Reduced Sensitivity of the N400 and Late Positive Component to Semantic Congruity and Word Repetition in Left Temporal Lobe Epilepsy

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ABSTRACT

We studied 14 patients with well-characterized refractory temporal lobe epilepsy (TLE), 7 with right temporal lobe epilepsy (RTE) and 7 with left temporal lobe epilepsy (LTE), on a word repetition ERP experiment. Much prior literature supports the view that patients with left TLE are more likely to develop verbal memory deficits, often attributable to left hippocampal sclerosis. Our main objectives were to test if abnormalities of the N400 or Late Positive Component (LPC, P600) were associated with a left temporal seizure focus, or left temporal lobe dysfunction. A minimum of 19 channels of EEG/EOG data were collected while subjects performed a semantic categorization task. Auditory category statements were followed by a visual target word, which were 50% "congruous" (category exemplars) and 50% "incongruous" (non-category exemplars) with the preceding semantic context. These auditory-visual pairings were repeated pseudo-randomly at time intervals ranging from ~10–140 seconds later. The ERP data were submitted to repeated-measures ANOVAs, which showed the RTE group had generally normal effects of word repetition on the LPC and the N400. Also, the N400 component was larger to incongruous than congruous new words, as is normally the case. In contrast, the LTE group did not have statistically significant effects of either word repetition or congruity on their ERPs (N400 or LPC), suggesting that this ERP semantic categorization paradigm is sensitive to left temporal lobe dysfunction. Further studies are ongoing to determine if these ERP abnormalities predict hippocampal sclerosis on histopathology, or outcome after anterior temporal lobectomy.

INTRODUCTION

Temporal lobe epilepsy (TLE) is well known to be associated with memory dysfunction and hippocampal sclerosis,[1] especially when epileptic seizures are poorly controlled. Patients with left TLE (LTE) often display deficits in verbal memory, out of proportion to their deficits in non-verbal memory and other cognitive domains.[2,3] In contrast, patients with right TLE (RTE) have more subtle memory deficits, evident mostly on intensive testing of spatial memory using material that cannot be easily encoded using verbal representations or strategies.[4,5]

ERP word repetition effects (i.e., ERP differences between new/old words) have been related to memory processes by many investigators. Specifically, the amplitude of a late positive component (LPC, or "P600") has been shown to be predictive of subsequent recall.[6] Also, when words are repeated in a list format, items remembered as familiar/old elicit larger LPCs than new or unrecognized items.[7,8] When words are repeated in a semantically predictable context, the amplitude of the LPC usually decreases.[9] The size of this LPC repetition effect has been related to verbal, but not nonverbal, memory abilities in normal subjects and in patients with memory disorders.[9] Therefore, it is likely that this ERP paradigm, which involves a semantic categorization task with incidental learning of repeated associations, may test the functional integrity of the dominant medial temporal lobe. Thus, either an absent[10] or asymmetrical[11] LPC repetition effect might predict the laterality of hippocampal sclerosis and neighboring temporal lobe pathology.

Other prior ERP studies have emphasized the relationship of the N400 component, which precedes the LPC, to verbal memory. The N400, reliably elicited by semantically unpredictable words, is an electrophysiological index of semantic integrative processes.[12,13] Helmstaedter et al.[14] found that the amplitude of the N400 recorded over the left lateral temporal cortex in patients with TLE correlated with

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immediate recall. In contrast, larger amplitudes of the N400 recorded in anterior medial temporal lobe (AMTL) depth electrodes were associated with better retention on delayed recall. Thus, the N400 amplitude, or its repetition effect (frequently absent in the epileptogenic temporal lobe) may also reflect verbal memory and/or dominant temporal lobe dysfunction. While the main N400 generators are thought to reside in the anterior fusiform gyrus bilaterally,[15,16] N400s can also be recorded in the parahippocampal gyrus,[16] inferior to the amygdala and in the hippocampal head.[17] The present study was conducted to test if scalp asymmetries of these ERP components, or their repetition effects, might reflect the side of epileptogenesis or temporal lobe pathology in patients with TLE. We hypothesized that abnormalities of the N400 and LPC would occur predominantly in those patients with a left temporal seizure focus. Also, it is possible that asymmetries of these ERP components, or their repetition effects might reflect the side of epileptogenesis.

METHODS AND MATERIALS

Patients

We studied 14 patients with refractory TLE, all of whom were candidates for epilepsy surgery at the University of California, San Diego Epilepsy Center. Each underwent an extensive inpatient evaluation that identified a primary seizure focus in either the left (n=7) or right (n=7) temporal lobe. Patients had Phase I video-EEG analysis of ictal events with a minimum of 21 scalp electrodes and sphenoidal electrodes. In some cases Phase II studies were performed with bilateral 5-contact foramen ovale electrodes and/or subdural strip electrodes placed over the lateral and basal temporal, and inferior and lateral frontal lobe. Presurgical evaluation also included history, exam, interictal EEG, neuroimaging studies (MRI with temporal lobe protocol), neuropsychometric studies, Wada test, and in some cases PET, magnetic source imagery, magnetic resonance spectroscopy, and psychiatric screening, where appropriate. Prior to surgery, patients were studied with cognitive ERPs and behavioral measures. All provided informed consent according to a protocol approved by the Human Research Protection Program at the University of California, San Diego. Ages ranged from 22 to 65 years (mean = 41.9 ± 12.7 (SD)). There were no significant intergroup differences in age (43.9 ± 11.4 yrs. in LTE vs. 39.9 ± 14.5 in RTE; $t_{12} = .57$, $p = .58$), years of education (13.4 ± 1.4 in LTE vs. 14.6 ± 1.5 in RTE; $t_{12} = 1.47$, $p = .17$), or mini-mental state exam scores (29.9 ± 0.4 in LTE vs. 29.0 ± 1.2 in RTE; $t_{12} = 1.87$, $p = .09$). There were six females in the RTE group and 4 females in the LTE group ($\chi^2 = 1.4$, $p = .24$). All were right-handed except for one RTE patient. All were receiving anti-epileptic drugs (AEDs) at the time of the ERP recordings, each typically requiring two anticonvulsants. The most common medications were carbamazepine (n=6), phenytoin (n=5), and lamotrigine (n=4). There were no significant differences between the LTE and RTE groups in the mean dosage of these medications, or in the frequency of taking specific AEDs. The mean seizure frequency per month (preoperative) was 20.9 (SD=31.9; median=6) in LTE and 20.6 (SD=43.9; median=3) in RTE (Mann-Whitney U=15.0, p=0.22). Exclusions included severe auditory or visual impairment (visual acuity poorer than 20/50 binocularly with correction), history of schizophrenia, other neurological diseases (e.g., stroke or tumors), or severe medical illnesses (e.g., active infections, hepatic, renal, pulmonary, or cardiac failure). Four of the 7 patients in each group had unilateral mesial temporal sclerosis in the epileptogenic hemisphere, evident on MRI or surgical histopathology (where available). Two patients in each group had focal MRI lesions in the epileptogenic temporal lobe (1 cavernous angioma in each group, 1 had gliosis in the right basal temporal lobe, 1 left anterior temporal noninvasive tumor), while 1 patient in each group had nondiagnostic MRI scans without hippocampal sclerosis or focal lesions.

Stimuli

The stimuli were 216 phrases describing a category (e.g., "A type of wood", "A breakfast food"), each followed by a single target word which either fit or did not fit the category. Categories and targets were selected from published norms,[18,19] or constructed by the experimenters with the aid of normative questionnaires. Half of the target words were medium typicality exemplars of the selected categories, usually the fourth or fifth most common exemplar (e.g., "cedar" and "pancake" for the categories above). Half of the targets were concrete nouns that were incongruent with their associated category, but matched for frequency of usage[20] (mean of 32, SD = 48) and word length (5.8 characters, SD = 1.6).

Each subject was assigned to one of three stimulus lists. Each list included 36 congruent targets presented once, 36 presented twice, 36 presented three times, and equal numbers of incongruent targets in the same repetition conditions, for a total of 432 trials. Half of the stimuli were congruent and half incongruent; half were new and half were repeats. The repeated targets were counterbalanced across the three stimulus lists, so that across subjects, each item appeared in each repetition condition. Repeated targets always appeared with the same category as on the first presentation. For singly repeated category-target pairings, the lag between first and second presentations was 0-3 intervening trials (spanning 10-40 seconds). For doubly repeated items, the lag for both second and third presentations was 10-13 intervening trials (spanning ~120 seconds).

General Procedure

Subjects were seated 125 cm from a microcomputer video monitor. Category statements were read aloud, followed approximately 1 second later by a target word presented visually for 300 ms. Subjects were instructed to sit quietly for 3 seconds following a target, then to say the per-

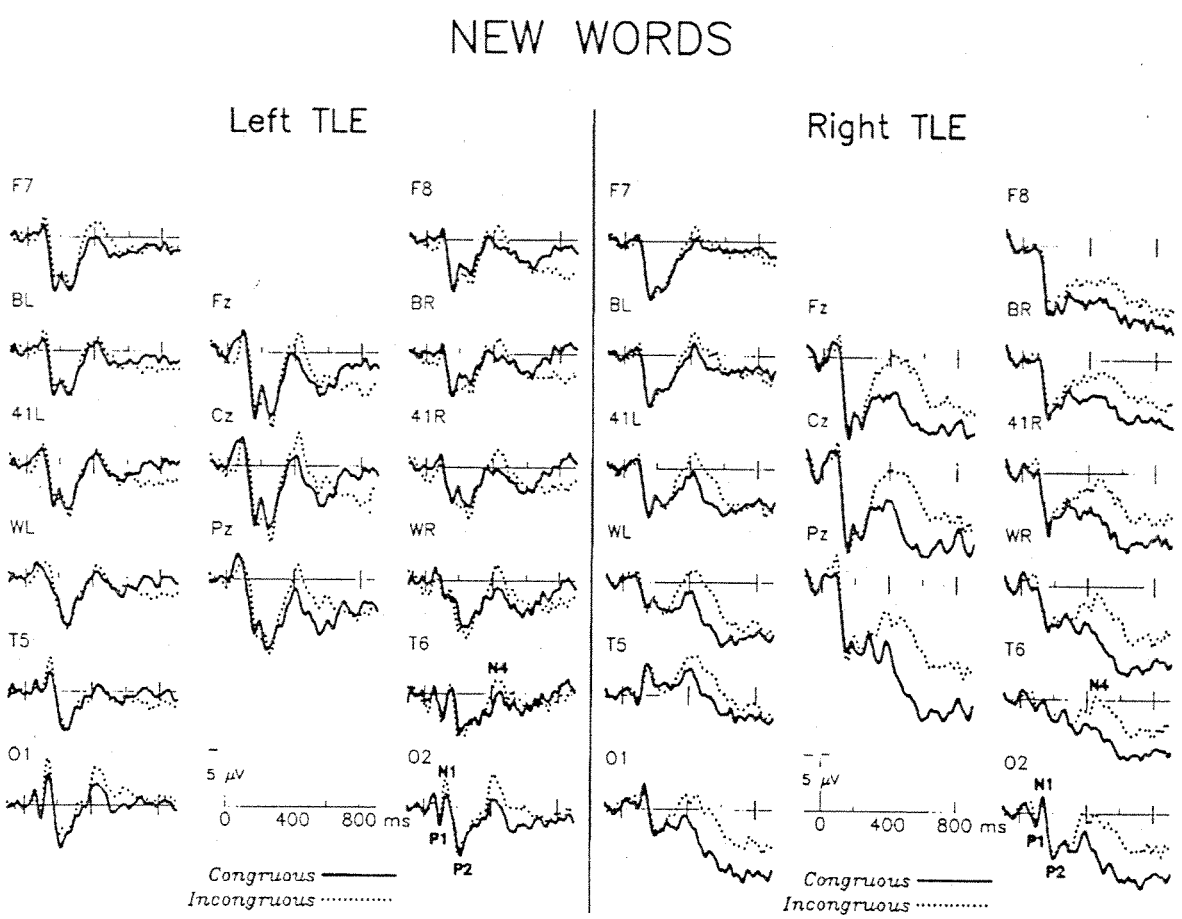

Figure 1.
Grand average ERPs of the left temporal lobe epilepsy (LTE) and right temporal lobe epilepsy (RTE) groups to new words that are semantically congruous and incongruous. Negative voltage is plotted up with left hemisphere electrodes on the left and right hemisphere electrodes on the right for both groups. The P1, N1 and P2 components have been identified at channel O2, and the N4 has been marked at channel T6.

ceived word aloud followed by a "yes" or "no" indicating whether or not it was an exemplar of the defined category.

Electrophysiological Recording

The electroencephalogram (EEG) was recorded from tin electrodes embedded in an elastic cap from 3 midline central (Fz, Cz, Pz), and lateral frontal (F7, F8), temporal (T5, T6) and occipital sites (O1, O2) placed according to the International 10-20 System.[21] Additional lateral sites included a pair placed halfway between F7 and T3 and F8-T4 (approximating Broca's area and its right hemisphere homologue, Bl and Br), a second pair 30% of the interaural distance lateral and 12.5% of the nasion-inion distance posterior to Cz (approximating Wernicke's area and its right hemisphere homologue, Wl and Wr), and a third pair 33% of the interaural distance lateral to Cz over the superior temporal lobe near Brodman area 41 (41L and 41R). All of the scalp electrodes plus the right mastoid electrode were referenced to the left mastoid during recording, then re-referenced off-line to an average of the left and right mastoids. Vertical eye movements and blinks were recorded via two electrodes, one below each eye, referenced to the mastoids; horizontal eye movements (Heog) were monitored by two electrodes at the outer canthi of the two eyes.

The EEG was amplified by Nicolet model SM-2000 digital amplifiers with a bandpass of 0.016-100 Hz and digitized on-line with a 250 Hz sampling rate. ERPs to the visual target words were averaged after off-line rejection of trials contaminated by artifacts[22] (e.g., eye movements, amplifier saturation, and excessive muscle activity) by a computer algorithm. Approximately 33 percent (33.2%) of trials were rejected for the LTE group, and 40.7% for the RTE group (t_{12} = 1.04, p = .29), leaving averages of approximately 256 accepted trials for the RTE group and 289 accepted trials for the LTE group. Even the patient with the fewest accepted trials (191) had at least 40 artifact-free trials averaged for each of the ERP conditions of interest (new congruous, new incongruous, old congruous, and old incongruous words).

RESULTS

Behavioral Data

Although mean performance on the category judgment task was near-ceiling for both groups, mean accuracy was

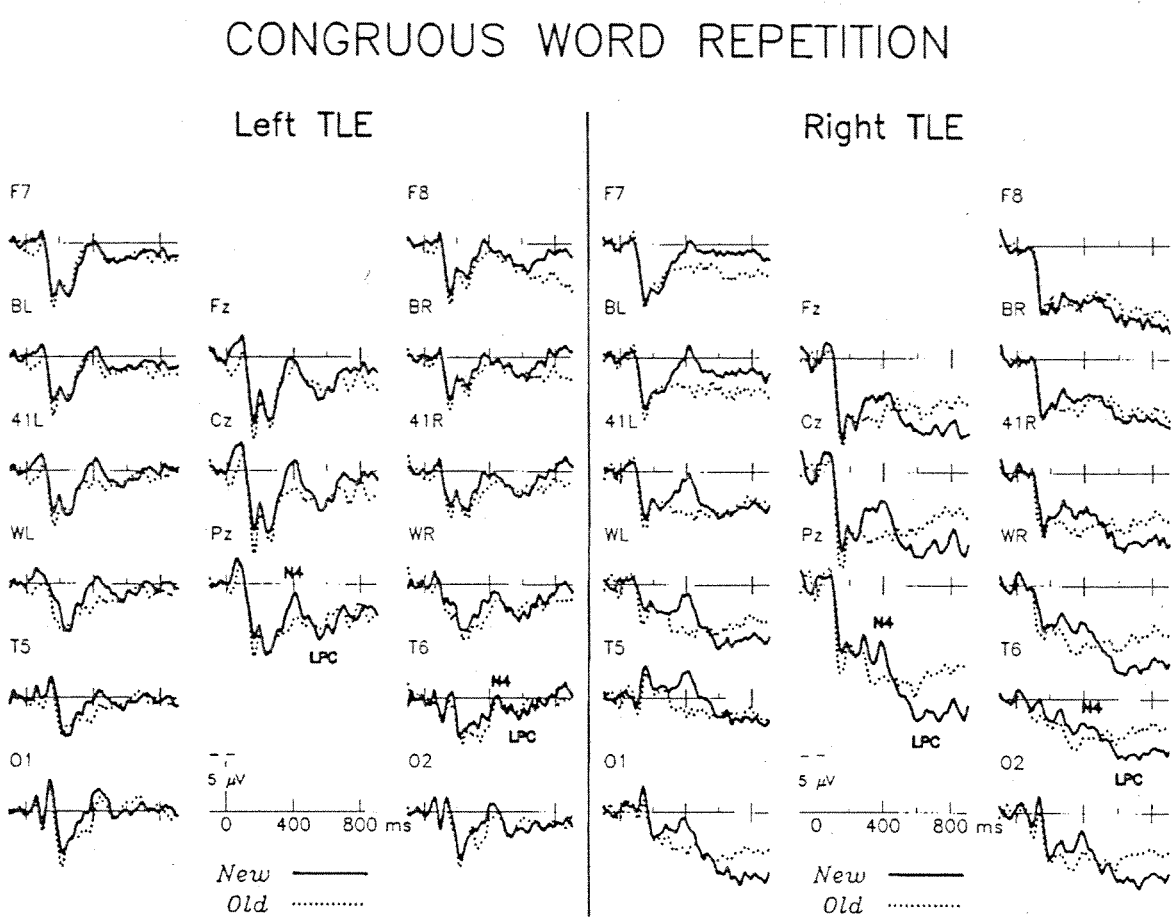

Figure 2.
Grand average ERPs for LTE and RTE groups elicited by new and repeated semantically congruous words. The N4 and Late Positive Component (LPC) are indicated at channels Pz and T6.

slightly higher in the RTE (99.2 ± 1.1%) than in LTE (98.3 ± 1.4%) patients. This was not a statistically significant difference (main effect of Group: ($F(1,12) = 1.45$, $p = 0.25$)). A main effect of Congruity was present ($F(1,12) = 11.3$, $p = 0.006$), which demonstrates that more errors occurred with congruous items than with incongruous items. There was no significant interaction between group and congruity ($F(1,12) = 0.45$, $p = .51$). The RTE group had 98.5% accuracy for congruous items and 99.9% accuracy for incongruous items, compared with 97.4% for congruous and 99.3% for incongruous items in LTE.

Event-related Potentials

The ERP results below describe: 1) the influence of semantic congruity on first presentation; 2) repetition effects for congruous words; 3) repetition effects for incongruous words.

1) Semantic congruity

Figure 1 shows the ERPs elicited by congruous and incongruous category words on first presentation. The waveforms were characterized by a P1 (peak latency at about 100 ms), a N1 (peak latency at about 150 ms) at temporal and occipital sites, and a P2 (peaks slightly after 200 ms) seen most clearly at posterior sites. The N400 elicited by incongruous words is most prominent between 300-500 ms in the bilateral temporal channels. In the RTE group the voltages are somewhat more negative over the left hemisphere during this epoch. The congruity effect, which begins at about 300 ms poststimulus onset in the RTE grand average, is less apparent in the LTE group. The LTE congruity effect is spatially restricted to midline and right hemisphere channels, starts slightly later (~350 ms), and is less sustained than in RTE. Mean amplitudes within the latency window of 300-550 ms poststimulus onset (both relative to a 100 ms prestimulus baseline) were computed to quantify the N400 amplitude and its repetition effect. These measures were submitted to a repeated-measures ANOVA with factors of Congruity and Electrode (for all scalp channels) or of Congruity, Hemisphere, and Electrode location (for all lateral channels). In the RTE group, repeated-measures ANOVAs of all scalp channels showed significant main effect of Congruity ($F(1,6) = 6.11$, $p = 0.048$) and Electrode ($F(14,84) = 4.75$, $\varepsilon = .23$, $p = 0.012$). Analyses of all lateral channels showed a significant effect of Hemisphere ($F(1,6) = 33.99$, $p = 0.001$), indicating larger negative voltages on the left. In the LTE group, there were no significant main effects of Congruity

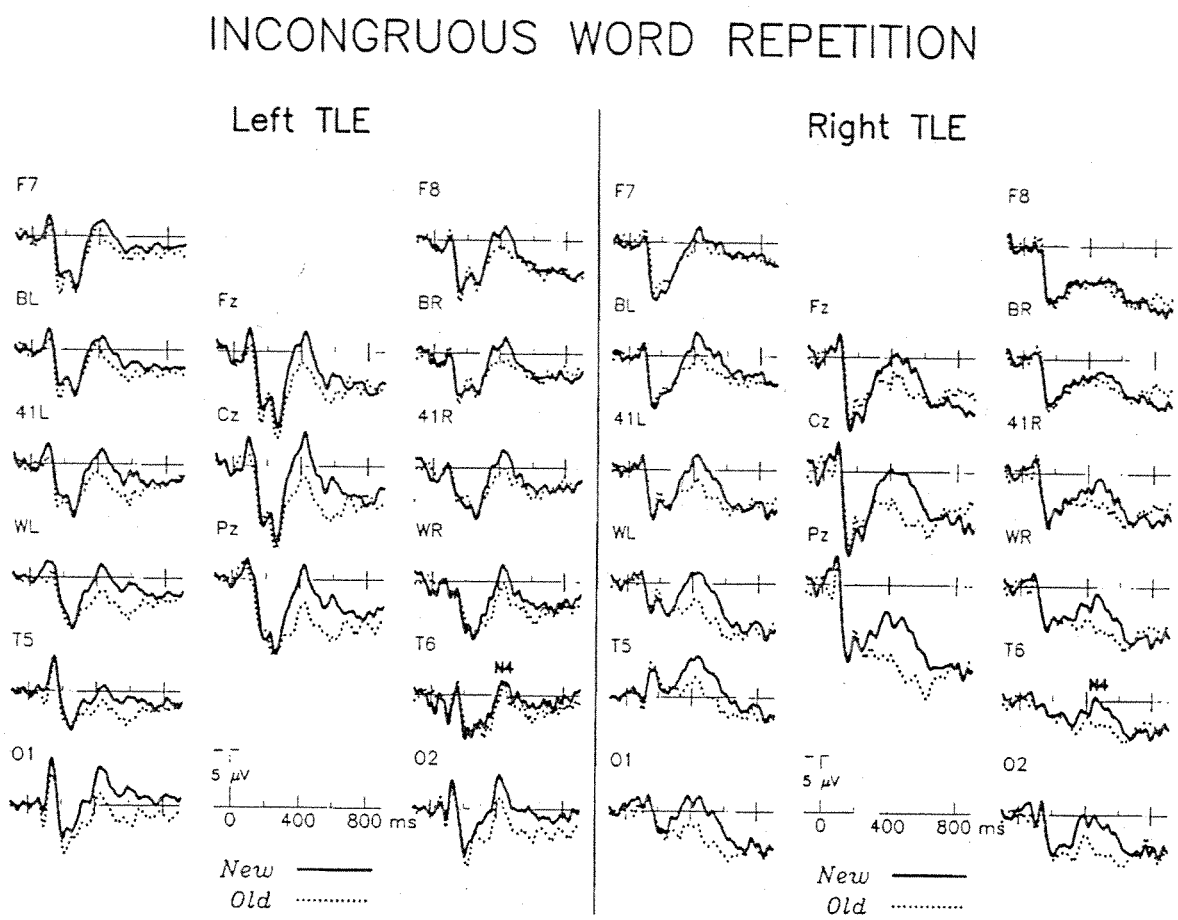

Figure 3.
Grand average ERPs from the LTE and RTE groups elicited by new and repeated semantically incongruous words. The N4 has been identified at channel T6.

(F(1,6) = 0.92, p = 0.38) or Electrode (p = .68). Analyses of all lateral channels showed no main effect of Hemisphere, but a 3-way interaction of Hemisphere x Congruity x Electrode was present (F(5,30) = 3.54, ε = .54, p = 0.038), indicating some preservation of the N400 congruity effect primarily in the right temporal channels.

2) Repetition of congruous words

Figure 2 shows the grand average ERPs elicited by the first and repeated presentations of congruous items, collapsed across repetition lag. In the RTE group, the new congruous words elicited a negative peak at ~400 ms post-stimulus followed by a late positivity, which peaked at ~600 ms post-stimulus. Both of these components are identifiable, but less pronounced in the LTE group. In the RTE group, both the earlier negativity and late positive component became smaller with repetition of these stimuli. This earlier portion of the "congruous word repetition effect," which started around 300 ms, differs from that normally seen in this paradigm.[9] Normal subjects have consistently shown decreased positivities to repeated congruous words, starting at ~500 ms, and minimal negative peaks (N400s) prior to this (and therefore no decreased negativities to repeated words prior to 500 ms). This early congruous word repetition effect showed a reversed polarity (more positive to repeated words) in our RTE group.

The ERPs to congruous items were analyzed by repeated-measures ANOVA with three factors: Repetition (all first vs. all repeated presentations), Latency window (300-550 and 550-800 ms), and Electrode location. A significant repetition X latency interaction was present (F(1,6) = 27.2, ε = .11, p = 0.017) in RTE, indicating the change in polarity of the congruous repetition effect between the "early" and "late" windows. A significant repetition X latency X electrode interaction was also present (F(14,84) = 37.5, ε = .20, p = 0.0001), reflecting that the repetition effect in the earlier ("N400") epoch had a distinct scalp distribution from that in the LPC epoch. Follow-up analyses showed that the early "congruous repetition effect" was statistically significant over left hemisphere channels (F(1,6) = 8.06, p = 0.03), and marginally significant over midline sites (F(1,6) = 5.2, p = 0.064). The late (LPC) repetition effect was significant over midline channels (F(1,6) = 6.8, p = 0.04), but did not reach significance across either left or right hemisphere channels (p = 0.99, and p = 0.12, respectively).

For the LTE group, there was no significant main effect of repetition (F(1,6) = .23, p = 0.65), nor a significant inter-

action of repetition X latency ($F(1,6) = 0.83$, $p = .40$), nor of repetition X electrode ($F(14,84) = 0.24$, $p = .86$). In contrast to the RTE group, there was neither a significant early congruous repetition effect over the left ($F(1,6) = 1.49$, $p = 0.27$), nor a significant LPC repetition effect at midline sites ($F(1,6) = 0.01$, $p = .92$).

3) Repetition of incongruous words

Repeated incongruous items elicited more positive ERPs than new items (Figure 3). This repetition effect, which occurred primarily in the N400 latency range, appears somewhat larger in the RTE group, and is fairly symmetrical in both groups. In the RTE group, repeated measures ANOVA of the 300-550 ms latency window revealed significant main effects of repetition ($F(1,6) = 6.17$, $p = 0.047$), and electrode ($F(14,84) = 4.27$, $\varepsilon = .19$, $p = 0.02$). Analyses of the lateral channels showed a main effect of hemisphere ($F(1,6) = 15.2$, $p = 0.008$), but no hemisphere X repetition interaction ($F(1,6) = 1.33$, $p = 0.29$). These data are most consistent with the repetition effect for semantically incongruous items resulting from a reduction in the amplitude of the N400 over both hemispheres in RTE. Analogous ANOVAs in LTE showed the effect of repetition did not reach statistical significance ($F(1,6) = 1.60$, $p = .25$). It should be noted that much of the repetition effect apparent in the LTE grand average was due to one outlier with a very large N400 repetition effect (~10 μV at temporal channels Wl and Wr). All other six patients with LTE had absent or small (< 1.5 μV averaged across Wl and Wr) N400 repetition effects, which were smaller than the mean (2.12 μV) and median (1.74 μV) amplitudes in RTE. The effects of electrode ($p=.62$) and hemisphere ($p=.83$) were also nonsignificant in LTE.

DISCUSSION

Abnormalities of the N400 and LPC ERP components were found in patients with LTE, which were not present in patients with RTE. Specifically, word repetition effects were reduced for both the LPC and N400 in LTE. Both of these components have been linked to memory processes in prior studies.[6,9,14] We postulate that the reduced LPC repetition effect in LTE is indicative of left medial temporal lobe dysfunction, which may be related to hippocampal sclerosis. It is likely that the present semantic categorization task (word repetition paradigm) selectively activates left temporal lobe structures and might therefore be preferentially sensitive to left over right hippocampal sclerosis. An fMRI study found much greater activation of the left medial temporal lobe (MTL) during a semantic decision task in RTE than in left LTE patients.[23] Prior intracranial ERP studies have shown that the hippocampus is capable of producing very large LPC-like potentials.[24] However, many other paralimbic cortices (e.g., entorhinal, perirhinal, and posterior cingulate) are also likely LPC generators. Grunwald et al.[17] reported that epilepsy patients with hippocampal sclerosis had reduced word repetition effects (of the AMTL-N400 usually recorded slightly anterior to the hippocampal head), unlike those patients without hippocampal sclerosis or hippocampal seizure foci. Their behavioral paradigm was an explicit recognition task to words repeated in a list format. Unfortunately, they did not present these data broken down by hemisphere of epileptogenesis in their TLE cohort. In an earlier report, Grunwald et al.[25] demonstrated that the amplitude of N400-like potentials recorded in the dominant medial temporal lobe correlated with verbal recognition abilities of patients with seizure foci in the nondominant hemisphere.

In the present study, we also found left TLE patients had reduced N400 repetition effects (to incongruous items). These incongruous words are more similar (than are the congruous words) to the word list paradigm of Grunwald et al.[17,25] in that they are not preceded by any supportive semantic context. Therefore, it is feasible that reduced N400 repetition effects at the scalp in LTE could also indicate hippocampal sclerosis, or hippocampal dysfunction. However, most intracranial studies have located the main N400 generators to be in the anterior fusiform gyrus, and occasionally in the lateral parahippocampal gyrus, as well.[16] Grunwald et al[25] report usually finding no significant N400 activity in the posterior or mid-hippocampus. Thus, the reduced N400 repetition effects in LTE could also be accounted for by dysfunction of the anterior fusiform gyrus or other neighboring extra-hippocampal structures (and not require dysfunction of the hippocampus).

A third ERP abnormality of our LTE group was a reduced N400 effect to congruity (incongruous vs. congruous new word contrasts). This finding may indicate abnormal semantic processing in LTE due to left temporal dysfunction. The slight increase in errors on the semantic categorization task in LTE suggests a mild deficit in semantic processing. Neuropsychological measures of language abilities also showed nonsignificant trends for poorer performance in LTE than RTE (e.g., Boston Naming Test[26] = 43 ± 13 vs. 51 ± 5; Category fluency[27] = 32 ± 14 vs. 38 ± 8 total for animals, fruits and vegetables). Even if inferior and lateral temporal cortices are not the source of seizure activity, it is plausible that these regions could become transiently or permanently affected by the propagation of seizure activity or even excitotoxicity mediated neuronal death. It is unlikely that the insensitivity to semantic congruity in LTE was due to medications (or attention) since these did not differ significantly from the RTE group.

Also interesting is the asymmetry of the N400 in the RTE group (decreased N400 amplitude on the right, relative to the left hemisphere), which is not normally elicited by this paradigm and may be a useful lateralizing sign of right temporal pathology. However, the RTE group had normal N400 congruity effects to new words and normal N400 repetition effects (new – old incongruous words) indicating functional N400 generators, perhaps of the dominant temporal lobe. Grunwald et al.[17] found a similar pattern of results in their

subset of patients without hippocampal sclerosis: smaller N400s ipsilateral to the extra-hippocampal seizure focus, but with preserved effects of word repetition. Since most of our RTE patients had MRI evidence of mesial temporal sclerosis (and had a similar frequency of seizures to our LTE group), it is likely that the scalp N400 repetition effect elicited by this paradigm is not dependent on the functional integrity of the right hippocampus. Rather, we favor the interpretation that this scalp N400 repetition effect is largely generated by the left inferior or medial temporal lobe, which should be functioning well in most RTE patients. However, dysfunction of the right inferior or medial temporal lobe is likely present in RTE and might give rise to the relatively diminished N400 amplitude over the right hemisphere.

Some prior ERP studies have also found asymmetries in TLE. Rugg et al.[28] reported asymmetrical new/old word differences with reduced effects over the epileptogenic hemisphere in patients with TLE, using a montage of 5 scalp electrodes referenced to a sterno-vertebral electrode pair. Lalouschek et al.,[11] who used pronounceable nonwords and geometric stimuli with 18 lateral scalp channels referenced to the vertex, found new – old effects of normal amplitude (between 300-600 ms) in RTE and LTE patients. However, the amplitude gradient from anterior to posterior (frontotemporal leads had larger negative voltages than parietal leads between 300-600 ms) was diminished ipsilaterally to the seizure focus in both groups. The authors were able to correctly classify the laterality of hippocampal pathology in 12 of their 14 TLE cases using this amplitude gradient measure.

Our finding of reduced ERP word repetition effects in LTE seems consistent with a prior study of epilepsy patients post-anterior temporal lobectomy.[10] Left, but not right, sided resections resulted in diminished new – old word differences to a fixed set of 10 target words that repeated in each block. While the left anterior lobectomy patient group had impaired recognition of the verbal targets, the degree of decrement in the ERP repetition effects did not depend on recognition accuracy. The authors interpreted these findings as follows: "although recognition can sometimes be reasonably accurate when the word-repetition effect is attenuated, the ERP difference nonetheless is closely related to a process that is important to normal performance on the memory task." In contrast, Rugg and colleagues,[28] using a continuous recognition task where each target word was repeated once, did not find a difference between right and left temporal lobectomy patient groups. Instead, both groups showed a decrement in their new – old ERP effects (300-600 ms), which was without any clear correlation to memory (recognition) performance. However, the apparent difference between these two studies could be quantitative rather than qualitative, in that Smith and Halgren[10] also found that the ERP repetition effect in their right anterior lobectomy group had a somewhat restricted topography, with decreased effects in right central and bilateral frontal channels.

Better predictors of post-surgery outcome, especially for post-operative memory deficits and seizure recurrence, are needed for patients with refractory epilepsy. Some past ERP studies have been promising in this regard. Grunwald et al.[29] showed that the amplitude of the N400 recorded in the right (non-dominant) anterior MTL correlated with verbal memory post-dominant temporal lobe surgery. This implies that memory processes mediated by the right temporal lobe may be critical in avoiding an amnestic deficit after the removal of dominant (left) MTL structures. Using invasive depth electrodes along the length of the hippocampus, Grunwald and colleagues[30] also found that a small N400 repetition effect contralateral to the side of surgery predicted seizure recurrence. Therefore, a reduced N400 repetition effect in the presumptively intact hemisphere may indicate occult bilateral pathology, bilateral epileptogenicity, and a poor surgical outcome.

Further ERP studies that attempt to replicate these results are needed. It would be clearly preferable to use scalp ERPs, instead of invasive depth recordings, if these can be validated to have satisfactory diagnostic utility. With improved noninvasive diagnostic procedures, most epilepsy centers less frequently require depth electrodes for diagnostic identification of the seizure focus in TLE. We are planning to follow this cohort and additional TLE patients with repeat ERP studies approximately 1 year after either anterior temporal lobectomy or gamma-knife therapy. It will be of interest to test the predictive value of N400 and LPC abnormalities with regards to post-operative neuropsychological abilities, histopathology and seizure recurrence. One might, for example, predict quite different prognostic meanings of an abnormal LPC repetition effect in LTE vs. RTE. If a reduced LPC repetition effect reflects left hippocampal sclerosis or left medial temporal lobe dysfunction, then patients with this ERP abnormality who then undergo left temporal resections should have good outcomes (with appropriate removal of the seizure focus), but those who receive right temporal resection might have greater risks of memory deficits and seizure recurrence. Combining the temporal resolution and signal-to-noise advantages of ERP studies with spatial resolution of fMRI or PET would be a promising strategy for characterizing temporal lobe function further in these patients with refractory TLE.

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REFERENCES

1. Babb TL, Brown WJ. Pathological findings in epilepsy. In: Engel J, (ed). Surgical Treatment of the Epilepsies. New York: Raven Press; 1987: 511-552.
2. Rausch R, Babb TL. Hippocampal neuron loss and memory scores before and after temporal lobe surgery for epilepsy. Arch Neurol 1993; 50: 812-817.
3. Loring DW, Meador KJ. Pre-surgical evaluation for epilepsy surgery. Saudi Med J 2000; 21: 609-616.
4. Breier JI, Plenger PM, Castillo R, et al. Effects of temporal lobe epilepsy on spatial and figural aspects of memory for a complex geometric figure. J Int Neuropsychol Soc 1996; 2: 535-540.
5. Helmstaedter C, Pohl C, Elger CE. Relations between verbal and nonverbal memory performance: evidence of confounding effects particularly in patients with right temporal lobe epilepsy. Cortex 1995; 31: 345-355.
6. Paller KA, Kutas M, Mayes AR. Neural correlates of encoding in an incidental learning paradigm. Electroencephalogr Clin Neurophysiol 1987; 67: 360-371.
7. Rugg MD, Mark RE, Walla P, Schloerscheidt AM, Birch CS, Allan K. Dissociation of the neural correlates of implicit and explicit memory. Nature 1998; 392: 595-598.
8. Rubin SR, Van Petten C, Glisky EL, Newberg WM. Memory conjunction errors in younger and older adults: event-related potential and neuropsychological data. Cogn Neuropsychol 1999; 16: 459-488.
9. Olichney JM, Van Petten C, Paller KA, Salmon DP, Iragui VJ, Kutas M. Word repetition in amnesia: electrophysiological measures of impaired and spared memory. Brain 2000; 123: 1948-1963.
10. Smith ME, Halgren E. Dissociation of recognition memory components following temporal lobe lesions. J Exp Psychol Learn Mem Cogn 1989; 15: 50-60.
11. Lalouschek W, Gerschlager W, Lehrner J, et al. Event-related potentials in patients with temporal lobe epilepsy reveal topography specific lateralization in relation to the side of the epileptic focus. Electroencephalogr Clin Neurophysiol 1998; 108: 567-576.
12. Kutas M, Van Petten C. Psycholinguistics electrified: event-related brain potential investigations. In: Gernsbacher M, (ed). Handbook of Psycholinguistics. New York: Academic Press, 1994: 83-143.
13. Chwilla DJ, Brown CM, Hagoort P. The N400 as a function of the level of processing. Psychophysiology 1995; 32: 274-285.
14. Helmstaedter C, Grunwald T, Lehnertz K, Gleissner U, Elger CE. Differential involvement of left temporolateral and temporomesial structures in verbal declarative learning and memory: evidence from temporal lobe epilepsy. Brain Cogn 1997; 35: 110-131.
15. Nobre AC, Allison T, McCarthy G: Word recognition in the human inferior temporal lobe. Nature 1994; 372: 260-263.
16. McCarthy G, Nobre AC, Bentin S, et al. Language-related field potentials in the anterior-medial temporal lobe: 1. Intracranial distribution and neural generators. J Neurosci 1995; 15(2): 1080-1089.
17. Grunwald T, Lehnertz K, Heinze HJ, Helmstaedter C, Elger CE. Verbal novelty detection within the human hippocampus proper. Proc Natl Acad Sci USA 1998; 95: 3193-3197.
18. Battig WF, Montague WE. Category items of verbal items in 56 categories: a replication and extension of the Connecticut category norms. J Exp Psychol 1969; 80: 1-46.
19. Shapiro SI, Palermo DS. Conceptual organization and class membership: normative data for representatives of 100 categories. Psychonomic Monogr Suppl 1970; 3: 107-127.
20. Francis WN, Kucera H. Frequency analysis of English usage: lexicon and grammar. Boston: Houghton Mifflin; 1982.
21. Jasper HH. Report to the committee on methods of clinical examination in electroencephalography. Appendix: The ten-twenty system of the International Federation. Electroencephalogr Clin Neurophysiol 1958; 10: 371-375.
22. Iragui VJ, Kutas M, Mitchiner MR, Hillyard SA. Effects of aging on event-related brain potentials and reaction times in an auditory oddball task. Psychophysiology 1993; 30: 10-22.
23. Bellgowan PS, Binder JR, Swanson SJ, et al. Side of seizure focus predicts left medial temporal lobe activation during verbal encoding.Neurology 1998; 51: 479-484.
24. Halgren E, Baudena P, Heit G, et al. Spatio-temporal stages in face and word processing. 1. Depth recorded potentials in the human occipital and parietal lobes. J Physiology 1994; 88: 1-50.
25. Grunwald T, Elger CE, Lehnertz K, Van Roost D, Heinze HJ. Alterations of intrahippocampal cognitive potentials in temporal lobe epilepsy. Electroencephalogr Clin Neurophysiol 1995; 95: 53-62.
26. Kaplan E, Goodglass H, Weintraub S. The Boston Naming Test. Philadelphia: Lea and Febiger; 1983.
27. Borkowski JG, Benton AL, Spreen O. Word fluency and brain damage. Neuropsychologia 1967; 5: 135-140.
28. Rugg MD, Roberts RC, Potter DD, Pickles CD, Nagy ME. Event-related potentials related to recognition memory: effects of unilateral temporal lobectomy and temporal lobe epilepsy. Brain 1991; 114: 2313-2332.
29. Grunwald T, Lehnertz K, Helmstaedter C, et al. Limbic ERPs predict verbal memory after left-sided hippocampectomy. Neuroreport 1998; 9: 3375-3378.
30. Grunwald T, Lehnertz K, Pezer N, et al. Prediction of postoperative seizure control by hippocampal event-related potentials. Epilepsia 1999; 40: 303-306.