

IT'S ABOUT TIME: LONG-TERM MEMORY OUTCOME FOLLOWING TEMPORAL LOBECTOMY

Verbal Memory Decline after Temporal Epilepsy Surgery?: A 6-Year Multiple Assessments Follow-up Study.

Alpherts WC, Vermeulen J, van Rijen PC, da Silva FH, van Veelen CW; Dutch Collaborative Epilepsy Surgery Program.

Neurology 2006;67:626–631. OBJECTIVE: To assess the long-term effects of temporal lobe epilepsy surgery on verbal memory.

METHODS: We assessed verbal memory performance as measured by a verbal learning test ("15 Words Test," a Dutch adaptation of Rey's Auditory Verbal Learning Test) before surgery and at three specific times after surgery: 6 months, 2 years, and 6 years in 85 patients (34 left temporal lobe [LTL] vs. 51 right temporal lobe [RTL]). An amygdalo-hippocampectomy and a neocortical temporal resection between 2.5 and 8 cm were carried out in all patients. RESULTS: LTL patients showed an ongoing memory decline for consolidation and acquisition of verbal material (both 2/3 SDs) for up to 2 years after surgery. RTL patients at first showed a gain in both memory acquisition and consolidation, which vanished in the long term. Breaking the group up into a mesiotemporal (MTS) group and a non-MTS group showed clear differences. The group with pure MTS showed an overall lower verbal memory performance than the group without pure MTS, in the LTL group more pronounced than in the RTL group. After surgery, both pathology groups showed an ongoing decline for up to 2 years, but the degree of decline was greater for the LTL patients with MTS compared with the non-MTS group. Becoming and remaining seizure-free after surgery does not result in a better performance in the long term. Predictors of postoperative verbal memory performance at 6 years after surgery were side of surgery, preoperative memory score, and age. CONCLUSIONS: The results provide evidence for a dynamic decline of verbal memory functions up to 2 years after left temporal lobectomy, which then levels off.

COMMENTARY

Both poorly controlled epilepsy and its treatment are associated with varying degrees of neuropsychological difficulty. Cognitive impairment may result from the underlying neurologic substrate giving rise to a patient's epilepsy, the negative effects of repeated seizures, or the effects associated with antiepileptic drug therapy, to name just a few important factors. Whether negative long-term or cumulative seizure effects on cognition exist is still a subject of debate (1); however, there is little doubt that successful epilepsy treatment that either decreases or eliminates factors associated with impaired cognition (e.g., becoming seizure-free, decreasing/eliminating antiepileptic drugs) can result in improved performance on neuropsychological tests.

For patients with localization-related epilepsy whose seizures cannot be adequately managed with medications, the best hope of successful therapy is surgical resection. Given the importance of the hippocampus and associated medial temporal lobe structures in the acquisition and formation of new memory traces, it follows that when seizures arise from the medial temporal lobe, there is a risk of significant postoperative memory decline; this risk is greater for patients undergoing surgery in the language-dominant hemisphere. Although multiple factors contribute to the surgical decision-making process, memory risks are strongly considered in patient selection and should be

viewed against the backdrop of expected cognitive change in the absence of surgical intervention. In both surgical and nonsurgical scenarios, an important factor is how neuropsychological performance may change over time. In most research studies, time is measured in increments of months and not years, and it is rare that multiple assessments are performed. Consequently, memory change typically is conceptualized as a static rather than dynamic process, and how cognition evolves over time while interacting with related factors, such as preoperative performance levels (2) or patient age (3), is incompletely understood.

Most reports describing post-temporal lobectomy memory change have examined relatively short periods of postoperative follow-up, typically on the order of 6–12 months in duration. As with any CNS lesion, there are multiple determinants of postsurgical functional outcome, including both the functional status of the tissue involved in the surgical resection (functional adequacy) and the functional status of remaining brain structures (functional reserve), particularly of the homologous brain regions to those included in surgery. Both components may be associated with a variety of effects, some of which may be beneficial (e.g., plasticity, leading to functional reorganization) and others that may be detrimental (e.g., degeneration from deafferentation).

When longer postsurgical intervals have been used to study memory change following anterior temporal lobectomy (ATL), it appears that a single follow-up assessment during the first postoperative year does not fully characterize longer-term memory outcomes. In a study of memory, using one of the longest (9–13 years) postsurgical follow-up periods included in any investigation, Rausch et al. observed that verbal memory

continued to decline beyond the first postoperative year (4). However, in addition to studying a relatively small patient cohort, Rausch et al. did not include preoperative MRI findings to characterize patients according to whether or not they displayed evidence of mesial temporal sclerosis (MTS). There were no cognitive evaluations between the initial postoperative assessment performed 1 year after surgery and the long-term follow-up; thus, two issues that could not be addressed were (i) the ongoing deterioration in verbal memory following left ATL and (ii) the time point at which the risk of progressive postoperative memory begins to wane. Also not addressed was the question of whether the presence or absence of MTS, which is a strong predictor of memory change following ATL, was associated with different temporal patterns of memory change following surgery.

The recent report by Alpherts and colleagues reveals a dynamic process of ongoing memory changes that, like the Rausch et al. study, suggests continuing memory decline beyond the first postoperative year. Unlike in the Rausch report, however, progressive postoperative memory deterioration was found to stabilize between the second and sixth postoperative year. As expected, Alpherts et al. observed significant memory decline in left ATL patients when tested 6 months after surgery. Right ATL patients had higher verbal memory scores at their 6-month follow-up compared to preoperative scores. Although memory improvement in right ATL patients is often attributed to practice effects from repeated exposure to the same memory stimuli, these results cannot easily be attributed to a simple practice effect since alternative memory test forms were used. When tested after 2 years, further verbal memory decline was observed in left ATL patients, while verbal memory in right ATL patients returned to preoperative levels. There appears to be a progression of verbal memory impairment following left ATL, even in patients who were rendered seizure-free. No further deterioration in verbal memory was reported when patients were tested during their 6-year follow-up. The progressive decline in verbal memory extending beyond 6 months was attributed to shrinkage of the hippocampal remnant, which has been shown to decrease in size throughout the first preoperative year.

It is when trying to understand the behavior of specific subgroups that many studies fall victim to small sample sizes. For example, using traditional statistical approaches, patients undergoing removal of a healthy, nonatrophied left hippocampus, and those with preoperative evidence of MTS both displayed comparable declines in verbal memory. Although this finding suggests a similar pattern of 2-year decline, regardless of whether MTS was present or not, comparison of the group means suggests that the outcome actually may have resulted from inadequate statistical power. When looking at delayed recall performance at each follow-up assessment, a differential pattern of memory change is suggested. From the second to the sixth

year follow-up, patients with left MTS improved on delayed recall (from 6.6/15 words to 7.3/15 words), whereas patients without MTS continued to decline slightly (from 8.2/15 words to 7.7/15 words). Although this effect was not statistically significant, it is consistent with literature suggesting increased risk for memory decline in patients with larger hippocampal volumes. However, the finding contrasts with one of the main conclusions put forth by Alpherts et al., which is that, based on a verbal learning performance summed across trials (rather than delayed verbal memory recall), the degree of memory decline is greater in left ATL patients with MTS than in those without MTS. Although a small sample, examination of delayed verbal memory performances raises the possibility that patients with left MTS may continue to experience verbal memory decline extending beyond the 2-year assessment point. Because nonsurgical patients with left temporal lobe epilepsy may continue to experience cognitive decline that is unrelated to seizure occurrence or antiepilepsy drug therapy, it is unclear whether the progressive memory decline seen in some left ATL patients more than 2 years after surgery simply reflects the progressive nature of the disease or some other currently unidentified mechanism.

The results of the Alpherts et al. study raise important issues that future reports might be careful to address. For example, is a similar dynamic pattern of postoperative change seen in other neuropsychological measures, in particular, in confrontation naming? Historically, confrontation-naming ability is considered a measure of semantic memory, reflecting general knowledge rather than the acquisition of new context-specific information, yet confrontation naming also is related to hippocampal structure (5) and function (6). In fact, confrontation-naming ability is a robust measure of dysfunction associated with left temporal lobe epilepsy (7,8), with well-established declines following left temporal lobectomy regardless of surgical technique (9). Thus, whether confrontation-naming declines follow the same dynamic time course as does delayed recall will be of considerable interest.

The inclusion of only surgical patients in the Alpherts et al. study resulted in primarily one issue being addressed, that is, the effects of left- versus right-sided ATL on neuropsychological outcomes. Thus, in order to study how memory changes over a similar time interval and to provide information regarding the relative risks of postsurgical memory change (4), it will be necessary to design a study with an appropriately matched nonsurgical control group. A control group of patients without a chronic neurological disease is necessary in any longitudinal study designed to assess ATL for which test-retest effects may exist. As reviewed in the previous issue of *Epilepsy Currents*, Hermann and colleagues determined that without such a control group, lack of cognitive decline on retest (i.e., of the expected practice effect) may incorrectly be interpreted as an

absence of cognitive deterioration, when in fact there is negative cognitive change (10,11). Such studies will provide valuable information for clinicians and patients to consider when evaluating treatment options, while simultaneously maximizing quality of life and overall cognitive health. Neuropsychological assessments performed only during the first postoperative year, appear inadequate to properly characterize longer-term neuropsychological outcomes following ATL.

by David W. Loring, PhD

References

1. Dodrill CB. Neuropsychological effects of seizures. *Epilepsy & Behavior* 2004;5(suppl. 1):21–24.
2. LoGalbo A, Sawrie S, Roth DL, Kuzniecky R, Knowlton R, Faught E, Martin R. Verbal memory outcome in patients with normal preoperative verbal memory and left mesial temporal sclerosis. *Epilepsy & Behavior* 2005;6:337–341.
3. Helmstaedter C, Reuber M, Elger CC. Interaction of cognitive aging and memory deficits related to epilepsy surgery. *Ann Neurol* 2002;52:89–94.
4. Rausch R, Kraemer S, Pietras CJ, Le M, Vickrey BG, Passaro EA. Early and late cognitive changes following temporal lobe surgery for epilepsy. *Neurology* 2003;60:951–959.
5. Seidenberg M, Geary E, Hermann B. Investigating temporal lobe contribution to confrontation naming using MRI quantitative volumetrics. *J Int Neuropsychol Soc* 2005;11:358–366.
6. Sawrie SM, Martin RC, Gilliam FG, Faught RE, Maton B, Hugg JW, Bush N, Sinclair K, Kuzniecky RI. Visual confrontation naming and hippocampal function: a neural network study using quantitative (1)H magnetic resonance spectroscopy. *Brain* 2000;123(Pt 4):770–780.
7. Busch RM, Frazier TW, Haggerty KA, Kubu CS. Utility of the Boston naming test in predicting ultimate side of surgery in patients with medically intractable temporal lobe epilepsy. *Epilepsia* 2005;46:1773–1779.
8. Raspall T, Donate M, Boget T, Carreno M, Donaire A, Agudo R, Bargallo N, Rumia J, Setoain X, Pintor L, Salamero M. Neuropsychological tests with lateralizing value in patients with temporal lobe epilepsy: reconsidering material-specific theory. *Seizure* 2005;14:569–576.
9. Hermann BP, Perrine K, Chelune GJ, Barr W, Loring DW, Strauss E, Trenerry MR, Westerveld M. Visual confrontation naming following left anterior temporal lobectomy: a comparison of surgical approaches. *Neuropsychology* 1999;13:3–9.
10. Hermann BP, Seidenberg M, Dow C, Jones J, Rutecki P, Bhattacharya A, Bell B. Cognitive prognosis in chronic temporal lobe epilepsy. *Ann Neurol* 2006;60:80–87.
11. Harden CL. New Evidence Supports Cognitive Decline in Temporal Lobe Epilepsy. *Epilepsy Curr* 2007; 7: 12–14.