Intracarotid Amytal memory test and hippocampal magnetic resonance imaging volumetry: validity of the Wada test as an indicator of hippocampal integrity among candidates for epilepsy surgery

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Objective. Intracarotid Amytal testing (the Wada test) has been used to lateralize language and identify patients who may be at risk for memory impairment after temporal lobectomy. The goal of this study was to determine the validity of the Wada test in the assessment of pathological conditions of the hippocampus among candidates for epilepsy surgery. The authors examined the correlation between the functional integrity of the hippocampus, measured using the Wada test, and quantitative measures of hippocampal pathology, determined by obtaining volumetric measurements of the hippocampus with the aid of magnetic resonance (MR) imaging.

Methods. The authors reviewed the relationship between memory scores on the Wada test and hippocampal volumes measured on preoperative MR images in 76 patients who underwent anteromedial temporal lobectomy and amygdalohippocampectomy for the treatment of medically refractory temporal lobe epilepsy. The data were analyzed with respect to their usefulness in lateralizing the seizure focus and predicting the long-term postoperative memory outcome.

Right and left hippocampal volume measurements did not correlate with one another (p > 0.1). Similarly, following a left carotid artery injection of Amytal the patients’ right hemisphere memory was not significantly related to their left hemisphere memory on the Wada test (p > 0.1). On the other hand, the patients’ right hemisphere memory significantly correlated with their right hippocampal volume (r = 0.51; p < 0.001) and their left hemisphere memory significantly correlated with their left hippocampal volume (r = 0.51; p < 0.001). Both right and left hemisphere memory scores correlated with the hippocampal volumetry ratio (r = 0.47 and r = 0.45, respectively; both p < 0.001). Lateralization of a seizure focus based on hippocampal volumetry results was significantly related to lateralization based on the results of the Wada test (r = 0.49; p < 0.01). The disparity between the Wada memory scores on ipsilateral and contralateral sides was significantly and inversely related to the change in verbal memory following temporal lobectomy (r = −0.28; p < 0.02). The preoperative hippocampal volumetry ratio also significantly and inversely correlated with the change in verbal memory after surgery (r = −0.31; p < 0.01).

Conclusions. The Wada memory test may be a valuable method of measuring the functional integrity of the hippocampus. The systematic study of MR imaging–acquired morphological data and Wada-acquired neuropsychological data may increase our understanding of the location of material-specific memory and the selection of eligible candidates for epilepsy surgery.

Key Words • epilepsy • magnetic resonance imaging • Wada test • memory • surgery • neuropsychology

Unilateral AMTR has proved to be efficacious in the treatment of medically refractory medial TLE. Patients undergo various preoperative tests to estimate the risk of memory loss associated with this procedure. Left- and, less often, right-sided AMTR may compromise the patient’s verbal and visuospatial memory, respectively. To determine the risks of memory deficits after unilateral AMTR, intracarotid amobarbital testing, also known as the Wada test, has been used to determine cerebral language dominance and lateralized memory support. The validity of the Wada test has recently been questioned, however, as more investigators report the use of noninvasive methods such as fMR imaging in the localization of function. In the majority of these studies the authors have reported less than 100% concordance between fMR imaging and the Wada test in localization of function, and a variation in fMR imaging activation patterns related to different evaluation paradigms.

To determine the efficacy of the Wada test in assessing pathological functional sites in the hippocampus, the results of memory performance during the Wada test could be correlated to specific measures of hippocampal anatomical integrity including morphological data obtained using MR imaging and the histopathological cell density of the resected hippocampus. The in vivo measurement of hippocampal volumetric asymmetry has been related to lateralized neuropsychological deficits. Previous studies by Loring and colleagues and Baxendale have reported a correlation between the Wada memory score...
The patient cohort was composed of 76 consecutive candidates for temporal lobectomy in whom a diagnosis of partial TLE had been made and who had undergone comprehensive presurgical workups, including preoperative memory assessment, MR imaging of the hippocampus, and a significant loss of pyramidal neurons on histopathologic examination of the resected hippocampus, which were consistent with the diagnosis of medial temporal lobe sclerosis. The inclusion of patients with a variety of pathologic conditions provided a wide range of hippocampal volumes, allowing for a more meaningful statistical analysis.

Before the language and memory assessment, all patients underwent cerebral angiography, in which the cerebral hemisphere suspected to harbor the epileptogenic focus was always studied first. After angiography, a hand-directed injection of sodium Amytal was given. The dose typically ranged between 100 and 130 mg (mode 130 mg, mean 128.75 ± 6.03 mg). The doses administered by the left and right injections were identical. Following the injection and during the period of maximal drug effect, language and memory were studied. The language examination consisted of simple naming of body parts, naming of common objects, repetition of simple and complex phrases, comprehension of complex ideational questions, and comprehension of simple commands. In addition, six to 10 drawings were presented to the patient for the memory study. Each item was presented on an 8 1/2 × 11–in card, and the patient was asked to name the object and instructed to remember it. After receiving the nondominant hemisphere injection, the patient attempted to name the object and it was also named by the examiner. This was done because following the dominant hemisphere injection, patients were unable to name objects and thus we named each one for them to facilitate recall and assure perception and encoding of stimuli. Both hemispheres were studied on the same day in all patients; there was a minimum of 30 minutes between recovery from the first injection and the second injection. Following each injection, a series of memory stimuli were presented for the memory study. The stimuli consisted of two common drawings (for example, one of a house and one of a dog), two printed words, a colored shape (for example, a green ball or a red triangle), and a simple arithmetic problem. Because changes in the testing protocol were made during the time period covered by this retrospective study, some patients also were shown four additional items (for a total of 10): two hard-to-name complex line drawings and two additional familiar objects. To account for the different number of stimuli used in some presentations, a percentage of retention (number of objects recalled divided by the number displayed to the patient) was calculated for the right and left hemisphere memory scores. A simple absolute difference score was used to determine lateralization, or the Wada difference (for disparity) score. The right hemisphere memory score (which was obtained by testing after the left-sided injection) was subtracted from the left hemisphere memory score. This yielded a positive Wada difference score if the left hemisphere memory was superior to that of the right hemisphere and a negative difference score if the right hemisphere memory score was superior to that of the left. A similar method was used to determine lateralization based on hippocampal volumetry.

Verbal Memory Outcome

A verbal memory assessment was performed preoperatively and 1 year after surgery by using the VSRT. On the initial trial of the VSRT, the patient was read 12 words and was immediately asked to recall them. During subsequent trials, the patient was reminded of the words he or she failed to recall. The test continued in this fashion until the patient recalled the entire list or until 12 trials were performed. Standard scoring of the VSRT results provide measures of

Clinical Material and Methods

Patient Population

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The average Wechsler Adult Intelligence Scale–Revised Full-Scale intelligence quotient for this group was 91.4 ± 13.4 (mean ± standard deviation). The mean age of the patients at the time of surgery was 32.4 ± 8.9 years (range 17.6–55.8 years) and 35 were women. The mean age of the patients at habitual seizure onset was 10.99 ± 10.6 years (range 3 months–41 years). Thirty-four patients had a history of febrile convulsions in the first 5 years of life. Twenty-five patients had other epilepsy-related risk factors, including head trauma, meningitis, encephalitis, and/or perinatal injuries.
bloc. The resection of the hippocampus was terminated as hippocampus, and parahippocamal gyrus were removed en bloc. Medial temporal structures including the amygdala, the lateral ventricle. The exposure of the hippocampus was continued in a medial fashion and the lateral temporal neocortex was exposed. Frontotemporal craniotomy was performed in the standard right-side volume).

Surgical Procedure and Outcomes

The senior author (D.D.S.) has previously described the technique of AMTR performed in this series. Briefly, a frontotemporal craniotomy was performed in the standard fashion and the lateral temporal neocortex was exposed. The superior temporal gyrus was spared and 3 to 3.5 cm of the temporal pole, were resected to expose the temporal horn of the lateral ventricle. The exposure of the hippocampus was further performed in the oblique coronal series, oriented orthogonal to the long axes of the hippocampi. The cursor was used to outline the hippocampi in five images anterior to the colliculi, including the midbody and tail, but excluded the pes. The volume was then calculated by multiplying the total number of pixels by the size of the pixel and by slice thickness. Normalization based on total brain volume was not performed. Hippocampal ratios were calculated using the following formula: (left-side volume – right-side volume)/(left-side volume + right-side volume).

Quantitative MR Imaging Volumetry of the Hippocampus

All MR imaging for this study was performed with the aid of a 1.5-tesla magnet by using axial and coronal long-repetition-time sequences and parameters described previously. Volumetric measurements were assessed on an oblique coronal series, oriented orthogonal to the long axes of the hippocampi. The cursor was used to outline the hippocampi in five images anterior to the colliculi, including the midbody and tail, but excluded the pes. The volume was then calculated by multiplying the total number of pixels by the size of the pixel and by slice thickness. Normalization based on total brain volume was not performed. Hippocampal ratios were calculated using the following formula: (left-side volume – right-side volume)/(left-side volume + right-side volume).

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Statistical Analysis

In this study the mean value of data are expressed as means ± standard deviations unless otherwise noted. To investigate whether the results of the Wada memory test are related to hippocampal volumes, we performed several analyses. First, a simple linear regression analysis between hippocampal volume measurements and Wada memory scores was performed. The Wada and hippocampal volumetry laterality index scores were calculated as described earlier. Laterality based on the Wada memory scores and hippocampal volumes were also compared using a simple linear regression analysis.

Preoperative measures of hippocampal functional integrity may identify those patients at the greatest risk of postoperative memory impairment. Consequently, we also evaluated the sensitivity of the Wada test in predicting memory outcome after resective surgery by using a simple linear regression analysis.

Results

The mean Wada memory scores (percentage of correct responses) following injection of the anesthetic agent ipsilateral to the seizure focus were 77.1 ± 27.7 for patients with left-sided seizure laterality and 82.3 ± 26.9 for those with right-sided seizure onset. Memory scores following the intracarotid injection of Amytal contralateral to the epileptogenic temporal lobe were 40.1 ± 26.8 and 57.1 ± 34 for patients with left- and right-sided seizure lateralization, respectively (Table 1). The difference between memory scores following the injection of the two hemispheres was significantly different for patients with both left and right TLE (p < 0.001 for both). After the intracarotid injection on the left side, the patients’ right hemisphere memory was not significantly correlated to their left hemisphere memory and vice versa (p > 0.1).

Right and left hippocampal volume measurements were not significantly correlated with one another (p > 0.1) (Table 2). The patients’ right hemisphere memory was significantly correlated with right hippocampal volume (r = 0.51; p < 0.001), and their left hemisphere memory was significantly correlated with left hippocampal volume (r = 0.51; p < 0.001). Both the right and left hemisphere memory scores were correlated with the hippocampal ratio (r = 0.47 and r = 0.45, respectively; both p < 0.001).

Absolute differences (any difference not equal to zero) between the right and left hemisphere memory scores during the Wada test, as well as absolute differences between the right and left hippocampal volumes, were used for lateralization. The rate of concordant lateralization, when compared with the side of surgery, was similar for the Wada difference and the MR imaging volumetry (80.822 and 86.667%, respectively). Lateralization of the seizure focus based on hippocampal volumetry measurements was significantly related to lateralization based on the Wada memory scores (r = 0.49; p < 0.01). The Wada memory difference between the left and right hemispheres in each patient

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TABLE 1

Wada memory scores by hemisphere and side of surgery*

<table>
<thead>
<tr>
<th>Factor</th>
<th>Surgery on Lt Side</th>
<th>Surgery on Rt Side</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Rt%</td>
<td>Lt%</td>
</tr>
<tr>
<td>mean</td>
<td>40.1</td>
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</tr>
<tr>
<td>SD</td>
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<td>4.4</td>
</tr>
<tr>
<td>SEM</td>
<td>27.7</td>
<td>26.8</td>
</tr>
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</table>

* Wada memory scores are based on the percentage of correct responses. Abbreviations: Lt% = left hemisphere memory score following a right hemisphere injection; Rt% = right hemisphere memory score following a left hemisphere injection; SEM = standard error of the mean.

TABLE 2

Correlation between Wada memory scores and hippocampal volume measurements*

<table>
<thead>
<tr>
<th>Wada Memory Score</th>
<th>Correlation Coefficient</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rt%, lt%</td>
<td>-0.17</td>
<td>0.15</td>
</tr>
<tr>
<td>rt%, lt HC volume</td>
<td>-0.19</td>
<td>0.11</td>
</tr>
<tr>
<td>rt%, rt HC volume</td>
<td>0.51</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>lt%, lt HC volume</td>
<td>0.51</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>lt%, rt HC volume</td>
<td>-0.15</td>
<td>0.20</td>
</tr>
<tr>
<td>lt HC volume, rt HC volume</td>
<td>-0.12</td>
<td>0.29</td>
</tr>
</tbody>
</table>

* HC = hippocampus.
Wada test and hippocampal MR imaging volumetry

was significantly and inversely related to the change in verbal memory (as measured using the VSRT) after temporal lobectomy ($r = -0.28; p < 0.02$). The preoperative hippocampal volumetry ratio also significantly and inversely correlated with the change in verbal memory after surgery ($r = -0.31, p < 0.01$).

Discussion

The intracarotid amobarbital (Wada) procedure remains the gold standard procedure for the evaluation of contralateral hemisphere memory support and lateralized memory dysfunction in patients who are candidates for temporal lobectomy. Moreover, an increasing body of research supports the use of the Wada memory test in the prediction of postoperative material-specific memory outcomes as well as seizure relief. Despite its widespread use, there is controversy regarding its reliability in the prediction of the functional integrity of the hippocampus. Factors unrelated to the patient’s hippocampal functional status, including Amytal dose and sedation level, may adversely influence the test results. To determine the utility of the Wada test in the evaluation of pathological conditions of the hippocampus, a correlation between Wada memory scores and more specific measurements of hippocampal anatomical integrity, such as cell density or MR imaging volume, may be helpful. Because hippocampal cell density can be found only unilaterally in some sections of the resected specimens, it can provide incomplete information regarding the status of both hippocampi. On the other hand, MR imaging volumetry provides a preoperative bilateral in vivo measurement of structural damage (neuronal loss and gliosis) in the hippocampus, facilitating the selection of the optimal treatment modality. Nevertheless, knowledge of structural integrity alone does not permit inferences regarding functional capacity.

The material-specific memory capacity of the hippocampus was first explored based on hippocampectomy studies performed at the Montreal Neurological Institute. The observation of significant memory difficulties in patients with bilateral hippocampal damage verified the important role of this structure in memory. Even though the hippocampus is known to play a critical role in memory, other extrahippocampal structures also are considered crucial in memory consolidation. Because the hippocampus is fed mainly by the posterior circulation, the efficacy of the Wada test to determine hippocampal status has remained uncertain, although slowing of EEG activity has been reported in the posterior hippocampus following intraarterial amobarbital injection. In the present study, the authors examined the correlation between Wada memory scores and hippocampal measurements obtained using MR imaging volumetry to determine the value of Wada results in assessing pathological conditions in the hippocampus. The strong statistical correlation between these variables may substantiate the value of Wada scores as a functional measure of hippocampal impairment. This has important prognostic implications for determining the safety of unilateral hippocampectomy and postoperative memory outcome among candidates for epilepsy surgery.

In some papers the authors have reported a limited correlation between left or right hippocampal volumes and the patient’s performance on verbal and visuospatial memory tasks on the Wada test or other neuropsychological tests, respectively. Other authors have not observed similar relationships, but report an association between asymmetries in these variables. These discrepancies may be accounted for by small sample sizes, which prevent a reliable statistical analysis, by variable volumetry techniques, and by the memory tasks used. The use of VSRT scores in this study is another factor that is different from the other studies. This learning task has been shown to be sensitive to the degree of hippocampal disease or injury, as well as providing a sensitive measure of change in verbal memory following temporal lobectomy. In previous studies the Logical Memory subset of the Wechsler Memory Scale has been applied to measure verbal memory. In at least one study such a method of testing was reported to be insensitive to hippocampal damage.

Hippocampal MR imaging volumetry has proved to be efficacious in the lateralization of the seizure focus in TLE. The lateralizing concordance rate of approximately 80% between Wada scores and MR imaging hippocampal measurements in this study is consistent with data in other reports and is evidence for the utility of the former in TLE localization. Additionally, if the Wada test is considered a measure of hippocampal functional status, it should assist in the prediction of memory outcome after hippocampectomy. In this study, patients with less disparity between Wada memory scores for the ipsilateral and contralateral hemispheres suffered a greater decline in memory, as assessed on the postoperative memory evaluation, regardless of the side of surgery. This may provide additional evidence for the role of Wada scores in predicting the risk of postoperative material-specific memory loss if the ipsilateral hippocampus is excised. Although our results provide further support for the hippocampal model of memory, the lack of a significant memory dysfunction after hippocampectomy among patients with poor ipsilateral memory scores may illustrate the significant role of the extrahippocampal neocortex or the contralateral hippocampus in mediating memory function.

We have attempted to calculate and compare the sensitivity and specificity of the Wada test and MR imaging volumetry of the hippocampus in predicting postoperative memory outcomes after temporal lobectomy to evaluate which test is superior. Because Wada test results significantly affected the selection of surgical candidates in our study, too few patients who underwent surgery had Wada results that predicted the risk of a postoperative memory deficit. Such a selection bias prevented an accurate evaluation of false-negative and true-negative results. This limitation rendered the measurement of sensitivity and specificity unreliable for the Wada test in the present analysis.

The Wada test undoubtedly has its inconsistencies and its deficiencies as an invasive test, but will continue to play an important role in the preoperative evaluation of patients considered for temporal lobectomy. Refinement in the techniques of fMR imaging will increase its role in the localization of function. Nevertheless, fMR imaging may not be able to determine the amnestic risks posed by surgery by determining the memory capacity of a particular hemisphere to ensure adequate memory support for the contralateral hemisphere. A neuropsychological battery of tests and structural imaging techniques will continue to supplement
The Wada test and fMRI imaging in the localization of memory in the temporal lobe. Over time these diagnostic modalities will evolve to a point at which they can be applied to understanding such sophisticated cerebral functions such as memory.

Conclusions

The analysis of the relationship between the morphological data obtained using fMRI imaging and the results of the Wada memory tasks confirms a correlation between hippocampal volume and memory evaluated using the Wada test. Wada memory and hippocampal volume asymmetries also appear to predict the lateralization of the seizure focus and the risk of postoperative memory dysfunction among patients with medically intractable TLE. A greater understanding of memory mechanisms will aid us to adapt the application of these diagnostic modalities to understanding the role of the hippocampi in memory functions.

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