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Poor presurgical performance on both verbal and visual memory measures is associated with low risk for memory decline following left temporal lobectomy for intractable epilepsy

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ABSTRACT – Studies have shown a lower risk for verbal memory decline following dominant anterior temporal lobectomy (ATL) among patients with poor, presurgical verbal memory scores. It is unclear however, if the risk of decline is increased in patients who also have reduced visual memory. Objective and subjective memory outcome following left ATL was examined in twelve patients with reduced presurgical visual and verbal memory scores. Only one patient demonstrated a meaningful decline in memory scores, with a decline in visual memory following surgery. Presurgically, this patient demonstrated poor memory bilaterally on Wada testing and small discrepancy in hippocampal volumes. She was also one of two patients who continued to have seizures post-surgery. This preliminary study suggests that patients with unilateral, left TLE and poor verbal and visual memory are unlikely to show meaningful memory declines following left ATL, particularly if they demonstrate expected patterns on Wada testing, hippocampal volume discrepancy (left < right), and postsurgical seizure-freedom.

Key words: temporal lobectomy, temporal lobe epilepsy, cognitive outcome, memory

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There has long been debate in the literature about which factors are more closely related to post-operative memory decline following temporal lobectomy for the treatment of epilepsy. Some studies have supported a functional reserve model (Bell *et al.* 2000, Grunwald *et al.* 1998, Koutroumanidis *et al.* 2000), which posits that changes in memory ability after surgery are largely related to the capacity of the contralateral mesial temporal structures to support memory following resection (Chelune 1995). Other studies have supported a functional adequacy model (Chelune *et al.* 1991, Chelune *et al.* 1992, Helmstaedter 2004, Helmstaedter and Elger 1996), suggesting that postoperative memory decline is related to the functional ability of the resected tissue rather than the contralateral tissue (Chelune 1995).

One of the primary purposes of neuropsychological assessment, prior to temporal lobectomy, is to assist in determining which patients are at risk of postoperative memory morbidity. Over the years, neuropsychologists have identified a number of presurgical variables that are related to cognitive outcome following temporal lobectomy. One of the most reliable predictors of postoperative memory outcome following temporal resection is preoperative memory ability. Specifically, individuals with higher preoperative memory scores are at greater risk of decline in memory following temporal resection than those with lower preoperative memory scores (Chelune 1995, Chelune *et al.* 1991, Chelune *et al.* 1992, Helmstaedter 2004, Helmstaedter and Elger 1996, Jokeit *et al.* 1997), supporting the functional adequacy model. This is particularly true for patients who undergo dominant temporal resections, with approximately 10 to 60% of patients demonstrating significant declines in verbal memory (Chelune *et al.* 1991, Lee *et al.* 2002, Stroup *et al.* 2003).

Although studies have shown limited decline in verbal memory scores following dominant temporal resection among patients with poor presurgical verbal memory scores (Chelune 1995, Chelune *et al.* 1991, Helmstaedter and Elger 1996, Martin *et al.* 2002), it is unclear if risk is increased in patients with poor presurgical scores on both verbal and visual memory measures as a result of limited functional reserve of the contralateral tissue (Chelune 1995). This study sought to examine postoperative memory outcome on objective and subjective memory measures following left anterior temporal lobectomy (ATL) in patients with reduced presurgical visual, as well as verbal memory.

Methods

A retrospective review of our center's Institutional Review Board-approved, comprehensive, neuropsychology epilepsy database was conducted. Patients were included in the study if they: 1) had been diagnosed with unilateral, left temporal lobe epilepsy (TLE); 2) underwent left ATL for treatment of medically intractable seizures; 3) had pathologically-confirmed, left mesial temporal sclerosis (MTS); 4) had preoperative standard scores of less than 80 on both the Auditory and Visual Delayed Memory Indices of the Wechsler Memory Scale – Third Edition [WMS-III (Wechsler 1997a)]; 5) had Full Scale IQ scores greater than 70, as measured by the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III [Wechsler 1997b]); and 6) were right-handed or confirmed as left hemisphere-dominant for speech, based on Wada testing. A total of 12 out of 492 patients in our center's IRB-approved neuropsychology epilepsy database met the inclusion criteria for the study. Demographic and epilepsy variables for these patients are provided in *table 1*.

Table 1. Demographic and seizure data for study patients.

	Age	Sex	Education	FSIQ	Age at seizure onset	Duration of epilepsy	Seizure outcome Engel class
Pt 1	16	M	9	79	10	6	Ia
Pt 2	18	F	12	77	5	13	IV
Pt 3	20	M	13	105	5	15	Ia
Pt 4	53	M	12	77	41	12	Ia
Pt 5	17	M	11	88	1	16	Ia
Pt 6	46	F	12	89	12	34	III
Pt 7	26	M	12	74	9	17	Id
Pt 8	24	F	12	71	7	17	Ia
Pt 9	43	F	12	78	11	32	Ia
Pt 10	36	F	12	83	23	13	Ia
Pt 11	20	F	13	99	1	19	Ia
Pt 12	20	M	10	85	13	7	Ib

Age, education, age at seizure-onset, and duration of epilepsy are reported in years.
M: male; F: female.

Neuropsychological evaluation

Patients in the study completed comprehensive, preoperative and postoperative neuropsychological evaluations, which included the WMS-III. Postoperative data on the Visual Memory Index were missing for Patient 3. Individual changes in WMS-III Auditory and Visual Delayed Memory Indices following left ATL were examined and evaluated using Standardized Regression Based Change Scores (SRBs) as well as Reliable Change Indices (RCIs) (Martin *et al.* 2002). Change scores that exceeded the 90% confidence interval (*i.e.* ± 1.64 standard deviations) were considered to be meaningful.

In addition to objective memory testing, patients completed the Memory Assessment Clinics Self-Rating Scale (MAC-S [Winterling *et al.* 1986]), a self-report rating scale for evaluating everyday memory functioning, both prior to and following temporal lobectomy. This measure produces two summary scores: ability (*i.e.* how well the patient is able to remember specific types of information) and frequency (*i.e.* how often specific memory difficulties occur). Raw scores were transformed into standard scores ($M = 100$, $SD = 15$) using available normative data (Crook and Larabee 1992). Thus, a standard score of 100 represents average memory abilities and/or an average frequency of memory complaints as compared to normal controls. Higher standard scores represent fewer and/or less frequent memory complaints, and lower standard scores represent greater and/or more frequent memory complaints. Change scores were then calculated for each of the two scales by subtracting preoperative standard scores from postoperative standard scores. Change scores that exceeded two standard deviations from the normative mean, in either direction, were considered significant (Crook and Larabee 1992).

Hippocampal volumes

As part of routine presurgical evaluations, each patient underwent magnetic resonance imaging (MRI) using a Siemens 1.5 Tesla SP system (Siemens, Erlangen, Germany). Multiple coronal T1 and T2 images, sagittal T1 cuts, and axial T2 and FLAIR images were acquired for all patients. Volumetric analyses were performed using home-made software running on a Silicon Graphics workstation. Coronal 3D T1-weighted MP-RAGE (magnetization-prepared, rapid gradient-echo) was used to draw outlines of the hippocampus and amygdala. The details of the sequence are: TR 11.08 ms, TE 4.3 ms, 10 degree flip angle, inversion time = 360 ms, slice thickness = 2 mm, no interslice gap, in plane FOV 230 mm^2, 256 x 256 matrix. In order to determine hippocampal volumes, the right and left hippocampal formations were measured from the coronal sections following the anatomic guidelines previously outlined by Watson *et al.* (1992).

Wada testing

Ten of the 12 patients in this study also underwent bilateral Wada testing, using intracarotid amobarbital (125 mg) or brevital (5 mg), as part of their presurgical evaluations. Percutaneous transfemoral catheterization of the internal carotid artery was performed under local anesthesia. Amobarbital or brevital was injected serially into each internal carotid artery. By convention, the epileptogenic side was injected first. Times to the first nonverbal and to the first verbal response following each injection were recorded. Language dominance was established using the criteria established by Benbadis *et al.* (1995). The time interval between the two hemispheric injections was at least 30 minutes. Up to 16 memory items were presented during the period of hemiparesis following each injection. The memory items included four items from each of four separate categories: pictures, designs, object words, and abstract words. The patient was asked to name and remember each stimulus item. Recall of the memory test items was assessed an average of 15 minutes following injection. Clinical and EEG evaluations ensured that the patient had returned to baseline functioning prior to the delayed recall memory assessment. Firstly, an unscored, free recall was elicited. A recognition paradigm was then administered that contained the target item as well as three stimulus foils. Each correct response on the recognition trial was given a score of 1. Incorrect responses were not scored, and no corrections were made for false positive errors. Memory scores following each injection were expressed as a ratio of correct items to total items administered during the period of hemiparesis following each injection. The total score was recorded with a maximum possible score of 16 for each side. Baseline memory performance was documented prior to Wada testing using the same procedure.

Results

WMS-III results

The mean interval between pre- and postsurgical neuropsychological evaluation was 10.83 months (SD = 4.55; range 7-22 months). Patients' pre- and postoperative Delayed Memory Index scores on the WMS-III are depicted in *figures 1* and *2*. No patients demonstrated a meaningful decline in Auditory Delayed Memory Index score following left ATL; however, Patient 1 showed a meaningful improvement on this index using RCIs to evaluate change. Three patients showed significant changes in Visual Delayed Memory Index score using the RCI as well as the SRB methodology. Specifically, Patient 2 showed a significant decline in this Index, whereas Patients 1 and 5 demonstrated significant improvements. In order to rule out the possibility that floor effects precluded a reduction in standard scores following surgery, raw scores were examined on the WMS-III subtests. All patients, with the exception of

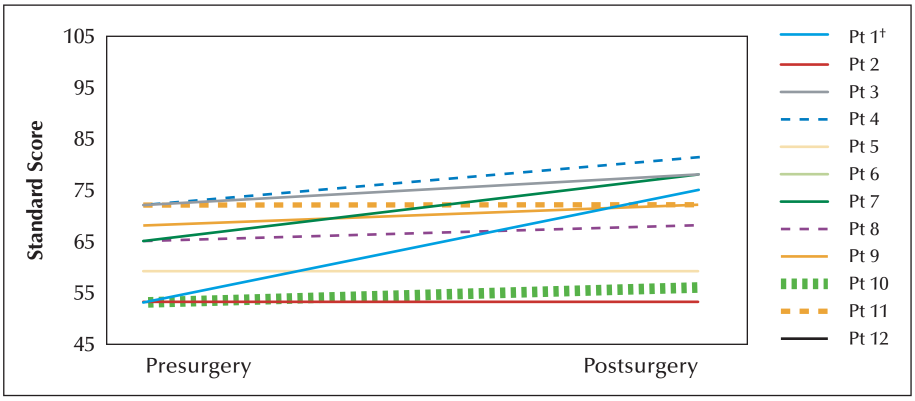

Figure 1. WMS-III Auditory Delayed Memory Index scores prior to and following left temporal lobectomy.
* Meaningful change as determined by Standardized Regression Based Change Scores (Martin *et al.* 2002).
† Meaningful change as determined by Reliable Change Indices (Martin *et al.* 2002).

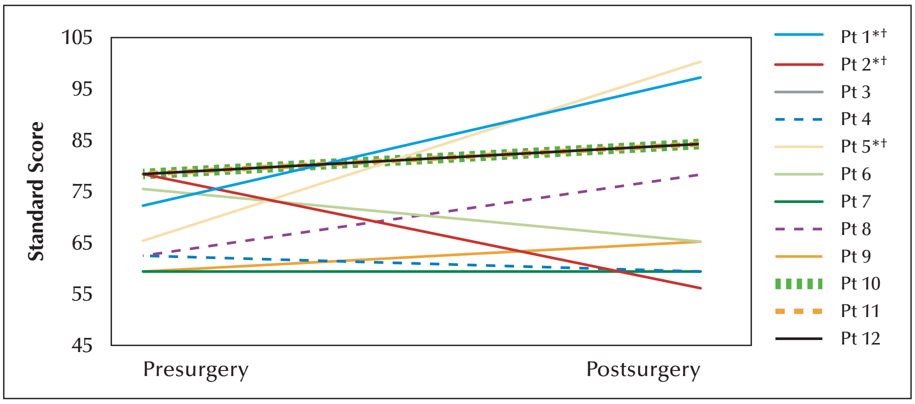

Figure 2. WMS-III Visual Delayed Memory Index scores prior to and following left temporal lobectomy.
* Meaningful change as determined by Standardized Regression Based Change Scores (Martin *et al.* 2002).
† Meaningful change as determined by Reliable Change Indices (Martin *et al.* 2002).

Patient 10 on verbal memory subtests, obtained scores above the floor presurgically and had potential to demonstrate a decline in raw test scores following surgery.

In order to understand which factors may have accounted for the decline in visual memory demonstrated by Patient 2, findings from this patient's preoperative investigations were examined. MRI findings (including hippocampal volumes), EEG findings, and Wada test results for each patient are summarized in *table 2*. Firstly, preoperative studies showed that Patient 2 had poor memory bilaterally on Wada testing. Only one other patient, Patient 3, demonstrated better memory performance following right *versus* left injection. All other patients showed the expected pattern given their left temporal epileptogenic focus. Secondly, Patient 2's data were notable in that the discrepancy between right and left hippocampal volumes prior to surgery was rather small. Only three other patients, Patients 5, 7, and 10, demonstrated a small discrepancy in hippocampal volumes. Finally, although Patient 2's typical automotor seizures did not recur following ATL, seizures arising from the left occipito-parietal region began approximately six months following surgery (Engel Class IV). Only one other patient, Patient 6, continued to have seizures after surgery (Engel Class III).

MAC-S Results

One patient, Patient 6, had missing data for preoperative MAC-S ratings. Of the remaining patients, only two demonstrated a significant change in MAC-S scores following left ATL *(table 3)*. Patient 10 reported a significant improvement on the Ability subscale, indicating a decrease in subjective memory complaints. In contrast, Patient 2 demonstrated significant decreases on both the Ability and the Frequency summary scores of the MAC-S, indicating a significant decline in subjective memory ability as well as an increase in the frequency of memory problems. Notably, this was the same patient who showed the problematic combination of factors noted above (*i.e.*, significant

Table 2. MRI findings, EEG findings, and Wada results.

	MRI findings			EEG findings		Wada findings			
	Pathology	Left hippocampal volume (cm^3)	Right hippocampal volume (cm^3)	Ictal EEG	Interictal EEG	Speech arrest left injection (seconds)	Speech arrest right injection (seconds)	Memory left injection	Memory right injection
Pt 1	left MTS	3.077	3.858	left temp	left temp 100%	124	0	12/16 (75%)	6/16 (38%)
Pt 2	left MTS	3.095	3.573	left temp	left temp 100%	195	34	8/16 (50%)	8/16 (50%)
Pt 3	left MTS	3.741	4.745	left temp	left temp 100%	195	0	3/12 (25%)	7/12 (58%)
Pt 4	left MTS	2.920	3.900	left temp	left temp 100%	48	0	11/16 (69%)	5/16 (31%)
Pt 5	left MTS	4.105	4.698	left frontotemp	left frontotemp	52	0	12/12 (100%)	11/12 (91%)
Pt 6	left MTS	2.826	4.712	left temp	left temp 94%; right temp 6%	85	0	7/8 (88%)	5/16 (31%)
Pt 7	left MTS	3.163	3.132	left temp	left temp 100%	106	0	11/16 (69%)	5/12 (42%)
Pt 8	left MTS	2.528	3.833	left temp	None	--	--	--	--
Pt 9	left MTS/diffuse insult in left hemisphere	2.874	4.083	left temp	left temp 60%; right temp 40%	177	189	10/12 (83%)	6/12 (50%)
Pt 10	bilateral MTS	2.331	2.464	left temp	left temp 100%	--	--	--	--
Pt 11	left MTS	2.539	4.357	left temp	None	130	0	9/12 (75%)	8/16 (50%)
Pt 12	left MTS/left parietal encephalomalacia	3.056	4.031	left hemispheric (maximum left temp)	left temp 100%	216	0	14/16 (88%)	11/16 (69%)

MTS: mesial temporal sclerosis; temp: temporal.

Table 3. MAC-S standard scores prior to and following left temporal lobectomy.

	Ability presurgery	Ability postsurgery	Change	Frequency presurgery	Frequency postsurgery	Change
Pt 1	96	101	+5	72	80	+8
Pt 2	116	65	-51*	94	65	-29*
Pt 3	95	96	+1	73	84	+11
Pt 4	72	79	+7	97	75	-22
Pt 5	97	108	+11	83	81	-2
Pt 6	--	91	--	--	68	--
Pt 7	84	85	+1	73	72	-1
Pt 8	79	82	+3	102	80	-22
Pt 9	85	74	-11	75	73	-2
Pt 10	64	100	+36*	59	86	+27
Pt 11	93	114	+22	85	89	+5
Pt 12	93	78	-15	85	64	-21

* Indicates change scores exceeding two standard deviations from normative mean.

decline in Visual Delayed Memory Index score, poor presurgical memory bilaterally on Wada testing, small discrepancy in hippocampal volumes, and seizure recurrence following surgery).

Discussion

Patients with reduced performance on both verbal and visual memory measures might be expected to demonstrate a decline in memory performance following left ATL due to limited functional reserve of the contralateral tissue. However, of the 12 patients in this study, 11 did not demonstrate meaningful declines in either verbal or visual memory performance and did not endorse an increase in subjective memory complaints following surgery. These data suggest that patients with unilateral left TLE due to MTS, and poor delayed memory scores (verbal and visual) are likely to be at low risk of memory decline following left temporal resection. This is particularly true for patients who demonstrate expected discrepancies in hippocampal volumes (left < right) and on Wada testing presurgically, and who are rendered seizure-free following surgery.

Only one patient in the current study, Patient 2, demonstrated a decline in memory scores and an increase in subjective memory complaints following left ATL. Interestingly, the objective memory declines were on measures of visual memory rather than verbal memory. Although visual memory decline is not typically associated with left ATL, reports in the literature have suggested that between 19 and 28% of such patients show significant declines on nonverbal memory measures when using statistical methods to control for practice effects at the individual patient level (Lineweaver *et al.* 2006, Martin *et al.* 1998). Patient 2's visual memory decline may, in part, be due to the fact that this patient continued to have seizures following surgery, which were localized to the left occipito-parietal region, suggesting that the patient's seizure focus was more widespread than originally thought and not limited to the temporal lobe. This is consistent with the literature suggesting that patients who continue to have seizures after temporal lobectomy have poorer cognitive outcomes as compared to those who are rendered seizure-free (Novelly *et al.* 1984, Sanyal *et al.* 2005). The patient also demonstrated poor memory bilaterally on Wada testing and a small discrepancy in left *versus* right hippocampal volumes, suggesting not only poor functional adequacy, but limited functional reserve in the contralateral hemisphere. In combination, these factors likely contributed to the objective and subjective changes in memory experienced by this patient.

Interestingly, fewer patients demonstrated declines on memory measures than would be anticipated given base rates reported in the literature. Using regression-based norms, verbal memory decline following dominant anterior temporal resection occurs in approximately 32 to 50% of patients (Lineweaver *et al.* 2006, Martin *et al.* 1998); however, none of the patients in this study demonstrated significant declines in verbal memory following surgery based on SRBs and RCIs. This likely reflects the fact that, *per* the inclusion criteria, all patients included in this study had reduced verbal memory scores prior to surgery. As reported previously, patients with low presurgical memory scores are at less risk of memory decline following temporal resection than those with intact verbal memory performance prior to surgery (Chelune 1995, Chelune *et al.* 1991, Chelune *et al.* 1992, Helmstaedter 2004, Helmstaedter and Elger 1996, Jokeit *et al.* 1997).

Findings from this study provide greater support for the functional adequacy model than the functional reserve model. The former model predicts that patients are at limited risk of further memory decline given their low verbal memory scores (*i.e.* limited functional adequacy) and the latter model predicts that patients are at increased risk of memory decline given their low visual memory scores (*i.e.* limited functional reserve). No patients in this study demonstrated verbal memory declines, providing support for the adequacy model. This conclusion also holds true if Wada findings are used to estimate adequacy and reserve. Using a cutoff of 75% correct memory performance to indicate adequate memory performance, all patients would have been considered to have limited functional adequacy based on performance following right-sided injection (assessing memory abilities of the left hemisphere) predicting limited risk for postsurgical memory decline. The only exception would be Patient 5, who demonstrated good memory performance on Wada bilaterally. In contrast, about half of the patients would have been considered to have adequate functional reserve, suggesting that 50% of patients would have been expected to demonstrate memory declines following surgery according to the functional reserve model. Since only one patient in this sample demonstrated memory decline, both cognitive test performance and Wada results in this study provide greater support for the functional adequacy model. This finding is consistent with most functional and structural studies to date, which provide greater support for this model (*e.g.* Chelune 1995, Chelune *et al.* 1991, Stroup *et al.* 2003, Kneebone *et al.* 1995, Trenerry *et al.* 1993).

There are several important limitations to the current study that should be noted. This study was based on a very small sample of patients with TLE, and rather strict criteria were used for selection. Firstly, all patients in this study had left TLE, and the results may not generalize to patients who undergo right temporal resections. Secondly, all of the patients in this study, with the exception of Patient 10, had unilateral left MTS as identified on MRI which was pathologically confirmed following surgery. Hence, these results may not generalize to patients with bilateral MTS or other pathologies (*e.g.* cortical dysplasia, tumor). Patients 9 and 12 were noted to have pathology in addition to MTS, but were likely still to be within the syndrome of left TLE given their seizure-freedom following surgery. Finally, all patients had Full Scale IQ scores greater than 70. A number of studies have suggested that patients with higher intellectual functioning and/or education levels have greater general cognitive reserve than patients with lower intellectual functioning (Oyegbile *et al.* 2004, Jokeit and Ebner 2007, Satz 1993). Therefore, it is possible that these patients were better equipped to compensate cognitively following surgery than those with lower levels of intellectual functioning. Hence, these findings may not generalize to patients with more global cognitive difficulties. Replication of this study in larger patient samples is clearly warranted to confirm these findings. □

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