The Wada test in the evaluation for epilepsy surgery

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ABSTRACT

The Wada test is the standard part of the pre-operative evaluation for epilepsy surgery. The procedure involves the slow injection of sodium amobarbital (typically 100-150mg) into the internal carotid artery following a transfemoral approach. The amobarbital anesthetizes the anterior two-thirds of the ipsilateral cerebral hemisphere for approximately 5-10 minutes. During this period of hemispheric anesthesia, assessment of expressive and receptive language can establish cerebral language representation. In addition, the procedure provides a reversible model to assess the risk of significant memory change following surgery. This is important because patients undergoing surgery involving the temporal lobe may experience significant memory decline following surgical resection of a temporal lobe seizure focus. This paper will present information about the use of Wada testing, and discuss issues involved in establishing cerebral language representation, lateralization of temporal lobe dysfunction, seizure and memory outcome prediction, and future directions of this technique.

Keywords: Language, memory, epilepsy surgery, temporal lobectomy, outcome.

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The Wada test is an accepted portion of the pre-operative evaluation for epilepsy surgery, and is considered the "gold standard" for establishing cerebral language dominance. The Wada procedure involves pharmacologically inactivating the cortex within one cerebral hemisphere for several minutes, during which time the patient is presented with multiple language and other cognitive tasks. Memory testing performed as a part of the Wada procedure is used to determine risk for post-operative memory decline. Wada memory scores may confirm seizure onset laterality, which may decrease the need for more invasive monitoring procedures, and can be used to predict seizure outcome following surgery.

The Wada procedure is non-standardized, and the goals are emphasized to different degrees at various epilepsy surgery centers. At some institutions, all epilepsy surgery candidates undergo Wada testing whereas other centers limit the procedure to those patients who are suspected of having anomalous language representation or are thought to be at risk for significant memory decline. In this review, we will provide an overview of Wada testing in patients undergoing evaluation for epilepsy surgery of the temporal lobe.

Language testing. The first attempt to pharmacologically inactivate cerebral language regions was made by Gardiner, who injected procaine directly into the cerebral cortex in two left-handed patients in an attempt to determine cerebral language representation in the cortical area to be resected. Wada later employed intracarotid amobarbital injection using a direct carotid stick to lateralize language. Interestingly, Wada's initial application of this technique was not with epilepsy surgery candidates, but rather was performed to establish language in patients undergoing electroconvulsive treatment so that stimulation could be applied to the non-language dominant hemisphere.2,3 Wada later applied this procedure to
epilepsy surgery candidates while he was a Rockefeller Fellow at the Montreal Neurologic Institute. There, with other pioneers in epilepsy surgery including Wilder Penfield, Herbert Jasper, and Brenda Milner, many of the advances in the development of functional brain measures were developed (e.g., stimulation mapping, neuropsychological testing) that continue to influence the evaluation and selection of patients for epilepsy surgery.

Establishing cerebral language dominance is based on clinical observation during a period of hemispheric anesthetia. The language dominant hemisphere injection is typically identified by the presence of global aphasia immediately following injection, with recognizable patterns of aphasia and progressive language recovery as the medication effects recede. Complete recovery of language function is generally present within 10 minutes following injection when employing amobarbital doses of 125mg or less.

Because the Wada test in a non-standardized procedure, there is considerable variability in the criteria employed to infer the presence of language. One survey reported that the percentage of "mixed speech dominance" varied between 0% and 60%. Object naming is used to assess language in the dominant hemisphere at most epilepsy surgery centers (93%). Other common measures of language include non-specified aphasic signs, counting ability, and word/phrase repetition. When testing the non-dominant hemisphere, however, criteria that are more heterogeneous are used to infer the presence of some language. Language assessment of the non-dominant hemisphere may include mouthing appropriately, groaning, singing, object naming, partial phoneme vocalization, serial rote speech, and expression of familiar words. Thus, it is not surprising to see such a wide range in "mixed speech dominance."

In one Wada series that we performed at the Medical College of Georgia, only two of 103 patients had exclusive right hemisphere language. Of the 22 patients with bilateral language, language was asymmetrically represented in 17 (13 L>R, 4 R>L). Exclusive right hemisphere language therefore seems to be relatively rare, a finding that has been supported by functional magnetic resonance imaging (fMRI) studies. Language representation, therefore, should be considered as a continuous rather than dichotomous variable.

Other studies highlight how different results may be reported based upon subject inclusion criteria or definition of linguistic impairment. In one study, 87% of right-handed and 62% of left-handed patients had left cerebral language dominance. In another report, 82% of right-handed patients were left language dominant, but only 30% of 30 left-handed patients were left language dominant. The contrasting results of left hemisphere language dominance in non-dextral patients highlight the difficulty when comparing results across studies - these differences may result from variations in patient inclusion characteristics (i.e. number of non-temporal surgical candidates) or may simply reflect classification differences. However, both reports indicated that right hemisphere language dominance is associated with early onset of seizures, injury, or lesion in the left hemisphere.

Bilateral language representation suggests less risk of language morbidity following resection involving functional language cortex. Consequently, definitions of language impairment have important patient care implications. In addition, the lateralizing value of neuropsychological testing may be altered when patients do not show a pattern of typical left cerebral language dominance. The effect of atypical language on neuropsychological test results is unclear, and there are no pathognomonic indicators of typical speech in standard neuropsychological test batteries. The literature on "crossed aphasia" (e.g., aphasia following acquired right hemisphere lesion in right-handed patients) suggests that situs inversus, or complete mirror representation of language and spatial dominance, can occur. However, it is rare. Crowding is the phenomenon of early left cerebral damage resulting in a transfer of language to the right brain but at the expense of spatial abilities. This literature, which may be more relevant to developmental or chronic disorders such as epilepsy, suggests that the effects of atypical language representation can be either global or limited, with magnitude of the lesion exerting a significant influence on other neuropsychological functions.

Wada testing will be used as a cornerstone to establish the validity of newer language techniques involving fMRI and magnetoencephalography (MEG). The variability in the definition of bilateral language associated with fMRI or MEG will pose the same validity threats to the newer procedures as with Wada testing itself. Further, the difference among centers in fMRI methodology (e.g., tasks, head coils, software analysis packages, thresholds, shimming) are likely greater than the differences in Wada methodology across centers. Functional MRI has also been used to investigate the validity of different aspects of language assessment commonly performed during the Wada, and has demonstrated that speech arrest, by itself, is a poor measure of language laterality. The literature indicates good concordance in samples that are unambiguously dominant. The agreement is not 100%, however, and there are reports of ambiguous or incorrectly lateralized language using fMRI.

Wada memory. Memory evaluation was introduced into the Wada test to predict whether the
hemisphere contralateral to a unilateral seizure focus can sustain memory function following temporal lobectomy. Milner hypothesized that the transient pharmacological effects of amobarbital on the temporal lobe ipsilateral to surgery would provide a model to predict memory outcome. If the patient could remember information presented during the period of hemispheric anesthesia, it could be inferred that the contralateral hemisphere had sufficient capacity of support memory, and thus, a severe post-operative amnesia would be avoided. When adequate recall cannot be demonstrated, the patient is considered at risk for significant memory impairment. Therefore, the patient may be excluded from further consideration as a surgical candidate, a more limited resection may be performed that spares the hippocampal zone, or additional testing may be performed to demonstrate adequate memory function.

The Wada testing has been criticized because the distribution of the intracarotid injection does not usually perfuse the hippocampus. However, depth recorded electroencephalogram slowing occurs in this region following intracarotid amobarbital administration. Single photon emission computed tomography (SPECT) studies performed at the time of amobarbital injection have demonstrated reduced regional cerebral blood flow (rCBF) to medial temporal structures in the majority of patients. Wada memory performance has also been associated with hippocampal cell counts, hippocampal sclerosis and MRI hippocampal volumes. Thus, there is a structural and functional relationship between Wada memory and the hippocampus.

Another method of validating the Wada memory test is the positive predictive value of post-operative memory outcome. Criteria related validity, however, cannot be established on a statistical basis since Wada memory performance is a criterion that affects surgical decision making, and hence, the independent and dependent variables are confounded. If the test is used to predict this outcome and avoid it, then there will be few instances in which the procedure will be undertaken when the predictor is positive. Nonetheless, one survey identified six patients who failed the Wada memory test (i.e., failed to recall events following injection of the hemisphere ipsilateral to subsequent surgery) and went on to demonstrate an amnestic syndrome following unilateral temporal lobectomy. There are also reports of false negatives, however, in which patients pass Wada memory testing and develop amnestic syndromes. Thus, the sensitivity and specificity of the procedure for accurately predicting the possibility of amnesia following temporal lobectomy may be determined by careful interpretation of additional clinical factors.

The interpretation of Wada memory testing has evolved to include prediction of lateralized cognitive dysfunction that is associated with a primary seizure focus. Asymmetry in the hemispheric memory scores shows a strong relationship to side of seizure onset in patients with temporal lobe epilepsy. In patients with other clinical data that is suggestive of unilateral onset but not conclusive, definite Wada memory test asymmetry may eliminate the need for invasive monitoring before surgery. In seizure onsets outside the temporal lobe, Wada memory asymmetries occur less frequently, but when they do occur are also predictive of side of seizure onset.

Patients are more likely to have poor memory performance following injection contralateral to a seizure focus if significant hippocampal sclerosis exists. This relationship presumably results from greater bilateral temporal lobe dysfunction associated with the injection. Minimal functional capacity is associated with severely sclerotic hippocampus consequently, contralateral amobarbital perfusion creates greater bilateral dysfunction with “failed” memory for the events following the injection. In contrast, injection of the hemisphere ipsilateral to the sclerotic hippocampus creates no additional functional deficit.

Not all patients with temporal lobe epilepsy “fail” the memory test following injection contralateral to the suspected seizure focus. Patients with mild sclerosis may demonstrate some memory impairment, but not complete failure, for events immediately following the injection. Again, presumably the functional capacity of the mildly sclerotic hippocampus is impaired, but still adequate to support some memory. The result is an asymmetry favoring the “normal” hippocampus, but without unilateral failure. Consequently, it is not necessary to demonstrate memory failure following one injection to confidently interpret memory asymmetry as reflecting unilateral seizure onset. The degree of asymmetry necessary for interpretation is dependent on the technique for testing memory.

### Predicting outcome. Memory outcome.

Wada memory performance is related to post-operative verbal memory performance. Patients with symmetrical Wada memory scores tend to be more likely to demonstrate a decline on laboratory measures of verbal memory following left temporal lobectomy. In contrast, patients with Wada memory asymmetry suggesting left unilateral temporal lobe impairment do not show similar declines in verbal memory following left temporal lobectomy. The picture is less clear concerning Wada memory test performance and right temporal lobectomy. As with other studies of memory outcome following right temporal lobectomy, no consistent relationship has been found between Wada memory test performance and visual-spatial memory. However, this may not necessarily be a reflection of adequacy of the Wada
memory test as it is a reflection of the criterion we are using to measure visual-spatial memory following right temporal lobectomy. If there is no clear relationship between right temporal lobectomy and visual-spatial memory outcome, it would be virtually impossible to predict this relationship using the Wada memory test, regardless of its efficacy.

The degree of memory decline depends upon both the functional status of the ipsilateral hippocampus/temporal lobe that will be included in the resection (functional adequacy) and on the functional status of the temporal lobe contralateral to the surgery that will be relied upon for the formation of new memory (functional reserve). When tissue that is still functionally contributing to memory formation is included in surgery, then there is a decline in memory performance associated with the resection of the functional tissue. Thus, the functional adequacy of the tissue to be resected is related to the type of memory changes observed post-operatively.

Patients undergoing anterior temporal lobectomy (ATL) are at risk for post-operative amnesia if the mesial temporal lobe contralateral to the surgery, which will be relied on during the formation of new memories, is diseased and non-functional. That is, temporal lobe impairment contralateral to the surgery suggests insufficient functional reserve to sustain new memory. Consequently, patients with impaired verbal and non-verbal memory may be considered to be at risk for memory decline since the global memory impairment may suggest bilateral temporal lobe dysfunction. Similarly, patients with a material-specific memory asymmetry in the direction opposite that which would be expected (e.g., material specific verbal memory impairment with right temporal seizure onset) raise the possibility of inadequate functional reserve contralateral to the planned surgery.

In one patient series at the Medical College of Georgia, patients who were seizure free at one year had larger verbal memory decline after left ATL for both word list learning (Verbal Selective Reminding Test) and prose passage recall (Wechsler memory scale revised (WMS-R) logical memory test) if they had smaller pre-operative Wada memory asymmetries. The predictive value of Wada memory asymmetry was present for both group data and for individual patients. Unilateral Wada memory scores following left hemisphere injection were not related to memory change. Thus, the hippocampus included in the resection and the one contralateral appears to be contributing to memory outcome prediction. Similar findings have been reported; left ATL patients who performed adequately following injection contralateral to the side of seizure onset displayed greater post-operative decline in the WMS-R verbal memory index and on Logical Memory. As with the sample at our center, no relationship between Wada memory and change in non-verbal memory following right ATL was observed. Thus, measurement of the interaction of both the temporal lobe to be resected and the temporal lobe contralateral to the resection appear necessary to accurately predict post-operative material-specific memory change.

Seizure outcome. Evidence of well lateralized temporal lobe dysfunction increases the likelihood of a good surgical outcome. Patients with significant volumetric MRI hippocampal asymmetries are more likely to have a good outcome following temporal lobectomy (Loring 1994 #5239; Sperling 1994 #10842; Perrine 1995 #10848). Since the presence of hippocampal atrophy is related to post-operative seizure frequency, and because Wada memory asymmetries are related to MRI hippocampal volume asymmetries, the association between Wada memory and seizure outcome would be anticipated. In one study, 89% of patients with Wada memory asymmetries were seizure free at one year follow-up. In contrast, only 63% of the patients without asymmetries were seizure free. In a study from the Cleveland Clinic, asymmetric Wada memory was reported to be highly specific but less sensitive for predicting seizure outcome following temporal lobectomy.

Future directions. Functional magnetic resonance imaging, holds promise as a non-invasive alternative to Wada language and memory testing. The potential advantages of fMRI include the localization, not simply the lateralization, of language distribution, avoidance of possible complications of Wada testing that are associated with the invasive angiography, minimizing or eliminating the need for subdural grid or intra-operative mapping of language, and exploration of other cognitive functions in relation to language during a single imaging session.

However, there are significant differences in the way in which fMRI and Wada information are obtained. Functional MRI relies on cognitive task, analogous to traditional neuropsychological testing, and requiring proper patient motivation and cooperation. Based upon imaging of activated brain regions during task performance compared with resting and control states, inferences about brain structures contributing to task performance are made. All regions in the network involved in successful task performance, either directly or indirectly, should show some degree of activation. However, since activity relative to a control state is measured, proper control for factors extraneous to the critical function is imperative. Even when the most rigorous control tasks are used, there is still the risk of attributing function to areas that are active in but not critical to a particular task performance.

The Wada test and fMRI results also answer a different question. Functional MRI is an activation procedure. In contrast, the Wada test is a deactivation procedure. Functional MRI is an
activation procedure. Brain regions are temporarily inactivated by perfusion of amobarbital, and the effects of drug inactivation on cognitive performance are assessed. Wada testing addresses the question of whether these tasks can be performed without the contribution of the affected brain regions. Although a region may be involved in task performance under ordinary circumstances, this region may not be necessary for task performance. Thus, Wada testing potentially provides a more appropriate technique to model the effects of surgery on post-operative cognitive function. In addition, the Wada test may be more appropriate for some patients that may be unable to reliably perform an activation procedure while remaining still (e.g., anxiety when placed in the MRI apparatus, patients with limited cognitive resources or attention problems).

Current studies of concordance between fMRI language mapping and Wada language results generally support the validity of fMRI language activation techniques. Reliable activation of expressive language areas, receptive language areas, and systems involved in reading have been identified. Furthermore, studies of normal volunteers have generally reported prevalence of atypical speech that is consistent with estimates based on the Wada test. However, in epilepsy patient populations, the concordance with Wada language results is not 100%11, and there are some reports of erroneous lateralization in patients, indicating that further study is needed.

There are both technical and theoretical issues to overcome when imaging memory for purposes of surgical planning. Although there are some recent reports of activation during retrieval tasks, imaging of encoding processes using fMRI is limited, with few reports of consistent, localized hippocampal activation. Since the hippocampus is critical for encoding and consolidation of memory, this is obviously an area for further work. There are currently no studies that report on concordance of fMRI with Wada test results, or studies that use fMRI to predict memory outcome following temporal lobectomy.

Summary and conclusions. Wada testing of language and memory continues to play a critical role in the evaluation of epilepsy surgery patients. In many patients, Wada testing measures functional deficits associated with known cerebral lesions, contributes to establishing laterality of seizure onset, and provides some estimate of the risk to memory following temporal lobectomy. There will continue to be procedural refinement based upon correlations with MRI volumetry, fMRI, and MR spectroscopy. More importantly, prediction of long-term cognitive outcome and seizure control is possible with the Wada test, and in conjunction with other neurological, functional, and psychometric assessment, facilitates selection of patients most likely to benefit from surgical treatment of epilepsy. Eventually, non-invasive measures of brain function, including fMRI will provide much of the same information as that derived from Wada testing. However, it remains to be established if a procedure that relies on activation can provide comparable date to the Wada test, which may provide a more accurate reversible model of the effects of surgery on cognition. Ideally, advances in fMRI and other imaging techniques will provide a complementary picture that proves on our ability to predict and avoid significant post-operative cognitive deficits.

References


