential that additional sampling outside the hippocampus proper, as with typical orthogonal SEEG exploration of the temporal lobe, will help avoid the risk of false positive when seizure activity or after-discharges involve temporal networks beyond the hippocampal formation. Conversely, we do not yet fully understand what stimulation parameters and protocols best achieve true functional disruption that can act as a surrogate for and therefore faithfully predict the outcomes of destructive procedures such as SLAH. In addition to stimulation parameter considerations, cognitive neuroscience considerations are important, as the effect of stimulation on memory is modified by factors such as patient encoding state (21) as well as anatomical location of the stimulation (e.g., grey versus white matter; 22).

In the current case, because of our present incomplete understanding of this relationship, we interposed a limited destructive procedure using radiofrequency ablation through the depth electrode, which also had no effect on memory in part validating the electrical stimulation results. As each patient case is unique, additional case series and a larger cohort will be necessary to ascertain the generalizability of this positive outcome for the electric Wada. This case may be an example of a false-positive Wada, related to the wide spatial distribution of anesthetic and its mismatch to the planned targeted surgical procedure (23). Finally, it will be important to understand the potential complementary nature of the electric-Wada to existing alternatives to the ICA-IAP such as fMRI (14) and nomograms (24). Given the urgent need for accurate prediction of memory outcomes post-surgically to guide the matching of individual patients to the optimal treatment, this translational combination of stimulation and memory testing presents an attractive and promising opportunity.

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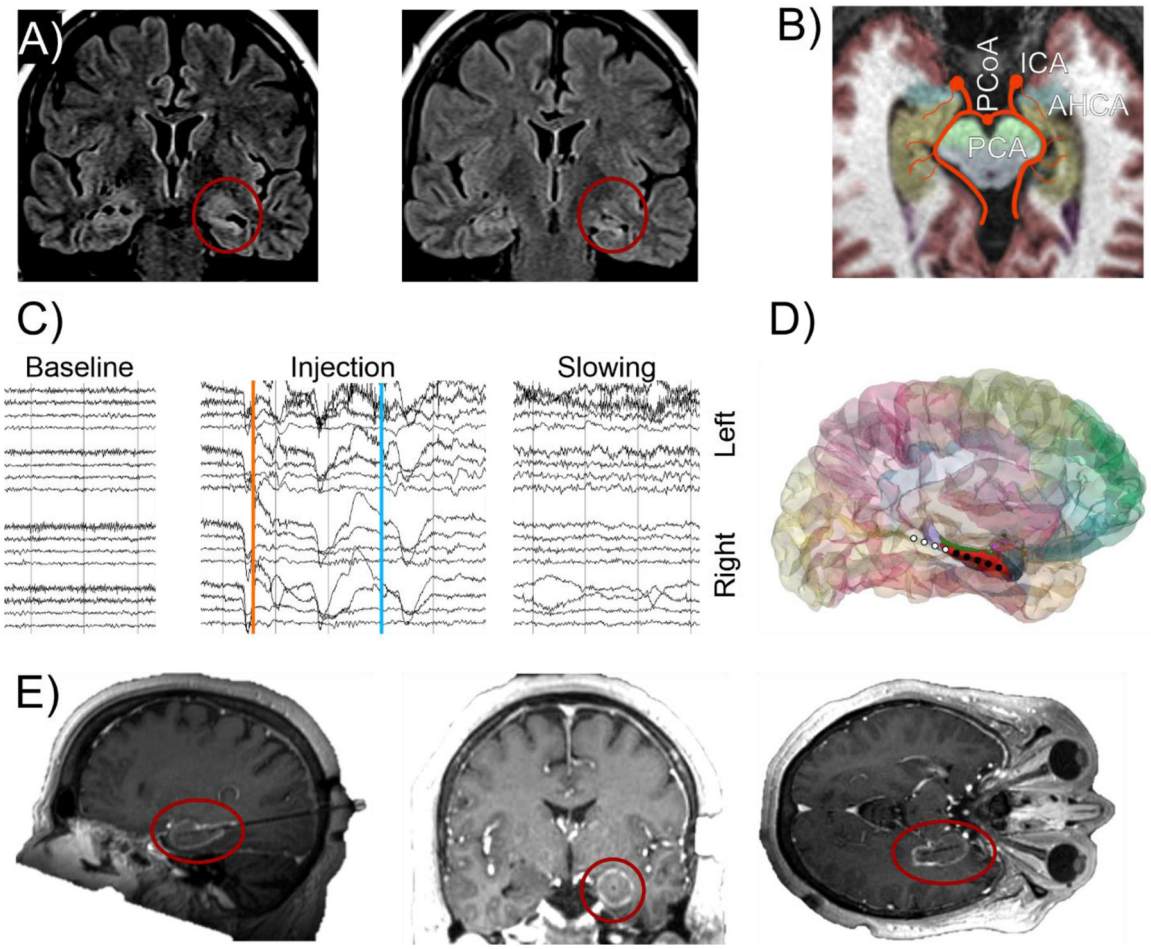

Figure 1. Patient neuroimaging, electrophysiology, and vasculature.

A) Coronal FLAIR image (radiologic convention) demonstrating findings of left mesial temporal sclerosis (red circle). **B)** During the ICA-IAP the electrophysiology showed left hemisphere slowing during left ICA injection, evidence that the ICA-IAP had its intended effect. The three traces come from a baseline period, the injection period with the orange line denoting the injection and the blue line note the onset of slowing, and a post-injection period showing marked left-sided slowing. **C)** Diagram of the vascular supply in this patient shows that the AChA (arising from the ICA) supplies the amygdala (cyan) and hippocampal head, while PCA branches supply the hippocampal body and tail. A left ICA injection of barbiturates, with spill over into the PCA across the robust PCoA, would be expected to anesthetize this patient's entire hippocampus (yellow). **D)** The electrode implanted in the left hippocampus for the purpose of performing an electric-Wada. Black circles denote electrodes in the hippocampus, white circles highlight additional (non-stimulated) electrodes. **E)** The extent of laser ablation as demonstrated by region of peripheral enhancement on this T1-w post-contrast image (red circle).

Table 1.

Pre- and Post-surgical neuropsych evaluation.

Test Name	Pre-Surgical Evaluation	Post-Surgical Evaluation
Language Measures		
Ponton-Satz Boston Naming Test	Raw=18/30, T=34	Raw=22/30, T=48
FAS Total (Letter Fluency)	Raw=14, T=31	Raw=33, T=58
Semantic Fluency (animals)	Raw=12, T=41	Raw=18, T=54
Attention		
RBANS Digit Span	Raw=9, T=53	Raw=10, T=57
Visuo-Perceptual, Visual-Spatial		
Rey Complex Figure Test Copy	Raw=22, T=19	Raw=32, T=42
Learning and Memory		
Auditory/Verbal Memory		
Rey Auditory Verbal Learning Test (RAVLT)		
RAVLT – Trial 1	Raw=5, T=40	Raw=7, T=47
RAVLT – Trial 5	Raw=8, T=24	Raw=9, T=32
RAVLT – 5-Trial Total	Raw=33, T=25	Raw=41, T=41
RAVLT – Immediate Recall	Raw=3, T=31	Raw=3, T=31
RAVLT – Delayed Recall	Raw=5, T=34	Raw=6, T=37
RAVLT – Recognition Hits	Raw=13/15	Raw=12/15
RBANS Story Memory	Raw=6, T=31	Raw=9, T=37
RBANS Story Recall	Raw=1, T=20	Raw=4, T=40
Visual Memory		
Rey Complex Figure Test – RCFT		
RCFT – Delayed Recall	Raw=6/36.0, T=20	Raw=10.5/36.0, T=31
RCFT – Recognition Recall	Raw=16/24, T=20	Raw=14/24, T=20
RBANS Figure Recall	N/A	Raw=9, T=40
Emotional Function		
Beck Depression Inventory – 2nd Edition	Raw=51, Severe	Raw=13, Mild