Leading Article

Pre-surgical evaluation for epilepsy surgery

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ABSTRACT

Neuropsychological testing may reflect subtle structural changes that may not be readily apparent with neuroimaging studies, and physiologic disruption of normal neural function secondary to epileptic activity. Neuropsychological testing is used during the pre-operative evaluation for epilepsy surgery to assess functional brain status, which, in turn, provides important information on the risks for post-operative neruopsychological deficits and also provides confirmatory evidence of seizure onset laterality in patients whose seizures originate in temporal lobes. This review will focus primarily on the pre-operative neuropsychological of candidates for temporal lobectomy surgery since they represent the majority of individuals undergoing ablative epilepsy surgery, and also because the literature and knowledge for the neuropsychology of temporal lobectomy far exceeds that of any other epilepsy surgical group.

Keywords: Neuropsychology, memory, Wada testing, temporal lobe epilepsy, surgical outcome.

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The medial temporal lobe, which includes the hippocampus, is a critical region in the formation of new memory. When hippocampal function is impaired, memory acquisition may rely on other brain structures, although memory is often not at the same levels compared to subjects without temporal lobe pathology. Further, repetitive seizures and interictal discharges may impair memory since they disrupt normal neuronal function of the brain including the temporal lobes. Because the hippocampus associated with a unilateral seizure onset is largely dysfunctional, and because seizures are typically improved or eliminated following surgery, anterior temporal lobectomy (ATL) does not typically worsen memory significantly and, in fact, memory may improve due to the reduction of seizures and the discontinuation of anti-epileptic medication. However, an amnestic syndrome may be created by unilateral temporal lobectomy if contralateral medical temporal dysfunction exists.[1] Although less severe than amnesia, a significant decline in material-specific memory may be present if the hippocampus included in the resection is still sufficiently functional to actively contribute to memory formation. In these cases, a material-specific verbal memory decline following left ATL that may be apparent and may limit vocational options. One goal of neuropsychological assessment, therefore, is the identification of patients who are at risk for significant post-operative memory decline, and this remains an important aspect of the pre-operative evaluation.

Strong material specific memory asymmetries obtained during pre-operative neuropsychological testing confirm seizure onset laterality in selected patients whose evaluations for localization have been suggestive but inconclusive.[1,2] In these cases, the need for invasive monitoring before surgery may be decreased. Although not a primary role of neurophsychological testing, neuropsychological results may provide information regarding the likelihood of becoming seizure free following surgery. Finally, as in patients with other neurologic disorders, neuropsychological assessment in epilepsy

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surgery candidates may identify psychiatric disorders and direct vocational rehabilitation.

Pre-operative neuropsychological assessment. Prior to the development of current structural imaging such as magnetic resonance imaging (MRI), and functional imaging techniques such as positron emission tomography (PET), single photon emission tomography (SPECT), and functional magnetic resonance imaging (fMRI), the goal of pre-operative neuropsychological testing was to identify patients at risk for significant post-operative memory impairment due to bilateral mesial temporal lobe dysfunction. Based upon neuropsychological testing and Wada memory results, patients could be excluded from surgery if the risk to post-operative memory function was thought to be too great. The developments and refinements in brain imaging have provided additional tools with which to evaluate risk for post-operative memory decline, and the emphasis of neuropsychology is now a more generalized assessment of functional status although the goal of assessing focal impairments has not been abandoned. Measurement of functional status is then used for making probabilistic predictions of behavior change. Although neuropsychology is based upon established brain-behavior relationships to measure functional status, neuropsychology does not identify cognitive profiles uniquely associated with specific etiologic brain changes. It plays a limited role in epilepsy diagnosis, which is primarily EEG based with appropriate clinical history, and instead provides results that are "consistent with" rather than "diagnostic of" a specific disease process.

Patients undergoing evaluation for epilepsy surgery typically receive neuropsychological evaluation pre and post-operatively. Differences in test selection exist among neuropsychologists and among centers, and differences also exist in what aspects of the evaluation are emphasized in any given epilepsy surgery program. However, most neuropsychology batteries typically include a combination of tests designed to assess intelligence, memory, language, visual-spatial functions, attention, sensory and motor function, and applied problem solving strategies. Personality, emotion, and quality of life are also frequently assessed.

Full scale IQ may be considered when evaluating a patient for epilepsy surgery since low IQs may reflect general impairment in which focal resection is less likely to be beneficial. Patients with generalized or multifocal areas of dysfunction have poorer post-operative seizure control although some mixed results have been reported.[3] Nonlateralized neuropsychological findings occur more frequently in poor outcome groups[4]; however, the concordance of the side of seizure onset and laterality of neuropsychological findings is not necessarily related to outcome.[5] Comparison of verbal IQ to performance IQ sometimes provides a suggestion of lateralized cerebral impairment in other neurologic populations, but the use of these measures in epilepsy surgery candidates is not generally informative.[6] For patients with baseline IQ scores of 75 and below, the odds of becoming seizure free following surgery were approximately 2:1.[7] These odds increased to 3:1 among patients with IQ scores of 76-109, and were 4:1 among patients with "high average" IQ scores and above. However, full scale IQ alone is rarely sufficient by itself to exclude an otherwise good candidate from surgery. Age of seizure onset is a predictor of full scale IQ, although seizure laterality and cerebral language are also related.

It is interesting to note that use of neuropsychological data to predict post-surgical outcome following ATL is in patients with suboptimal findings who are expected to have a lower likelihood of good seizure outcome.[8] In cases with other consistent clinical findings, a group with an already high base rate of surgical success, neuropsychological test results may actually reduce predictive accuracy.

In the evaluation for anterior temporal lobectomy, neuropsychology continues to emphasize memory function. Although the hippocampus is at times discussed as the only critical temporal lobe structure contributing to memory, it does not work in isolated and is part of a network for memory acquisition that also involves neocortex.[9] The relationships between left and medial temporal lobe and verbal memory and between the right medial temporal lobe and visual/ non-verbal memory are well known.[10,11] Patients with left temporal seizure onset tend to perform more poorly on verbal memory measures whereas patients whose seizures arise in the right temporal lobe tend to perform more poorly on non-verbal memory tasks. The relationship between right temporal lobe function and visual memory, however, is much more variable and the inference to right temporal lobe dysfunction is necessarily less reliable.[12,13]

The association between verbal memory and the left temporal lobe and hippocampus is robust and has been confirmed by different institutions with different approaches. Neuron loss and MRI volume of the left temporal lobe and hippocampus has been associated with pre-operative verbal memory performance.[14,15] Common tests of verbal memory include word list learning, paired-associated learning, and memory for short story passages.[16,18] Non-verbal memory may assess memory for simple geometric designs, complex geometric designs, or faces.[12,18-21] Most often, immediate and delayed memory of approximately 30 minutes is obtained.

Patients with strongly lateralized material-specific memory asymmetries in the direction opposite of that which would be expected based upon clinical seizure variables (e.g. normal verbal memory with impaired visual memory in a patient with left seizure onset) are generally considered to be at greater risk for memory decline compared to a patient with a memory asymmetry consistent with the side of seizure focus

(e.g. left seizure onset with impaired verbal and normal visual memory). Material-specific memory asymmetries inconsistent with laterality of seizure onset suggest that contralateral functional impairment exists which is not reflected in other studies. Attempts at large-scale replication of reported visuospatial memory deficits and right ATL have been unable to reliably reproduce selective visuospatial memory impairment, and visuospatial memory impairments may be impaired in patients with left temporal seizure onset and normal in right temporal lobe seizure patients. Thus, visuospatial memory performance alone does not typically play a prominent role in assessing risk for post-operative memory decline although reports continue to report selective visual memory deficits associated with right temporal lobe impairment.[22]

Language testing usually includes measures of naming, fluency, reading, writing, repetition, and comprehension. In general, most basic language functions are preserved, with patients able to understand and execute basic language tasks. However, the ability to generate words on command may be affected by a variety of epilepsy-related variables since this task is time based.

In addition, the ability to name may be impaired in patients with seizures from the language dominant hemisphere, and it has been suggested that many of the verbal memory deficits described following left anterior temporal lobectomy may in fact reflect naming impairment.[23,24] The distinction between the two is important on an applied basis. Often times, patients will complain of having a memory deficit when they cannot "remember" names. Thus, patient histories will be biased based upon the vocabularies parients use to describe their deficits.

Many complex partial seizures arise in lateral, orbital, or medial frontal regions. However, neuropsychological correlation to deficits associated with frontal seizure onset is not only less well lateralized compared with memory deficits in TLE, but also is less well localized to the frontal lobes. For example, a common measure used to assess frontal lobe function is the Wisconsin Card Sorting Test (WCST). However, WCST performance may be decreased in patients with post-central lesions and may be normal in certain cases of confirmed frontal lobe pathology.[25] Further, WCST deficits may be present both in patients with temporal lobe seizure onset and in patients with frontal seizure onset.[26] Generative fluency tasks are also commonly used as measures of frontal lobe function, and preliminary evidence has been presented to suggest the utility of comparing word generation to figure generation in discriminating left from right frontal seizure patients.[27] However, its prospective application for individual patient prediction is not universally agreed upon.[28] Neuropsychological testing in other non-temporal seizure patients is used primarily to establish whether anticipated cognitive deficits in those areas are present and is not typically employed for prognostic purposes.

Personality and psychosocial function. Neuropsychological testing of epilepsy surgery candidates not only consists of examination of cognitive abilities, but also includes assessment of personality and psychosocial status. Personality and psychiatric factors are viewed by some epilepsy centers as contraindications to surgery, with the presence of serious psychopathology such as severe psychosis or severe depression, personality disorders, or frequently non-epileptic seizures decreasing the likelihood of surgical intervention.[29] Patients are rejected from surgery due to perceived risk for post-operative psychiatric deterioration, difficulty in patient management during evaluation and treatment, and the potential need for extensive resources and intervention during post-operative care. However, other centers do not consider there to be any psychiatric contraindication. The disparity in views may be due to the differences in patient population in patient management. A well-controlled, large-scale study of psychiatric morbidity is needed to resolve this issue.

The neuropsychological evaluation for epilepsy surgery may also involve the assessment of psychosocial status, including mood and the patient's perception of his quality of life. Although cognitive abilities and psychological adjustment interact, with poorer adjustment present in patients with greater cognitive impairnents, there is still a large area of independence between cognition and quality of life. Increasingly, psychosocial factors and quality of life are considered in the evaluation for epilepsy surgery. Fraser reported that 40% of job failures in epilepsy were due to emotional/attitudinal problems. The most commonly employed measure of personality is the Minnesota Multiphasic Personality Inventory (MMPI-2). Examples of psychosocial and quality of life measures include the Washington Psychosocial Seizure Inventory[30] and the Quality-of-Life in Epilepsy Inventory.[31] Evaluating psychosocial status, including mood and the patient's perception of his quality of life, offers unique information that is largely independent of cognitive ability.[32,34]

The Wada test and effects of atypical language. The Wada test is used to determine cerebral language lateralization and to assess memory pre-operatively[35,36] and is often considered to be part of the neuropsychological evaluation and since neuropsychologists often direct it. The procedure involves injection of typically 75-150mg of sodium amobarbital following a transfemoral approach into a single internal carotid artery, which pharmacologically inactivates the distribution of the ipsilateral anterior and middle cerebral arteries for several minutes. During this time the patient is presented with multiple cognitive tasks. Three main

goals of Wada testing exist in the context of epilepsy surgery evaluation, although these goals and the procedure itself vary among centers. These goals include: 1) establishing cerebral language representation, 2) predicting patients who are at risk for developing a post-surgical amnestic syndrome, 3) identifying lateralized dysfunction to help confirm seizure onset laterality. Many variations in the intracarotid amobarbital procedure exist including differences in drug administration (e.g. dosage, concentration, and injection rate) and method of behavioral assessment (e.g. type and timing of stimuli). These procedureal variations contribute to differences in results across centers.

Information derived regarding pre-operative language lateralization is used by many epilepsy centers to determine the need for pre-operative grid studies or intraoperative cortical mapping, and may be considered when planning the extent of surgical resection. Most epilepsy surgery centers (93%) assess confrontation naming as a criterion for establishing speech lateralization for the dominant hemisphere in addition to the presence of aphasic signs (78%), counting ability (80%), and phrase repetition (61-65%).[37] In contrast, more heterogeneous criteria are used to infer the presence of speech representation in the non-dominant hemisphere such as mouthing words, singing ability, object naming, partial phoneme vocalization, serial wrote speech, and expression of familiar words. Thus, the variability in reported bilateral language representation ranging from 0% to 60% should not be surprising. We believe that the presence of paraphasic responses is the strongest evidence of language representation in the hemisphere being studied.

Test sensitivity is particularly important when inferring exclusive right hemisphere language representation. Speech arrest, for example, may be present following right cerebral injection and may be unrelated to language representation.[38] In addition, patients with "right cerebral language dominance" by Wada testing have developed transient aphasia following left hemisphere surgery, indicating some left hemispheric language representation.[39] Similarly, other "right cerebral language" dominant patients by Wada testing have had left hemisphere language areas identified during cortical stimulation mapping using subdural electrodes.[40] Thus, many patients considered right cerebral language dominant may have some mild left hemisphere language presentation as well. Our experience at the Medical College of Georgia is that the majority of patients who are not left cerebral language dominant have varying degrees of bihemispheric language representation, with exclusive right hemisphere language represenation rarely observed.[41] Right hemisphere language may also be observed without corresponding shift in handedness, and may be present in some dextral patients with either left temporal seizure onset[42] or right temporal seizure onset.[43]

Since many patients may have altered cerebral language representation associated with their seizures, inferences concerning lateralization based upon neuropsychological deficits in patients with atypical cerebral language representation should be made with caution. When patients have altered cerebral language represenation from an early left hemisphere lesion, there may be a decline in visual spatial processing that occurs as the right hemisphere takes over some or all of the language function typically subserved exclusively by the left hemisphere.[44] This pattern was termed "crowding" by Teuber, and occurs when "one hemisphere tries to do more than it had originally been meant to do.[45] On a strictly neuropsychological pattern basis, these patients present with relative preservation of language performance but relatively poor visual spatial skills. This is a neuropsychological pattern that usually would be expected in patients with right rather than left cerebral impairment.

Altered cerebral language representation can also affect the lateralizing value of material-specific memory asymmetries. There have been two cases in our patient series at the Medical College of Georgia that illustrate the caution required for making inferences in these cases. In one case, a right-handed patient with right cerebral language dominance and minor left hemisphere language representation developed a transient aphasia following right temporal lobectomy, confirming the right cerebral language dominance.[43] However, memory testing during unilateral electrical hippocampal simulation with depth electrodes indicated reliance on left hemisphere mesial temporal lobe structures for verbal memory. Further, one-year follow-up neuropsychological assessment demonstrated an increase in verbal learning and decrease in visual memory, a pattern associated with patients with left cerebral language dominance who have undergone right temporal lobectomy. This patient demonstrates the uncoupling of language and memory indicating that verbal memory and language dominance are not necessarily linked.

In another patient with exclusive right cerebral language representation, a permanent anterograde amnestic syndrome developed following right ATL.[46] Pre-operative neuropsychological performance revealed impaired verbal memory and normal non-verbal memory, a pattern that would be expected if completely crossed cerebral lateralization were present and one that would indicate an absence of risk to significant memory decline. Wada memory, in contrast, suggested a risk for amnesia with none of the memory objects presented immediately after right hemisphere amobarbital injection correctly recognized. The results of these two patients

demonstrate that baseline neuropsychological testing may falsely lateralize material-specific memory functions in patients with atypical cerebral language dominance.

Early left hemisphere lesions are associated with an increased incidence of atypical language representation.[47] However, there is apparently some difference between the sexes regarding the "window" of reorganization with females having a relatively short window (i.e., with reorganization most likely during the first year of life).[48] The length of this window is more difficult to define for males but may extend until puberty. The period during which a shift to left-handedness can occur does not appear to be affected by sex, with both males and females having a relatively short time window.

There are also early effects of left hemisphere damage that alter language representation within the hemisphere. Although the factors are the same as those associated with a transfer of function from the left to right hemisphere, such as early seizure onset, poor verbal IQ, left handedness, and right hemisphere memory dominance, these factors should alert the neurosurgeon to the possibility of encountering essential language areas in the anterior temporal lobe (1.5-3.5 cm from the temporal tip).[49] In general, early onset of dominant temporal lobe seizure foci leads to a more widespread or atypical distribution of language areas.[50]

Post-operative neuropsychological outcome. Post-operative memory change. The development of global amnesia is rare. However, patients undergoing unilateral ATL are at risk for experiencing decline in material-specific verbal memory functioning following left ATL, and decline in visuospatial memory following right ATL. Although not as devastating as a global amnesia, significant verbal memory decline may interfere with quality of life including occupational function.[51] As with the pre-operative evaluation, however, the consistency of material specific impairment with subsequently post-operative decline memory change is more consistent in patients with left TLE. Verbal memory decline following dominant hemisphere temporal lobectomy is more frequently described by patients than changes in non-verbal memory following right ATL. In addition, decline in verbal memory is easier to demonstrate neuropsychologically.

Greater risk of memory decline is associated with resection of a relatively non-sclerotic hippocampus which presumably has greater residual functional capacity. Larger memory declines following left ATL are observed in patients with minimal left hippocampal sclerosis.[14,52] Similarly, poorer memory outcome is seen following resection of relatively non-atrophic left hippocampus as reflected by MRI volumetry.[52] These studies suggest that patients without evidence of hippocampal pathology are more likely to experience decline in verbal memory following left ATL since functional tissue is included in the mesial temporal lobe resection.

Despite the risk of post-operative memory decline, not all patients will have poorer memory at their follow-up neuropsychological examination. Eliminating the disruptive effects of the seizure focus and decreasing or eliminating anti-epileptic medications are both factors that increase general cognitive abilities including memory. These factors contribute to greater improvement in material-specific memory performance for measures contralateral to the seizure focus and memory (i.e. improved visual memory following left temporal lobectomy, and improve verbal memory performance following right temporal lobectomy). In both cases, the material-specific memory typically associated with the laterality of seizures and surgery remains constant or declines.

Baseline memory assessment itself also provides a measure of risk to memory change following temporal lobectomy. Patients with normal verbal memory are likely to have less atrophy of the left hippocampus. Higher pre-operative memory and language performances are associated with greater decline following left ATL.[16] In contrast, no similar relationship is present for visuospatial memory change following right ATL, a finding consistent with the lack of specificity of visuospatial memory impairment and right TLE.

Risk for significant post-operative memory decline depends, in part, on the level of pre-operative memory impairment and two other factors. First, memory must be sufficiently intact in order to have the potential for decline following surgery. Second, even when declines occur that are noticeable to the family, there must be sufficient tests sensitivity of the neuropsychological instruments employed to measure a decline and avoid what is referred to as floor effect of the neuropsychological measures. High functioning patients with intact verbal memory show the greatest verbal declines post-operatively, and this decline does not appear to be explained solely on the basis of statistical regression to the mean. Chelune et al[16] reported that patients with Wechsler Memory Scale – Revised Verbal Memory Index scores which were in the average range or greater (i.e. scores > 90) had a 75% chance of experiencing a 10% decline in verbal memory at their 6-month follow-up.

Patients who are not seizure free following surgery are also more likely to show greater verbal impairments than those without post-operative seizures[21,53] although verbal memory impairment may be present in seizure free patients. Patients older than 40 years of age may be at increased risk for greater post-operative memory decline.

Post-operative language change. Decline in language function provides the rationale for

functional cortical speech mapping during surgery. Although acute language deficits are common following temporal lobectomy, they largely resolve over longer intervals.[54] However, there appears to be greater risk for a decline in confrontation naming following dominant ATL in patients without an identifiable early risk factor for the development of seizures.[54] Hermann et al found no statistical group decline in language in patients who underwent stimulation mapping during surgery.[55] When examined on an individual basis, however, several patients demonstrated significant language decline although factors affecting this variability could not be identified. The same investigators compared post-operative language in patients who received mapping to those who did not, in a consecutive patient series at the same epilepsy center.[56] They found few group differences. The only pre- to post-operative change in patients undergoing left ATL who were not mapped was on a confrontational naming task, and was on the order of one-half standard deviation. This study suggests that mapping provides some benefit in avoiding mild anomia following surgery.

A collaborative study attempting to parcel out some of the surgical factors associated with naming decline examined pre- to post-operative change following left ATL in four surgical groups: (a) tailored resections with intraoperative language mapping (b) tailored resections with extraoperative language mapping, (c) standard resections with sparing of superior temporal gyrus, and (d) standard resections including excision of superior temporal gyrus. Results showed significant decline in visual confrontation naming following left ATL, regardless of surgical technique. Across surgical approaches, the risk for decline in visual confrontation naming was associated with a later age of seizure onet and more extensive resection of lateral temporal neocortex.[57]

Patients who undergo surgery encroaching on primarily language areas, of course, may experience greater language decline. In cases in which seizures arise near primarily language regions, mapping is thought to decrease the magnitude of language decline although good post-operative data do not exist. Multiple subpial transection may be performed in language regions, although this approach is generally better tolerated in motor regions rather than language regions.[58]

Seizures play a signficiant role in limiting employment, and improved seizure status following surgery decreases the unemployment rate, but this is generally not related to neuropsychological status.[59] In addition, employment gains may take a significant amount of time to be realized, with some reported in the literature taking up to 6 years. Employment outcome is also influenced by pre-surgical work experience.[60] In both cases, seizure control is a significant factor that allows individuals to drive, obtain additional education, and in increase general quality of life.

Future directions. Neuropsychological testing and Wada evaluation will continue to play a prominent role in the evaluation of epilepsy surgery patients. In many patients, they not only measure functional deficits with known cerebral lesions, but these measures also contribute to establishing laterality of seizure onset, some estimate of the risk to memory following ATL, and provide information predictive of post-operative seizure outcomes. With both approaches, however, there will continue to be procedural refinement based upon correlations with MRI volumetry, fMRI, and MRI spectroscopy, as well as correlations with long-term cognitive, vocational, and seizure outcome. New non-invasive measures of brain function (e.g. fMRI and magnetoencephalography (MEG)) are likely to eventually provide much of the same information as that derived from neuropsychology and Wada testing. However, it remains to be established if a procedure that relies on activation of cognitive functions can provide comparable data to the Wada test, which as an inactivation procedure, more directly models the effects of surgery on cognition. Neuropsychology will continue to be necessary to characterize a full range of behavior that will assess in vocational placement and management issues. Nevertheless, there continues to be an important need for continued refinement in the ability to predict and avoid significant post-operative cognitive deficits. Greater understanding of the interaction between cognitive, psychiatric, and quality of life variables, and how these factors contribute to the overall outcome of epilepsy surgery, will provide a richer description of post-surgical results than simply reporting post-operative seizure frequency.

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