Wada memory asymmetries predict verbal memory decline after anterior temporal lobectomy

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Article abstract—We examined Wada memory and neuropsychological memory function in 34 nonlesional patients who underwent anterior temporal lobectomy (ATL) and who were seizure free at 1-year follow-up. Patients who displayed a decline on verbal memory measures that exceeded 1 SD after left ATL had significantly smaller left/right Wada memory asymmetries than left ATL patients without a significant verbal memory decline. When Wada memory asymmetries were used to predict verbal memory decline after left ATL in individual patients, similar statistically significant effects were present. No significant relationship between Wada memory and postoperative memory was present in right ATL patients, and postoperative memory function was not related to Wada memory performance after either left hemisphere or right hemisphere injection alone. We conclude that Wada memory asymmetries provide one measure of the risk to material-specific decline in verbal memory after left ATL.

NEUROLOGY 1995;45:1329-1333

The Wada test (intracarotid amobarbital procedure) is used to assess language and memory function during the preoperative evaluation for anterior temporal lobectomy (ATL).[1] Milner et al[2] introduced memory testing during the period of hemispheric anesthesia to assess whether patients were at risk for postsurgical amnesia due to significant hippocampal pathology contralateral to the side of surgery. The goals of Wada memory testing, and the Wada memory protocols themselves, vary among epilepsy surgery centers. Wada memory performance may be used to identify patients at risk for global amnesia[3] or to lateralize temporal lobe dysfunction associated with a unilateral seizure onset,[4,5] and is related to postoperative seizure outcome.[6,7]

Decline in verbal memory after left ATL is a robust phenomenon.[8-10] Although not as devastating as a frank amnesia, significant verbal memory decline may interfere with quality of life including occupational function.[8] The usefulness of Wada memory testing to predict postoperative material-specific memory change is unresolved.[3] In the present report, we describe the relationship between Wada memory asymmetries and decline in material-specific memory function after ATL.

Methods. Patient records were retrospectively examined to identify adults who underwent ATL due to refractory complex partial seizures with or without secondary generalization and who underwent neuropsychological testing during their 1-year postoperative evaluation. Patients with temporal tip resections sparing hippocampus and those with radiologic evidence of structural lesions other than hippocampal sclerosis were excluded. No patient had surgery that included resection of non–temporal-lobe structures. Only patients who were seizure-free at 1-year follow-up were included to avoid confounding the effects of continued seizure activity on postoperative neuropsychological performance. Patients with amobarbital doses during the Wada test greater than 125 mg were not included because doses greater than 125 mg are associated with poorer Wada memory performances.[11] Thirty-four patients (left ATL = 17; right ATL = 17) were identified who met these criteria. Four patients, all left seizure onset, had mixed cerebral dominance by Wada language testing.

Laterality of seizure onset was determined by evaluation of multiple scalp/sphenoidal ictal recordings with simultaneous audio-video recording of behavioral phenomena. Results from MRI, neuropsychological testing including Wada testing, and where available, ictal and interictal single photon emission computed tomography, were also considered in order to determine seizure onset laterality.

All patients underwent ATL that included the anterior 3 to 4 cm of the hippocampus. Electrocorticography was recorded in all patients. Subpial dissection/aspiration was used to resect the anterior temporal lobe. Lateral temporal

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Presented in part at the 47th annual meeting of the American Academy of Neurology, Seattle, WA, May 1995.

Received October 24, 1994. Accepted in final form December 21, 1994.

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cortex, amygdala, and hippocampus were removed separately as en bloc specimens. Portions of adjacent parahippocampal and fusiform gyri were removed in all cases.

Mean age of habitual seizure onset was 10.1 years (SD = 9.7) for left ATL patients and 9.9 years (SD = 8.6) for right ATL patients. Average Wechsler Adult Intelligence Scale–Revised Full Scale IQ was 88.3 (SD = 11.3) for left ATL patients and 92.6 (SD = 8.6) for right ATL patients. Left and right ATL groups did not differ with respect to age at initial assessment (left ATL = 29.6 years, SD = 11.5; right ATL = 28.1 years, SD = 9.0), education (left ATL = 12.4 years, SD = 2.1; right ATL = 12.9 years, SD = 2.0), and both groups contained comparable numbers of men and women. Memory was tested by the Selective Reminding Test,[12] Logical Memory subtest from the Wechsler Memory Scale–Revised (WMS-R),[13] Rey-Osterrieth Complex Figure Test,[14] and WMS-R Visual Reproduction subtest.[13] All patients were administered the Selective Reminding Test. Two patients (one left ATL, one right ATL) did not complete the Complex Figure Test due to seizure development during the preoperative evaluation. The WMS-R subtests were added later in our patient series, and only 24 patients in this sample were administered the Logical Memory subtest and the Visual Reproduction subtest (left ATL = 11; right ATL = 14).

The Selective Reminding Test is a serial word learning procedure containing 12 words. The patient is prompted only for those words not recalled on the immediately preceding trial. Continuous Long-Term Retrieval (CLTR), measuring the ability to recall words without further reminding, was our dependent learning measure.[15] The Logical Memory subtest assesses prose passage recall immediately after paragraph presentation and again after a one-half–hour delay.

The Complex Figure Test consists of a geometric shape that contains 18 scorable elements. After the patient copies the figure, immediate and 30-minute delayed recall are obtained. The delayed recall measure was our dependent measure for this test.[15] The Visual Reproduction subtest presents simple geometric designs for 10 seconds, and immediately after each presentation, an immediate recall is obtained. In addition, recall after a 30-minute delay is obtained.

Wada protocol. Carotid catheterization was executed by a transfemoral approach, and cerebral angiography was performed before Wada assessment. Left and right Wada evaluations were separated by at least 30 minutes, and the order of amobarbital administration was sequentially alternated across subjects. Patients were administered 75 to 125 mg of amobarbital as a single bolus injection over 4 to 5 seconds. Patients earlier in the series received up to 125-mg injections and later patients received 100-mg injections. The average dose was 101.4 mg (SD = 12.2) for left hemisphere injections and 107.3 mg (SD = 21.8) for right hemisphere injections.

After assessment of eye gaze deviation and simple comprehension, which took approximately 30 to 45 seconds, eight common objects were presented. Objects were displayed in the central visual field and in the visual field ipsilateral to the injection for 4 to 8 seconds each. The names of the objects were repeated twice to the patient.

Memory was assessed after return to baseline as demonstrated by both normal mental status and normal strength with absence of asterixis. Object recall was tested by a recognition format, with the eight target items interspersed with 16 foils. Objects were presented in a randomized sequence, and patients indicated whether each object had been presented earlier during the test. A correction of one-half the number of false positive responses was subtracted from the number correctly recognized to correct for possible response bias and guessing.

Two Wada memory difference scores were calculated. Memory scores after injection ipsilateral to the seizure focus minus memory scores obtained after contralateral injection (ipsi − contra) were calculated, in which a higher score indicated greater performance asymmetry in the predicted direction. For analyses involving seizure onset laterality, left injection minus right injection difference scores (L − R) were calculated in which positive scores indicated greater left temporal lobe dysfunction; negative scores indicated greater right temporal lobe dysfunction.

Table 1. Neuropsychological memory measures (standard deviation) obtained pre- and postoperatively and Wada memory difference scores

	Left ATL	Right ATL	Significance
Selective Reminding preoperative	71.5 (35.5)	91.8 (32.6)	
Selective Reminding postoperative	45.1 (34.7)	98.2 (31.0)	† ‡
Logical Memory I preoperative	21.5 (8.3)	25.3 (4.4)	
Logical Memory I postoperative	16.7 (7.1)	25.9 (4.8)	†
Logical Memory II preoperative	13.6 (8.2)	19.7 (3.4)	
Logical Memory II postoperative	11.6 (8.9)	22.1 (5.3)	NS
Complex Figure preoperative	13.1 (4.9)	16.9 (4.7)	
Complex Figure postoperative	15.1 (7.0)	17.4 (5.9)	NS
Visual Reproduction I preoperative	33.9 (4.3)	34.1 (3.6)	
Visual Reproduction I postoperative	33.6 (4.6)	34.1 (4.7)	NS
Visual Reproduction II preoperative	25.1 (8.6)	27.4 (7.9)	
Visual Reproduction II postoperative	27.2 (9.7)	26.8 (9.2)	NS
Left-right injection Wada memory	4.2 (2.4)	−3.4 (3.1)	†
Ipsilateral Wada memory*	2.3 (1.0)	2.4 (1.9)	NS

ATL Anterior temporal lobectomy.
I Immediate.
II Delayed.
* Injection ipsilateral to seizure focus.
† Significant focus effect.
‡ Significant focus × surgery interaction.

Results. Means and SDs for each of the principal dependent measures are included in table 1. The first set of analyses was performed to identify which memory measures were associated with unilateral temporal lobe dysfunction. Each of the primary dependent neuropsychological memory measures were submitted to 2 (focus: left versus right) × 2 (surgery: pre- versus postoperative) mixed design ANOVAs. The Wada memory results were analyzed by a one-way ANOVA.

Verbal memory. A significant main effect of focus was present for CLTR ($p = 0.0005$) and for the focus × surgery interaction ($p = 0.015$). For immediate

Logical Memory, a significant main effect of focus ($p = 0.003$) was present, with the focus × surgery interaction effect approaching statistical significance ($p = 0.067$). For delayed Logical Memory, a significant main effect of focus was present ($p = 0.001$); no significant surgery or focus × surgery interaction effects were present.

These analyses were repeated, restricting the sample to only patients with left cerebral language dominance, and similar results were observed. A significant CLTR focus ($p = 0.0001$) and focus × surgery interaction ($p = 0.028$) were present. For immediate Logical Memory, both focus ($p = 0.002$) and the focus × surgery interaction ($p = 0.029$) reached statistical significance. For delayed Logical Memory, a significant effect of surgery was present ($p = 0.00001$) with a trend for the surgery × focus interaction ($p = 0.06$). Due to the similarities in both sets of analyses, the sample was not restricted to left language dominant patients in subsequent analyses due to power considerations associated with a larger sample.

Visual memory. No significant focus, surgery, or focus × surgery interaction effects were present for any measure of visual-spatial memory employed.

Wada memory. Wada memory performance, employing the (L − R) hemisphere difference score, was submitted to a one-way ANOVA by using focus as the grouping variable. With the (L − R) difference score, positive values suggest left temporal lobe dysfunction and negative scores indicate right temporal lobe impairment. This group difference was significant at a very high level of statistical significance ($p < 0.00001$). A similar analysis by using (ipsi − contra) injection memory score asymmetries rather than (L − R) injection differences did not differ between the left and right ATL group.

Postoperative memory decline. Given the absence of any laterality effect on measures of visual memory, the relationship between Wada memory asymmetries and memory decline after surgery was examined only in the sample of left ATL patients and only for verbal memory measures.

For this series of analyses, patients were grouped according to whether they displayed a significant decline in verbal memory. Significant memory decline was operationally defined as a decrease greater than 1 SD based on performance of left ATL patients described in previous reports.[15,16] For the Selective Reminding Test, a decline of 40 CLTR points was considered significant.[15] For immediate Logical Memory, a decline of 6 points was considered significant, and for delayed Logical Memory, a decline of 7 points was considered significant.[16]

Of the sample of 17 left ATL patients, seven patients displayed significant CLTR decline. Patients who displayed no CLTR change had mean memory asymmetries of 5.3 (SD = 1.9), and the patients with an apparent CLTR decline had Wada memory asymmetries of 3.0 (SD = 2.2). This difference is statistically significant ($p = 0.037$). Of the sample of 15 patients who were administered immediate Logical Memory, nine patients displayed significant memory decline. Patients who displayed no immediate Logical Memory change had an average Wada memory asymmetry score of 5.8 (SD = 1.5), and those with an evident decline had an average of 3.0 (SD = 1.9). This difference is statistically significant ($p = 0.009$). Five patients had delayed Logical Memory scores that exceeded 1 SD. Patients who displayed no delayed Logical Memory change averaged 4.7 (SD = 2.5), and those with a decline had an average difference score of 3.0 (SD = 1.0). This difference failed to reach statistical significance ($p = 0.18$).

Table 2. Relationship of individual verbal memory decline to presence of Wada memory asymmetries*

n = 17	**CLTR decline**	**No change**	**Significance**
No Wada asymmetry	4	1	
Wada asymmetry	3	9	$p < 0.03$
n = 15	**LM I decline**	**No change**	**Significance**
No Wada asymmetry	5	0	
Wada asymmetry	5	5	$p < 0.02$
n = 15	**LM II decline**	**No change**	**Significance**
No Wada asymmetry	3	2	
Wada asymmetry	3	7	NS

* Wada asymmetries of at least 2.5 are considered meaningful. Verbal memory declines exceeding 1 SD are considered significant.
CLTR Continuous Long-Term Retrieval.
LM I Logical Memory, immediate.
LM II Logical Memory, delayed.

This series of analyses was repeated by using Wada memory scores after left hemisphere injection alone and after right hemisphere injection alone rather than the left-right hemisphere asymmetry scores. No statistically significant results were obtained.

Prediction of individual decline. The ability of Wada memory asymmetries to predict individual verbal memory decline after left ATL was investigated by a likelihood ratio chi-square analysis (table 2). Based on the parametric analyses of Wada memory asymmetries in patients displaying either a CLTR or immediate Logical Memory decline in which Wada memory differences of 2.3 and 2.8 objects were obtained, a Wada memory difference of at least 2.5 objects was our criterion for performance asymmetry. Statistically significant differences were present for CLTR decline ($p < 0.03$) and immediate Logical Memory decline ($p < 0.02$).

Discussion. Wada memory has not been routinely used to predict memory change. For example, Jones-Gotman[3] stated that the Wada test "is used to predict global amnesia and not to estimate the severity of material-specific memory impairment that might occur after surgery" (p. 204). However, smaller Wada memory asymmetries in the present patient series are associated with a greater decline in verbal memory after left ATL. When applied on an individual patient basis, Wada memory asymmetries of 2.0

objects or fewer were associated with an increased risk of verbal memory decline after left ATL.

The standard conceptualization of Wada memory is that it models the effects of temporal lobectomy, and therefore the principal memory measure considered is the performance after injection ipsilateral to the seizure focus. However, in this patient series, no relationship was obtained between material-specific verbal memory decline and Wada memory performance after left hemisphere injection alone. Although we also observed no direct relationship between verbal memory decline and Wada memory performance after the contralateral injection, the relative contribution of both the ipsilateral and contralateral hemispheres, expressed as the interhemispheric difference score, is associated with change in memory after left ATL. Thus, the contribution not only of the side to be resected, but also the contralateral side, is important to predicting subsequent verbal memory function.

Patients are more likely to fail Wada memory testing after contralateral injection if significant hippocampal sclerosis exists.[17-19] This relationship is presumably due to the degree of bilateral temporal lobe dysfunction created by the injection. In patients with mild sclerosis, the contralateral side is significantly impaired due to the disruptive effects of amobarbital. The epileptogenic hippocampus, with only minimal sclerosis, has residual functional capacity and can contribute to new memory acquisition. In contrast, there is less functional hippocampal capacity with severe sclerosis, and consequently, contralateral amobarbital perfusion creates greater bilateral temporal lobe dysfunction with a concomitant increase in the likelihood of Wada memory failure. Thus, the contralateral Wada memory study is an indirect measure of the degree of mesial temporal sclerosis and contributes valuable information to the preoperative evaluation.[20]

Greater risk of memory decline after ATL exists in patients with relatively nonsclerotic hippocampus, and by extension, residual hippocampal function. Hermann et al[10,21] reported greater verbal and nonverbal memory declines in patients with minimal left hippocampal sclerosis. Trenerry et al[22] described poorer verbal and visual memory outcome after resection of relatively nonatrophic left hippocampus as reflected by MRI volumetry. The relationship of Wada memory asymmetries to verbal memory outcome is consistent with these reports.

Because the presence of hippocampal atrophy is related to postoperative seizure frequency[23] and because Wada memory asymmetries are related to MRI hippocampal volume asymmetries,[24] the association between Wada memory and seizure outcome would be anticipated. In fact, several centers have reported that Wada memory asymmetries are related to the likelihood of becoming seizure-free after ATL.[6,7] The relationship of Wada memory to material-specific postoperative memory is less straightforward. We observed a significant decline in verbal memory after left ATL but no effect of right ATL on visual-spatial or verbal memory. Our Wada memory procedure employed stimuli purposely selected to be dually encodable. Thus, the lack of explicit measures of material-specific verbal Wada stimuli may have been expected to produce null results. However, reliable verbal memory deficits associated with left temporal lobectomy, absence of an effect on visual memory, and greater subjective general memory problems after left temporal lobectomy suggest that these constructs are not fully distinguishable.

There are many factors related to memory decline after ATL directly or indirectly associated with hippocampal structure and function. In the present report, we cannot determine what unique information may be provided by Wada memory testing. However, for seizure outcome prediction, Sperling et al[7] demonstrated that Wada memory contributed information beyond that provided by other clinical factors (eg, age of earliest possible brain abnormality). Thus, studies with larger sample sizes are necessary to evaluate the unique contribution of each variable to the prediction of postsurgical memory change. However, Wada memory asymmetry, by itself, appears useful in predicting significant verbal memory loss after left ATL.

References

1. Loring DW, Meador KJ, Lee GP, King DW. Amobarbital effects and lateralized brain function: the Wada test. New York: Springer-Verlag, 1992.
2. Milner B, Branch C, Rasmussen T. Study of short-term memory after intracarotid injection of sodium Amytal. Trans Am Neurol Assoc 1962;87:224-226.
3. Jones-Gotman MJ. Commentary: psychological evaluation; testing hippocampal function. In: Engel J, ed. Surgical treatment of the epilepsies. New York: Raven Press, 1987.
4. Loring DW, Meador KJ, Lee GP, et al. Stimulus timing effects on Wada memory testing. Arch Neurol 1994;51:806-810.
5. Wyllie E, Naugle R, Chelune G, Lüders H, Morris H, Skibinski C. Intracarotid amobarbital procedure: II. Lateralizing value in evaluation for temporal lobectomy. Epilepsia 1991;32:865-869.
6. Loring DW, Meador KJ, Lee GP, et al. Wada memory performance predicts seizure outcome following anterior temporal lobectomy. Neurology 1994;44:2322-2324.
7. Sperling MR, Saykin AJ, Glosser G, et al. Predictors of outcome after anterior temporal lobectomy: the intracarotid amobarbital test. Neurology 1994:44;2325-2330.
8. Ivnik RJ, Sharbrough FW, Laws, ER. Anterior temporal lobectomy for the control of partial complex seizures: information for counseling patients. Mayo Clin Proc 1988;63:783-793.
9. Frisk V, Milner B. The role of the left hippocampal region in the acquisition and retention of story content. Neuropsychologia 1990;28:349-359.
10. Hermann BP, Wyler AR, Somes G, Dohan FC, Berry AD, Clement L. Declarative memory following anterior temporal lobectomy in humans. Behav Neurosci 1993;108:3-10.
11. Loring DW, Meador KJ, Lee GP. Amobarbital dose effects on Wada memory testing. J Epilepsy 1992;5:171-174.
12. Hannay JH, Levin HS. Selective reminding test: an examination of the equivalence of four forms. J Clin Exp Neuropsychol 1985;7:251-263.
13. Wechsler D. Manual for the Wechsler Memory Scale—Revised. New York: The Psychological Corporation, 1987.
14. Loring DW, Martin RC, Meador KJ, Lee GP. Psychometric

construction of the Rey-Osterrieth complex figure: methodological considerations and interrater reliability. Arch Clin Neuropsychol 1990;5:1-14.
15. Loring DW, Lee GP, Martin RC, Meador KJ. Material specific learning in patients with partial complex seizures of temporal lobe origin: convergent validation of memory constructs. J Epilepsy 1988;1:53-59.
16. Chelune GJ, Naugle RI, Lüders H, Awad IA. Prediction of cognitive change as a function of preoperative ability status among temporal lobectomy patients seen at 6-month follow-up. Neurology 1991;41:399-404.
17. Rausch R, Babb TL, Engel J Jr, Crandall PH. Memory following intracarotid amobarbital injection contralateral to hippocampal damage. Arch Neurol 1989;46:783-788.
18. Sass KJ, Lencz T, Westerveld M, Novelly RA, Spencer DD, Kim JH. The neural substrate of memory impairment demonstrated by the intracarotid Amytal procedure. Arch Neurol 1991;48:48-52.
19. O'Rourke DM, Saykin AJ, Gilhool JJ, Harley R, O'Connor MJ, Sperling MR. Unilateral hemispheric memory and hippocampal neuronal density in temporal lobe epilepsy. Neurosurgery 1993;32:547-581.
20. Kneebone AC, Chelune GJ, Dinner D, Awad IA, Naugle GJ. Use of the intracarotid amobarbital procedure to predict material specific memory change following anterotemporal lobectomy [abstract]. Epilepsia 1992;33(suppl 3):87.
21. Hermann BP, Wyler AR, Somes G, Berry AD, Dohan FC. Pathological status of the mesial temporal lobe predicts memory outcome from left anterior temporal lobectomy. Neurosurgery 1992;31:652-657.
22. Trenerry MR, Jack CR Jr, Ivnik RJ, et al. MRI hippocampal volumes and memory function before and after temporal lobectomy. Neurology 1993;43:1800-1805.
23. Jack CR, Sharborough FW, Cascino GD, Hirshorn KA, O'Brien PC, Marsh WR. Magnetic resonance based imaging-based hippocampal volumetry: correlation with outcome after temporal lobectomy. Ann Neurol 1992;31:138-146.
24. Loring DW, Murro AM, Meador KJ, et al. Wada memory testing and hippocampal volume measurements in the evaluation for temporal lobectomy. Neurology 1993;43:1789-1793.

No association of the 11778 mitochondrial DNA mutation and multiple sclerosis in Japan

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Article abstract—Leber's hereditary optic neuropathy (LHON), a maternally inherited disease causing severe bilateral visual loss in young men, is linked to 12 point mutations in mitochondrial DNA, the most common of which is at the nucleotide position 11778. The 11778 point mutation has also been detected in several patients with possible multiple sclerosis (MS), especially women with severe visual loss in both eyes. Because frequent and severe optic neuropathy is a feature of MS in Japan, we screened 80 Japanese MS patients for the presence of the 11778 mutation by mutation-specific polymerase chain reaction. Eighteen women with MS had bilateral optic neuropathy, but none had the mutation at 11778. There is no association between Japanese MS and the 11778 mitochondrial DNA mutation.

NEUROLOGY 1995;45:1333-1334

Leber's hereditary optic neuropathy (LHON), a maternally inherited disorder characterized by severe acute visual loss in both eyes in young men, is associated with 12 point mutations in mitochondrial DNA (mtDNA), including 11778.[1] Harding et al[2] reported eight women with the 11778 mutation who had bilateral optic neuropathy and either multiple sclerosis (MS) or white matter lesions in MRI but without clinically definite MS. This relation between an MS-like illness and the 11778 mutation was also supported by Flanigan and Johns.[3] Because most LHON patients in Japan have the 11778 mutation[4] and Japanese MS patients have more frequent and severe optic neuropathy compared with white patients with MS,[5] Japanese MS is suitable for determining the relation between MS and the 11778 point mutation.

In this study, we screened 80 unrelated, clinically definite Japanese MS patients by mutation-specific polymerase chain reaction (PCR) and confirmed 18 MS patients at high risk, ie, women with severe bilateral visual loss, by restriction enzyme analysis of PCR-amplified mtDNA.

Methods. Peripheral blood DNA was isolated by routine methods from 80 Japanese patients with clinically definite MS according to the criteria of McDonald and Halliday.[6]

PCR was carried out according to Saiki et al[7] with the following primer pair: 5′-ATACTCTTCAATCAGCCACATAGC-3′ (LHON-I), corresponding to mtDNA light-

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Received October 13, 1994. Accepted in final form December 17, 1994.

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