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Limbic ERPs predict verbal memory after left-sided hippocampectomy

Thomas Grunwald,[CA] Klaus Lehnertz, Christoph Helmstaedter, Marta Kutas,[2] Nico Pezer, Martin Kurthen, Dirk Van Roost[1] and Christian E. Elger

Departments of Epileptology and [1]Neurosurgery, Bonn University Medical Center, Sigmund-Freud-Str. 25, 53105 Bonn, Germany; [2]Departments of Cognitive Science and Neuroscience, University of California, San Diego, CA, USA

[CA]Corresponding Author

SURGICAL removal of the dominant medial temporal lobe regions runs a considerable risk of verbal memory deficits which may be compensated for postoperatively by corresponding regions in the non-dominant medial temporal lobe. We examined this possibility by recording event-related potentials (ERPs) to words from the medial temporal lobes of patients with left-sided temporal lobe epilepsy (TLE) undergoing presurgical evaluation. N400 amplitudes in the right anterior medial temporal lobe predicted the postoperative verbal recall performance of individual patients with surprising accuracy, indicating that intracranial recordings can be used to quantify the functional capacities of the right hemisphere that can compensate for the verbal memory deficits after loss of medial temporal lobe structures in the left hemisphere. *NeuroReport* 9: 3375–3378 © 1998 Lippincott Williams & Wilkins.

Key words: Epilepsy surgery; Event-related potential (ERP); Memory; Temporal lobe

Introduction

Surgery has proven quite effective in patients with pharmacoresistant temporal lobe epilepsies (TLE). Unilateral hippocampal sclerosis, in particular, is associated with positive seizure control following surgery. However, surgical relief from epileptic seizure activity may come at the expense of neuropsychological deficits. Thus, during the evaluation of patients being considered for epilepsy surgery it is necessary to estimate the potential risk of postoperative neuropsychological deficits.

Since the initial reports on H.M. it has been known that bilateral hippocampectomy leads to profound amnesia.[1] Numerous other studies have confirmed the importance of medial temporal structures for declarative memory processes.[2–4] The known neuropsychological risks of unilateral hippocampectomy, however, seem to be confined primarily to the language-dominant hemisphere. Specifically, unilateral removal of medial temporal lobe structures in the left hemisphere often yields verbal memory deficits.[5] Since postoperative performance varies from patient to patient and there are reported cases of verbal memory improvement after left temporal lobe surgery, it may be that medial temporal structures in the non-dominant hemisphere contribute to performance after surgery. Several factors have been found to correlate with changes of verbal memory after left hippocampectomy, including hippocampal volumes and amount of hippocampal sclerosis.[6–8] Although these studies document the neuropsychological sequelae of the removal of left medial temporal lobe structures in these patients as a group, no single factor that predicts the specific postoperative verbal memory performance in any given individual patient has yet been identified. Prognosis from Wada testing may be promising[9] but has been found to be variable.[10]

Recordings of intracranial event-related potentials (ERPs) in TLE-patients have identified some negative potentials in the human medial temporal lobe related to registration of infrequently occurring events (e.g. MTL-P300), and others related to word processing in both anterior medial temporal lobes (e.g. AMTL-N400).[11–15] We have found that AMTL-N400s to words recorded in the dominant hemisphere are correlated with preoperative verbal recall performance.[16] Since these potentials can be elicited in both temporal lobes, they may prove useful in predicting the functional plasticity of bilateral medial temporal lobe structures involved in various memory processes.

To examine the extent to which the non-dominant temporal lobe contributes to postoperative verbal memory performance we recorded intracranial event-related potentials from depth electrodes within the medial temporal lobes of 40 patients with left TLE prior to surgery. Our aim was to use these potentials to predict the patients' verbal recall performance 3 months after temporal lobectomy or selective amygdalo-hippocampectomy.

Patients and Methods

Eighteen women and 22 men between 14 and 52 years (mean 32 ± 11) with left TLE in whom depth electrodes were implanted because seizure origin could not be localized non-invasively participated in the study. All patients were right-handed and had left-hemispheric language dominance according to results of neuropsychologial testing and/or the intracarotid amobarbital procedure (Wada test). Eight patients underwent left anterior temporal lobectomy; in 32 patients a selective amygdalo-hippocampectomy was performed. At the time of postoperative neuropsychological testing, 30 patients (75%) were seizure free. Informed consent was obtained from all patients and the study was approved by the local medical ethics committee.

Details of recording procedures and the location of electrodes have been described elsewhere.[15–17] In short, ERPs were recorded from bilateral depth electrodes implanted stereotactically along the longitudinal axis of the hippocampus with the amygdala as target of the most anterior contact and were referenced to extracranially linked mastoids. Electrical responses to false or missing reactions were not included in the averages. If visual inspection showed ERP data to be contaminated by spikes or sharp waves, recordings were repeated the following day. In two patients recordings from the focal side were not considered for the present studies as they were contaminated by epilepsy-specific potentials. Recordings were amplified with a bandpass filter setting of 0.003–85 Hz (12 dB/oct.), 12 bit A/D converted, and sampled at a rate of 173 Hz per channel. Amplitudes were measured relative to the mean amplitude of a 200 ms pre-stimulus baseline. In an oddball paradigm patients pressed a button to detected targets (60 events) among 240 frequent stimuli. Stimulus duration was 100 ms with an inter-stimulus interval varying randomly around 1200 ± 200 ms. For correlation and regression analyses the maximal MTL-P300 was defined as negative peak within the latency range 300–650 ms. In a word recognition paradigm 300 frequent nouns were presented (duration 200 ms) once every 1800 ± 400 ms. Seventy-five words were repeated with a delay of 3 ± 1 words intervening and 75 with a longer delay of 14 ± 4 intervening stimuli. Patients were asked to indicate whether an item was old or new by pressing one of two buttons. For statistical analyses the maximal AMTL-N400 potential was defined as largest negative peak from 300–600 ms. These measurements were also subjected to repeated measures ANOVA (F-test with Greenhouse–Geisser corrections for p values).

Pre- and postoperative verbal memory performance was assessed by a verbal learning and memory task on which patients with left TLE have been shown to perform more poorly with respect to free recall after a 30 min delay than either right TLE patients or normal controls.[5,18] Delayed verbal recall is a task on which patients with removal of the left hippocampus are very likely to show deficits.[19]

Results

Words seen for the first time in the experiment elicited a negative component peaking around 400 ms (AMTL-N400) in both anterior medial temporal lobes. Upon repetition, the AMTL-N400 was reduced in amplitude only on the non-epileptogenic side (repetition × side interaction, $F(1,37) = 4.63$, $p < 0.05$; t-test for paired samples of AMTL-N400 amplitudes on the non-epileptogenic side: $p < 0.0005$). Visual oddball stimuli elicited a pronounced negativity peaking around 500 ms (MTL-P300) in both hippocampi. These potentials were significantly smaller on the side of the epileptogenic focus ($p < 0.0005$; see Fig. 1).

There was no correlation between right and left MTL-P300 and postoperative verbal memory performance. By contrast, the amplitudes of right but not left AMTL-N400s to words on initial presentation correlated significantly with the number of words that patients could recall after a 30 min delay ($r = 0.81$, $p < 0.0005$) and with the percentage postoperative change relative to the preoperative performance ($r = 0.71$, $p < 0.00005$; Fig. 2).

Patients' age as well as the duration of the disease correlated negatively with postoperative free recall performance (age: $r = -0.40$, $p < 0.05$; duration: $r = -0.40$, $p < 0.05$) and the percentage of postoperative change (age: $r = -0.34$, $p < 0.05$; duration: $r = -0.41$, $p < 0.01$) as well as with right (but not left) AMTL-N400 amplitudes (age: $r = -0.54$, $p < 0.0005$; duration: $r = -0.44$, $p < 0.005$).

In a backward stepwise regression analysis with the percentage of postoperative change as dependent and various ERP amplitudes as well as age and the duration of the disease as independent variables, only right and left AMTL-N400 amplitudes; MTL-P300 amplitudes, age and the duration of epilepsy did not. Together the medial temporal N400 potentials from the right ($\beta = 0.75$; $t = 6.562$, $p < 0.00005$) and left hemispheres ($\beta = -0.27$; $t = -2.335$, $p < 0.05$) accounted for 56% of the variance of postoperative

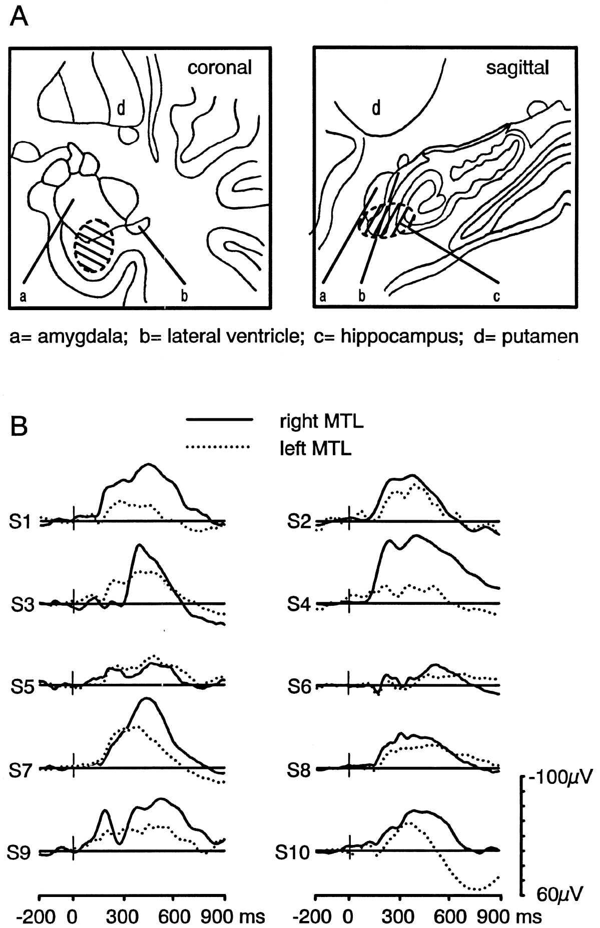

FIG. 1. Area of electrode locations at which maximal AMTL-N400s were recorded within the right temporal lobe and examples of potentials from 10 patients. (**A**) Schematics of recording sites of AMTL-N400s to words. Hatching spans the area of recording sites across all patients. (**B**) Examples of AMTL-N400s to initial presentations of words. Solid line: recording from the right (non-focal) mesial temporal lobe (MTL); dashed line: recording from the left (focal) mesial temporal lobe.

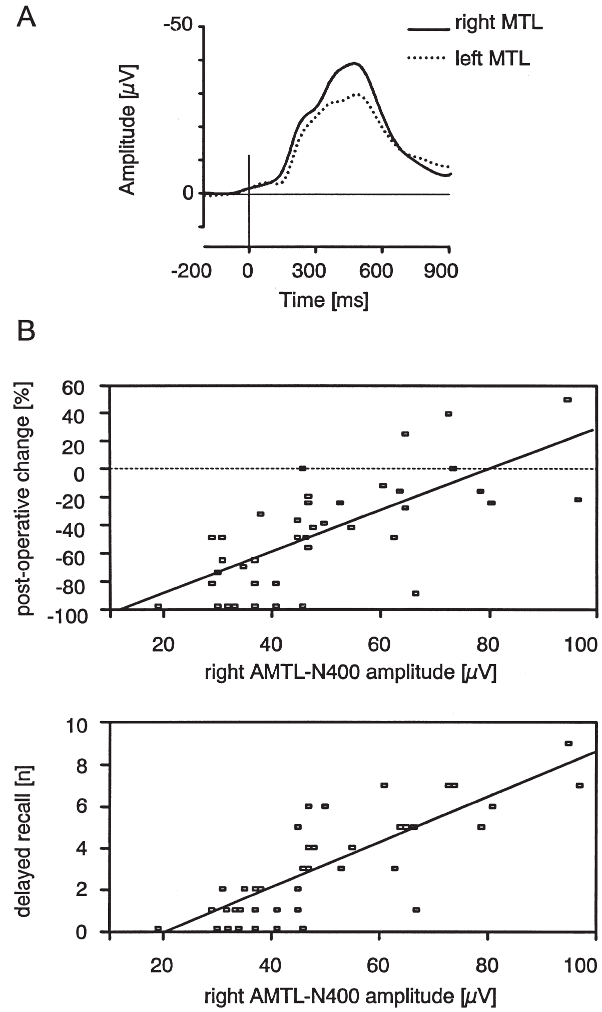

FIG. 2. Grand averages of AMTL-N400s to words and relationships between right AMTL-N400s and postoperative verbal memory performance. (**A**) Grand averages of AMTL-N400s to initial presentations of words ($n = 40$). Solid line: recording from the right (non-focal) mesial temporal lobe (MTL); dashed line: recording from the left (focal) mesial temporal lobe. (**B**) Scatter diagrams of percentage of postoperative change of delayed recall for words ($\beta = 0.75$, $p < 0.00005$) and absolute postoperative delayed recall performance ($\beta = 0.81$, $p < 0.00005$) regressed onto right AMTL-N400 amplitudes. Note that there are three patients with a positive change, i.e. a better performance postoperatively compared with preoperatively.

change in delayed free verbal recall performance after left-sided hippocampectomy. By contrast, only right AMTL-N400s entered the regression equation predicting the postoperative free recall performance ($\beta = 0.81$; $t = 8.238$, $p < 0.00005$), accounting for 65% of the variance.

Discussion

Several studies have shown that the AMTL-N400 is generated by parahippocampal structures of the anterior medial temporal lobe near the collateral sulcus, and that the MTL-P300 is generated intrahippocampally.[20–22] Here we find that the amplitude of limbic N400s to words but not of the limbic P300 to rare target stimuli predicts postoperative delayed verbal recall performance. This finding is consistent with the sensitivity of the N400 to lexical semantic manipulations[23] and the view that the mesial temporal cortex adjacent to the hippocampus proper critically contributes to human memory processes (for a review see Ref. 24).

Based on hippocampal volume or neuronal loss it appears that the greater the degree of pathology in the epileptogenic left hippocampus, the less of an impact its surgical removal has on an individual's verbal memory performance postoperatively.[11] Thus, we might have expected a negative correlation between left AMTL-N400s and postoperative verbal memory performance. While we did not find such a correlation, our multiple regression analyses do show that the larger the AMTL-N400 in the left hemisphere preoperatively, the greater the drop in postoperative free recall performance. Not surprisingly, the effects of surgically removing left MTL-structures are more marked the better they were functioning preoperatively. The correlation we found between right AMTL-N400 amplitude and postoperative free recall indicates that the greater the functional integrity of right MTL-structures the more likely these are to compensate for loss of the functionality of the removed left MTL-structures. The surprising accuracy with which only the right and not the left AMTL-N400s predict delayed verbal recall performance postoperatively suggests that upon removal of the left hippocampus, the non-dominant medial temporal lobe contributes to or takes over at least some of the functions that were preoperatively subserved by the dominant hemisphere.

The inverse relation between right AMTL-N400 amplitude and age and duration of TLE may reflect both the known decline in the number of hippocampal neurons with advancing age[25] and the observed bilateral loss of hippocampal neurons in patients with unilateral TLE.[26] Since postoperative verbal memory performance is worse the older the patients and the longer that they have had epilepsy, it would seem that surgery of the dominant medial temporal lobe for relief of medically intractable seizures should be performed earlier than later.

Conclusion

Our findings indicate that the functional integrity of the right hippocampal formation is crucial for verbal memory performance after left hippocampectomy. These data cannot be used to determine whether this is a consequence of the interhemispheric transfer of functions or postoperative recruitment of preexistent functional capacities of the right medial temporal lobe. In any case, our results do show that it is possible to use the amplitude of the AMTL-N400 in the right temporal lobe to words to predict neuropsychological outcome of surgery to the left medial temporal lobe in individual patients, and thereby, protect candidates at risk from profound, surgically-induced verbal memory deficits.

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