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The Brain's Orienting Response (Novelty P3) in Patients with Unilateral Temporal Lobe Resections

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Abstract

The brain's orienting response is a biologically primitive, yet critical cognitive function necessary for survival. Though based on a wide network of brain regions, the lateral prefrontal cortex and posterior hippocampus are thought to play essential roles. Indeed, damage to these regions results in abnormalities of the novelty P3 or P3a, an event-related potential (ERP) sign of the orienting response. Like other ubiquitous markers of orienting, such as the galvanic skin response, the P3a habituates when novel events are repeated. Here, we assessed habituation of the P3a in patients who had undergone unilateral anteromedial resection of the medial temporal lobe (AMTL), including the entire hippocampus, for relief of pharmacologically intractable epilepsy. Eight left- and 8 right-AMTL patients and 16 age- and education-matched controls heard frequent standard tones, infrequent targets (requiring reaction times) and equally infrequent, unique novel, environmental sounds. The novel sounds repeated 2 blocks after their first presentation. In controls, novel repetition engendered a reduction in P3a amplitude, but this was not the case in either left- or right-AMTL patients. We conclude that bilaterally intact hippocampi are necessary for the brain to appreciate that a repetition of a novel sound has occurred, perhaps due to disruptions in ipsilateral hippocampal-prefrontal pathways and/or between the left and right hippocampi.

Keywords

orienting response; habituation; novelty detection; epilepsy; medial temporal lobe; P3a; P3b

1. INTRODUCTION

The ability to detect a novel, potentially biologically-significant, event in the continuous stream of environmental "noise" is critical for survival. The brain's response to such deviant events has been termed the orienting response (Lynn, 1966; Sokolov, 1990). The physiological components of this response serve to enable the organism to bring the event into awareness (engendering a shift in attention), evaluate its significance, and determine

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whether behavioral action is necessary. Ubiquitous markers of the orienting response include, for example, the galvanic skin response (GSR), heart-rate slowing, pupillary dilation and the novelty P3 (or P3a), a component of the scalp-recorded event-related potential (ERP; Friedman, Cycowicz, & Gaeta, 2001; Ranganath & Rainer, 2003; see below).

Over the last four decades, the ERP technique has been the method of choice when assessing the brain's response to novelty because it can track the underlying neural events (and putative cognitive processes) at the speed with which these processes unfold. Therefore, ERPs have an advantage over peripheral measures, such as GSR and pupillary dilation, as well as other central nervous system indices, such as hemodynamic activity based on fMRI, all of which can take seconds to reach maximum amplitude.

The brain's response to novelty has most often been assessed using variants of the "novelty-oddball" paradigm. In the canonical version of this task, three stimulus events are presented: a frequent standard (e.g., 80 percent probability of occurrence), an infrequent target (10 percent occurrence), to which the participant is instructed to respond via reaction time (RT), and an equally-infrequent series of unique novel events (10 percent occurrence) about which the subject is not instructed prior to the experiment. Two prominent and well-studied ERP components are elicited in this paradigm. The response to targets takes the form of a large-magnitude positive-going activity at about 300–600 ms that displays an amplitude maximum over the posterior regions of the scalp (Squires, Squires, & Hillyard, 1975). Similarly, the activity elicited by the uninstructed novels is a large-amplitude positivity, although it occurs somewhat earlier (~250–300 ms) and displays an amplitude maximum over midline fronto-central scalp relative to the target positivity (Courchesne, Hillyard, & Galambos, 1975). A large body of research suggests that the two components reflect unique cognitive functions (reviews by Friedman, et al., 2001 and Ranganath & Rainer, 2003). To distinguish these novel- and target-related events in the electrical record, they have been labeled, respectively, the P3a and the P3b (Squires et al., 1975) and these designations will be used here.

Habituation or reduction of the P3a with repeated novel presentations is one of the key characteristics identifying it as a cerebral component of the orienting response. This is so because other, ubiquitous measures of this response, such as the GSR, also show habituation with repeated occurrences of environmental stimuli. For example, Sokolov, (1963) demonstrated that stimuli initially evoking a large orienting response no longer did so when they were repeated. Habituation of this response has been interpreted to indicate the formation of some type of memory for the previous event, which then modifies the orienting response to repeated presentations. Sokolov (1963) also proposed that novel stimuli engender processes that permit construction of neural traces for these new events. As repeated incidences occur and the neural representation or template is formed, it is then compared continuously to incoming information (see also Fabiani & Friedman, 1995). Habituation of the orienting response takes place when the constructed representation satisfactorily matches the external stimulus. As a result, future encounters with this, no longer novel, item will be facilitated. Importantly, P3a amplitude reduction to novel sounds is associated with diminution of the GSR when the two are recorded simultaneously (Weisz & Czigler, 2006). Hence, the P3a is thought to reflect the output of a relatively early-onset, control system, which brings the deviant event into consciousness to determine whether it is sufficiently salient to require goal-directed action (Gaeta, Friedman, Ritter, & Cheng, 2001). Here we used the P3a as a neural proxy for the orienting response in an investigation of habituation in patients who had undergone unilateral, anteromedial-temporal lobe (AMTL) resection for the relief of pharmacologically intractable epileptic seizures.

The medial temporal lobes have been shown to be one of the critical generators in a distributed cortical network that contributes to the scalp-recorded P3a. This conclusion is based on studies of patients with hippocampal lesions (Knight, 1996), intracranial EEG recordings (Halgren et al., 1995) and hemodynamic neuroimaging studies (Strange & Dolan, 2001). For example, in a pioneering investigation, Knight, (1996) studied the P3a elicited by novel events in patients with unilateral posterior hippocampal lesions due to infarction of the posterior cerebral artery. Knight, (1996) used a typical, three-stimulus novelty oddball paradigm as described earlier. One key finding was that, compared to controls, hippocampal patients produced abnormal brain activity to the novel auditory and somatosensory events. That is, the P3a to novel events was dramatically reduced in both modalities over the frontal regions of the scalp. The other critical result was that, by contrast with the P3a, the P3b to targets, which is thought to reflect decision-related processes (Polich, 2007), was of similar magnitude in the patients and controls at posterior scalp locations where this brain activity is typically largest. A third important finding was that, by contrast with controls, hippocampal patients did not demonstrate habituation of the GSR elicited by shocks to the median nerve in a separate experimental session. Based on these findings, Knight, (1996) concluded that posterior hippocampal cortex was an important element in the network of brain regions that give rise to the orienting response.

That the hippocampus is involved in the brain's response to novelty undoubtedly stems from its role in the encoding of memories and, in particular, its preferential response to novel events (Habib, McIntosh, Wheeler, & Tulving, 2003; Strange & Dolan, 2001; Ranganath & Rainer, 2003). For example, Strange & Dolan, (2001), using a verbal-oddball task, observed that the hemodynamic response recorded in the hippocampus exhibited habituation over repeated trials, in highly similar fashion to what has been demonstrated in several investigations of the P3a to auditory and visual novel events (Courchesne, 1978; Friedman & Simpson, 1994; Knight, 1984). Thus, these hemodynamic data join the ERP data in suggesting that the hippocampus is a critical component in the network that produces the orienting response.

In accord with its putative association with attentional capture, the P3a also receives contributions from frontal cortex. This supposition is based on a variety of sources including hemodynamic (Friedman, Goldman, Stern, & Brown, 2009; Kiehl et al., 2005), intracranial EEG (Halgren, Marinkovic, & Chauvel, 1998), and scalp-recorded ERP methods (Knight, 1984). In a seminal investigation and one of the first lesion-based examinations of the intracranial generators of the P3a, Knight, (1984) demonstrated that the dorsolateral prefrontal cortex made significant contributions to the scalp-recorded P3a evoked by novel environmental sounds. Patients with left or right unilateral-dorsolateral damage, like their hippocampally-lesioned counterparts, showed a dramatic diminution in P3a magnitude over frontal scalp regions (see also Daffner et al., 2000). Moreover, in highly similar fashion to the GSR measures recorded in the posterior hippocampal patients of Knight, (1996), his earlier investigation of prefrontal patients showed that, whereas controls evinced reliable habituation of single-trial P3a amplitudes over frontal scalp, the patients with lateral prefrontal lesions did not. Taken as a whole, the posterior-hippocampal and prefrontal-lesion data suggest that the neural sign of the orienting response depends upon intact hippocampal-prefrontal circuits.

Nonetheless, one difficulty with lesion-based methods for inferring brain function is that, because the lesions are accidents of nature, there is no control over the size and extent of the damaged tissue. Hence, regions other than those in which the investigator is interested are often impacted, making it difficult to conclude definitively that a circumscribed location in the brain is critically involved in the cognitive function under consideration. In the current study, we attempted to remedy this situation by recruiting epilepsy patients who had

undergone standardized, precise unilateral resection of the AMTL, including the entire hippocampus, to treat pharmacologically refractory seizures (Spencer, Spencer, Mattson, Williamson, & Novelly, 1984). We were interested in attempting to replicate the results published by Knight, (1996) who, as described earlier, used the novelty-oddball task to determine the role of the posterior hippocampus in novelty detection and evaluation. To advance knowledge further, we built repetition of novel environmental sounds into the design (Kazmerski & Friedman, 1995) to determine whether the putative central index of the orienting response would or would not show habituation in patients with unilateral AMTL removals.

Moreover, Knight (1996) averaged his data over left- (N=3) and right- (N=4) posterior hippocampal patients, which precluded a determination of whether there might be a differential response to the repetition of novel stimuli in left- and right-posterior hippocampal patients. Hence, in the current study, the data were averaged separately for left- and right-AMTL patient groups. Nonetheless, there are scant data concerning the processing of environmental sounds in AMTL patients to which we could turn for aid in prediction and interpretation of the current neural data. As far as we can determine, only one recent study (Bidet-Caulet et al., 2009) indicates that identification of and short-term memory for environmental sounds are impaired, relative to controls, in patients with either left- or right-AMTL removals. Hence, expectations could only be supported by the ERP data reviewed earlier and the findings of Bidet-Caulet, et al., (2009).

The critical role of the medial temporal lobe (including major contributions from the hippocampus) in the encoding of memory representations engendered by novel events suggests that patients with left- and right-AMTL excisions (including unilateral removal of the entire hippocampus) might not show habituation of the orienting response. This result would be in agreement, as noted earlier, with the GSR data recorded by Knight (1996). This type of finding could be interpreted to indicate that, lacking bilaterally intact hippocampi, might lead to insufficiently detailed representations or templates of the initial environmental sounds with which to support habituation (Fabiani & Friedman, 1995). Nonetheless, there was no firm basis for predicting differential repetition-induced habituation in the two patient groups. On the other hand, based on Knight's (1996) finding that target P3b magnitude was relatively unaltered by left- and right-sided posterior-hippocampal damage it was predicted that the decision-related P3b component at posterior scalp locations would be relatively intact in the left- and right-AMTL groups.

2. MATERIALS AND METHODS

2.1. Participants

Eight pharmacologically refractory temporal lobe epilepsy patients who had undergone left AMTL resection (LAMTL; 6 males, mean age 33.0 years, range 20–48 years), 8 patients who had undergone right AMTL resection (RAMTL; 4 males, mean age 42.5, range 35–51 years), and 16 age- and education-matched controls (11 males, mean age 35.2, range 21–49 years) participated. The results of between-group (controls, LAMTL, RAMTL) ANOVAs confirmed that there were no group differences in age or years of education ($F_s < 2.9$, $P_s > 0.05$; see Table 1). All patients had undergone complete removal of the ipsilateral hippocampus and amygdala (described below). LAMTL patients were tested on average 2.2 years (SD = 1.5 years) following surgery, and RAMTL patients were tested on average 2.3 years (SD = 2.7 years) postoperatively. With the exception of one LAMTL and one RAMTL patient, all patients were taking anti-seizure medications at the time of testing. All participants were native English speakers and had normal or corrected-to-normal vision. The study was approved by the New York State Psychiatric Institute's Institutional Review Board and all subjects signed informed consent and received payment for their participation.

2.2. Surgical procedures

The resections for all patients in this study were performed as described by Spencer and colleagues (Spencer, et al., 1984; see also Hamberger, Seidel, McKhann, & Goodman, 2010). The resection included approximately 3.5 cm of the anterior middle and inferior temporal gyri, removal of the uncus/amygdala (without extending superior to the level of the anterior choroid fissure), and complete removal of the hippocampus (including the tail, posterior to the crossing of the choroid plexus over the hippocampus) and adjacent parahippocampal gyrus. Hippocampal resection was performed en bloc, with a 3.5–4 cm length specimen (measured without “straightening” the specimen). The magnitude of the resection varied only to the extent that hippocampal size varies among patients. Hippocampal removal was confirmed via post-operative MRI scans, which can be seen for an exemplar LAMTL patient in Figure 1. This figure depicts the extent of MTL resection in the post-operative T2-weighted MR images. The entire hippocampus and amygdala in the left hemisphere have been removed. The magnitude of the neocortical excisions did not differ reliably between RAMTL and LAMTL groups ($t(14) = -1.4$ ($P > 0.16$). The mean ($\pm$ SD) for the LAMTL group was 3.3 (± 0.4); the mean value for the RAMTL group was 4.0 (± 1.2).

2.3. Neuropsychological assessment procedures

Participants were assessed with a set of neuropsychological tests in a session prior to electroencephalographic (EEG) recording (Table 1). A between-group ANOVA revealed differences in the laterality quotient ($F(2,27)=4.1$, $P<0.05$, $\eta^2 = 0.23$) as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). LAMTL and RAMTL patients did not differ in handedness ($t<1$), whereas controls were more strongly right-handed than RAMTL patients ($t(22) = 2.5$, $P<0.05$). Between-group (controls, LAMTL, RAMTL) ANOVAs demonstrated that the groups did not differ reliably in IQ or any of the other measures listed in Table 1 ($F_s<3.5$, $P_s > 0.05$).

Patients underwent a battery of episodic memory tests, which included subtests from either the WMS-R or WMS-III. The Logical Memory I and II and Visual Reproduction I and II scores from this battery are listed in Table 1. t -tests of differences between LAMTL and RAMTL groups did not reveal significant differences in the Logical Memory I, II or the Visual Reproduction I scores ($P_s > 0.25$). However, the RAMTL group performed worse than the LAMTL on Visual Reproduction II ($t(10) = 3.24$, $P < 0.009$; see Table 1). Nonetheless, based on the normative data tables provided in the WMS manual, the scores in Table 1 indicate that both patient groups scored well within the average range on these indices of episodic memory.

Unlike the WMS measures, which only patients received, patients as well as controls participated in a recency/recognition, episodic-memory paradigm based on Milner, Corsi, & Leonard (1991) and modified for application to aging by Fabiani & Friedman (1997). Participants were presented with two identically-constructed sequences of stimuli. One sequence consisted of words and the other of line drawings of common objects. The first 129 stimuli in each sequence were information-only trials during which participants examined each single stimulus silently for future memory testing. Starting with trial 130, test trials alternated with information-only trials. Test trials were identified by a question mark interposed between the two stimuli in the display. Two types of test trials were possible: recency trials ($N=60$), and recognition trials ($N=30$), which were intermixed randomly throughout the sequence. On recency trials, participants viewed two stimuli that they had previously seen at different times. On recognition trials, participants viewed a previously-seen stimulus and a foil or new item. In both cases, the participant's task was to indicate which of the two stimuli had been presented most recently. In the case of recognition, only

one item would have been previously seen and therefore would have been, by definition, the most recent. Responses involved either a right button press (if the item displayed on the right was the one seen most recently) or a left button press (if the item on the left was the one seen most recently). For purposes of this report, composite recency and recognition scores were obtained by averaging across picture and word presentations. For complete methodological details, the reader is referred to Fabiani & Friedman (1997).

All participants underwent audiometric testing at frequencies of 250, 500, 1000, 2000 and 4000 Hz. The decibel (dB) level at which all stimuli were presented was adjusted for any subject who showed a mean hearing loss greater than 0 dB averaged across frequencies and ears by increasing from 75 dB the intensity of the stimuli by the mean dB hearing loss. This resulted in mean dB presentation values ($\pm$ SD) for the controls of 87.1 (9.1), for the LAMTL patients of 84.9 (6.6) and for the RAMTL patients of 87.6 (12.1).

2.4. Stimuli and Procedures

The stimuli were pure tones and environmental sounds. The pure tones were 500 Hz (high tone) and 350 Hz (low tone), with durations of 336 ms. The environmental sounds were 48 unique sounds that have been described in detail by Fabiani, Kazmerski, Cycowicz, & Friedman, (1996). They were chosen from six categories: animal, bird, human, musical instrument, environmental and electronic. The sounds varied in duration from 159 to 399 ms (mean = 336 ms; SD $\pm$ 61), and were matched for peak equivalent sound pressure level to the pure tones using a dB meter.

The experiment consisted of three phases. The first was a short practice block for the standard auditory oddball task, in which infrequent targets (which required an RT response) and frequent standards (which did not require a response) occurred randomly intermixed. The second was comprised of 2 blocks of the standard oddball task. The third phase consisted of 10 blocks of a novelty oddball task, in which infrequent targets, equally infrequent novels, and frequent standards were presented. As in the standard oddball blocks, only targets required a response in the novelty oddball blocks. For all blocks, pure tones and environmental sounds were presented with an inter-stimulus interval of 1000 ms. Sounds and pure tones were presented binaurally via headphones. Stimuli were randomized separately for each subject, with the restrictions that a target or a novel could not occur as the first or the last stimulus, and that two targets or novels could not be presented sequentially.

2.4.1. Standard oddball task—Subjects heard high and low pure tones in random order. One tone was presented 80 times and was designated the standard and the other tone was presented 20 times and was designated the target. There were two blocks each with 100 trials.

2.4.2. Novelty oddball task—Following the standard oddball task, subjects were presented with 10 blocks, each comprised of 64 standard tones, 8 target tones and 8 novel, environmental sounds. To maintain novelty, at least initially, subjects were not informed of the occurrence of the novel stimuli. There were 48 unique, environmental sounds, 32 of which were repeated (see below). In the first two novelty oddball blocks, all of the novel events were new, while in the rest of the blocks only half were new. The 16 sounds that did not repeat (labeled “unique”) comprised half of the novel items in the first two and last two blocks (four in each block). Repetition of the novel stimuli occurred two blocks after their initial presentation, such that, for example, the environmental sounds initially presented in the first block were repeated in the third block.

For all tasks, subjects were instructed to press a button with their left or right thumb on a hand-held response device (emphasizing speed and accuracy equally) as soon as they heard the target tone. The tone that served as target and hand of response were counterbalanced across subjects. RTs between 100 and 1100 ms post-stimulus were accepted as correct responses.

2.5. Electroencephalographic (EEG) Recording Procedures

EEG was recorded from 32 sites¹ using an Electrocap (Electrocap International, Inc.) for scalp placements and disposable Ag/AgCl electrodes for the face and mastoids (see Fabiani & Friedman, 1995 for details). All electrodes, including the mastoids, were referred to nosetip. Horizontal and vertical electrooculograms (EOG) were recorded bipolarly with electrodes placed, respectively, at the outer canthi of both eyes and above and below the right eye. EOG and EEG were recorded continuously with a 5.3 s time constant (30 Hz high frequency cutoff), and digitized at 200 Hz. The analysis epoch extended from 100 ms before and 900 ms post-stimulus. Eye movement artifacts were corrected off-line (Gratton, Coles, & Donchin, 1983).

2.6. Data Analyses

Only those ERPs associated with correct responses were analyzed. The target P3b from the standard-oddball blocks and the P3a to novel sounds from the novelty-oddball blocks were measured. These targets were used to avoid contamination of the P3b with a second P3-like component that is often present in the ERPs elicited by targets during novelty oddball blocks (see Friedman & Simpson, 1994). Because we were interested in whether and how each patient group differed from controls, analyses were performed comparing controls to LAMTL patients and controls to RAMTL patients. Analyses of Variance (ANOVAs) were performed on component amplitude (P3a, P3b) and RT and accuracy measures using the SPSS version 17 repeated measures program for Windows. For all ANOVAs, degrees of freedom were adjusted for repeated measures with two or more levels using the Greenhouse-Geisser procedure (uncorrected *df* values along with the corresponding epsilon (ϵ) values are reported below; *P* values reflect the epsilon correction). Significant interactions were followed up using simple effects and/or Tukey HSD post-hoc tests, calculated using degrees of freedom from the Greenhouse-Geisser adjustment. Partial η^2 (ηp^2) is presented as an estimate of main and interaction effect sizes. The construction of the ANOVAs is detailed in the corresponding results sections.

3. RESULTS

3.1. Behavioral Data

3.1.1 Standard Oddball and Novelty Oddball blocks—All participants performed well, with a mean target hit rate well above 90 percent in both standard and novelty oddball tasks, and very few false alarms (FA) to standards in oddball and novelty blocks and to novels in novelty blocks (Table 2). Independent-sample *t*-tests on accuracy, FAs to

¹Standard placements (International 10–20 system, Jasper, 1958) included: Fz, Cz, Pz, F7, F8, T3, T4, T5, T6, O1, O2 and left and right mastoids. LET = left eye top; RET = right eye top. Non-standard placements were as follows: (Fp1' 16% of the distance on the midline from the back to the front of the cap in front of Fz and laterally on the left hemisphere 10% of the distance from ear to ear), Fp2' (homologous to Fp1' on the right hemisphere), F3' (33% of the distance on a line between Cz and F3 on the left hemisphere, closer to F3), F4' (homologous to F3' on the right hemisphere), C3' (60% of the distance on a line between Cz and C3 on the left hemisphere, closer to C3), C4' (homologous to C3' on the right hemisphere), P3' (65% of the distance on a line between Pz and P3 on the left hemisphere, closer to P3), P4' (homologous to P3' on the right hemisphere), N1 (50% of the distance on a line between F3 and T3 on the left hemisphere), N2 (homologous to N1 on the right hemisphere), N3 (50% of the distance on a line between P3 and T3 on the left hemisphere), N4 (homologous to N3 on the right hemisphere), N5 (midway on a line between the left preauricular depression and the canthus of the left eye), N6 (homologous to N5 on the right hemisphere).

standards and novels, and RTs, comparing each patient group separately to controls, did not reveal any significant differences ($ts < 1.5$, $Ps > 0.1$).

3.1.2. Recency/Recognition Task—To analyze these data, a between-subjects Group ANOVA with the repeated-measures factor of Test Type (recency, recognition) was performed. One control participant and one RAMTL participant were removed from the data set due to extremely poor performance on both recency and recognition trials. As the data in Table 1 suggest, the ANOVA revealed a significant effect of Test Type ($F(1,27) = 53.9$, $P < 0.0001$, $\eta^2 = 0.66$), with recognition performance ($M = 65.1$ percent) greater than recency performance ($M = 51.4$ percent). However, neither the main effect of Group ($F < 1$) nor the interaction of Group and Test Type ($F < 1$) were reliable.

3.2. ERP Data²

3.2.1. Effects of temporal lobe resection on P3b—Figure 2 shows that, in each of the three groups, targets in oddball blocks elicit parietally-focused P3bs that appear to be of similar amplitude for the controls and LAMTL patients. By contrast, P3bs in the RAMTL group are less positive, particularly over central sites, where the waveforms fall below baseline (i.e., negative-going).

In order to ensure that P3b amplitudes were compared at their maxima in all three groups, the time window for the P3b analysis was chosen based on its latency. For each group, P3b latency was defined as the most positive peak at Pz between 200 and 600 ms. This procedure returned peak latencies for the controls of 380 ms, for the LAMTL patients of 364 ms, and for the RAMTL patients of 378 ms. Latencies for the LAMTL and RAMTL patients were separately compared to controls with independent-samples t-tests. These revealed no significant differences in P3b peak latency ($ts < 1$). Consequently, based on the mean latency of 375 ms (averaged across groups) a time window of 350–400 ms (i.e., ± 25 ms) was chosen for the between-group comparison of P3b amplitudes.

As suggested by Figure 2, a between-group ANOVA with the repeated-measures factor of Electrode (Fz, Cz, Pz) comparing P3b amplitudes between LAMTL patients and controls did not reveal group differences (main effect of group $F(1,22) = 1.3$, $P > 0.1$). Although the analysis did return a significant Group by Electrode interaction ($F(2,44) = 3.5$, $P = 0.05$, $\epsilon = 0.74$, $\eta^2 = 0.14$), post-hoc testing failed to confirm significant differences at any of the three electrode sites ($ts < 1.75$, $Ps > 0.05$). By contrast, comparing P3b amplitudes between RAMTL patients and controls revealed a significant main effect of Group ($F(1,22) = 5.9$, $P < 0.05$, $\epsilon = 0.75$, $\eta^2 = 0.22$), indicating that, compared to RAMTL patients, P3b was more positive in controls. The interaction of Group and Electrode was also reliable ($F(2,24) = 4.7$, $P < 0.05$, $\epsilon = 0.75$, $\eta^2 = 0.18$). Post hoc testing at separate electrodes confirmed a difference only at Cz ($t(22) = 3.0$, $P < 0.01$), but not Fz or Pz ($ts < 2.0$, $Ps > 0.05$). The lack of a significant attenuation at Pz suggests that the parietally-maximal P3b may be intact in RAMTL patients. Nonetheless, the between group difference at Cz might have been due to superimposed negative-going activity in the RAMTL patient group (Figure 2).

²For the ERP data described in the following sections, the mean number (and range) of trials entering the oddball target average (Figure 1) was 23 (20–24) for the LAMTL group, 20 (14–24) for the RAMTL group, and 22 (15–24) for the controls. The mean number (and range) of trials entering the oddball standard averages were 162 (154–173) for the LAMTL group, 144 (109–170) for the RAMTL group, and 161 (137–175) for the controls. The mean number (and range) of trials entering the novel 1 plus unique averages (Figure 4) were 41 (34–48) for the LAMTL group, 37 (29–45) for the RAMTL group, and 39 (29–45) for the controls. The mean number (and range) of trials entering the novel 1 average was 28 (23–32) for the LAMTL group, 26 (20–31) for the RAMTL group and 26 (18–30) for the controls. For the novel 2 data, these values were 28 (22–32) for the LAMTL group, 27 (21–31) for the RAMTL group, and 28 (19–32) for the controls.

3.2.2. Effects of temporal lobe resection on P3a—Due to the predicted differential effects of novel repetition on P3a in patients and controls, novel repetitions (i.e., second presentations) were excluded from the peak analysis of P3a. Hence, this analysis was performed using only trials that represented first presentations of novel events, including unique novels as defined in the methods. As depicted in Figure 3, first-presentation novels elicit fronto-centrally distributed novelty P3a's in control and LAMTL groups. However, the P3a is more posteriorly-focused in RAMTL patients, possibly due to the superimposed central negative-going activity. As observed for the target P3b, the P3a is of similar magnitude in controls and LAMTL patients, but attenuated, particularly over central sites, in RAMTL patients.

In order to ensure that P3a amplitudes were measured at their maxima, like the P3b, the time window for P3a analysis was chosen based on its latency. For each group, P3a was defined as the most positive peak at Cz between 200 and 500 ms. This procedure resulted in mean values of 282 ms for the controls, 296 ms for LAMTL patients and 293 ms for RAMTL patients. Independent-samples *t*-tests comparing each of the patient groups separately to controls revealed no significant latency differences at Cz ($ts < 1$). Consequently, based on a mean latency of 290 ms across groups, a time window between 265 and 315 ms (i.e., ± 25 ms) was chosen for the between-groups comparison of P3a amplitudes.

As suggested by the ERPs depicted in Figure 3, the results of the between-group (LAMTL, control) ANOVA with the repeated-measures factor of Electrode (Fz, Cz, Pz) confirmed that P3a amplitudes did not differ between LAMTL patients and controls ($F < 1$). The ANOVA comparing RAMTL's P3a amplitudes to those of controls, also did not reveal a reliable main effect of Group ($F(1,22) = 4.0, P > 0.05$). However, the interaction of Group and Electrode was significant ($F(2,44) = 3.8, P < 0.04, \epsilon = 0.82, \eta^2 = 0.15$). Post-hoc testing indicated that the interaction was driven by the greater positivity of the controls compared to that of the RAMTL group at Cz only ($t(22) = 2.4, P < 0.03$), but not Fz or Pz ($ts < 1.7, Ps > 0.05$).

3.2.3. Effects of temporal lobe resection on habituation of the P3a to novel sounds—To determine if the P3a would be reduced after repeated novel presentation, as was expected for the controls, P3a amplitudes elicited by first and second presentations were compared. As depicted in Figure 4, P3a amplitudes appear to decrease for second compared to first presentations in the control group. By contrast, no visible P3a amplitude reduction is observed in either group of patients. Hence, only the data of the control group were used to extract P3a peak latency. The difference waveform between the ERPs to novel 1 and novel 2 was computed and the peak latency of this difference at Cz was measured between 200 and 500 ms. This procedure resulted in an averaged peak latency across the 16 controls of 327 ms. Therefore the time window between 300 and 350 ms was chosen for the amplitude analyses.

To assess whether habituation had occurred, ANOVAs with the repeated-measures factors of Repetition (first, second) and Electrode (Fz, Cz, Pz) were performed on the P3a averaged voltages (300 – 350 ms), separately for each group. This analytic approach was taken because we had predicted that the controls would show habituation whereas the two patient groups would not. Furthermore, in his original investigation, Knight (1996) employed a highly-similar statistical strategy. The control-group ANOVA revealed that Repetition caused a significant amplitude reduction (main effect of Repetition ($F(1,15) = 4.4, P = 0.05, \eta^2 = 0.23$). The interaction of Repetition and Electrode ($F(2,30) = 3.5, P > 0.05$) was not significant. By contrast, statistically-reliable P3a differences between first and second novel presentations were not obtained for either LAMTL or RAMTL patients ($Fs < 1$; Figure 4), suggesting that removal of either left or right AMTL was associated with the lack of an habituation effect.

3.2.4. Is the superimposed negative-going activity in RAMTL patients a general phenomenon?—To rule out the possibility that the dramatically reduced P3b and P3a in the RAMTL patients' data was due to a generalized negativity that occurred to all stimulus events, the ERPs elicited by the standards in the standard oddball blocks were measured. If the negative-going differences between the RAMTL and control group were present for the standards, this would suggest a general phenomenon, nonspecific with respect to either novel or target detection.

Figure 5 depicts grand-averaged waveforms elicited by standards in standard-oddball blocks superimposed at Cz in the 3 groups of participants. There is an N1 component at approximately 100 ms, which appears larger in the RAMTL group. Similarly, the subsequent N2 component also appears larger in the RAMTL patients. The reduction in magnitude of P3a to novels and P3b to targets in the RAMTL patients was greatest at Cz. Therefore, the P3a and P3b latency windows (respectively, 265–315 ms and 350–400 ms) used to determine whether there were reliable differences between the RAMTL patients and controls in the target and novel waveforms at Cz were also employed for this analysis. Independent-samples t-tests indicated that, for the 265–315 ms window, neither LAMTL ($t(22) = 1.1, P > 0.05$), nor RAMTL ($t(22) = 1.1, P > 0.05$) patients differed reliably from controls. Similarly, for the 350–400 ms window, neither LAMTL ($t(22) < 1$), nor RAMTL ($t(22) = 2.1, P > 0.05$) patients differed reliably from controls. Taken together, these results suggest that the negative-going activity was not present in the standards relative to that engendered by targets and novels.

3.2.5. Is the superimposed negative-going activity possibly due to anti-seizure medication differences between the LAMTL and RAMTL groups?—To assess whether the number of anti-seizure medications prescribed for the RAMTL patients may have contributed to the anomalous negative-going activity, the number of medications was tallied for each participant. These values were missing for one LAMTL patient. The mean number (and range) of prescribed medications was 1.4 (1 – 2) for the LAMTL group and 1.2 (0 – 3) for the RAMTL group. These values did not differ reliably ($t < 1$).

3.2.6. Is the altered morphology of the RAMTL group's waveforms due to differences in P3 latency variability?—Both on the individual-participant and group levels, increased latency variability could artificially modify the morphology of the waveforms and thus engender amplitude effects on the group level that might actually be due to increased latency variability.³ It is well known that P3 latency and RT are related (Johnson, Simon, Henkell, & Zhu, 2011). Hence, we assessed this possibility in two ways. First, each individual participant's oddball target RT distribution was divided at the median and ERP averages were computed for fast (at or below the median) and slow (above the median) RTs. These individual averages were then grand-averaged across the participants within each group (Figure 6A). The mean ($\pm$ SD) fast and slow RTs for the LAMTL group were, respectively, 378 ms (± 96) and 502 ms (± 99); for the RAMTL group these values were 352 ms (± 120) and 485 ms (± 164); for the controls, these values were 330 ms (± 81) and 430 ms (± 107).

Second, the median RT was found for the 16 AMTL patients and the 16 controls. Based on the across-subject median RT, participants were classified as fast or slow responders within each of these two groups. These individual averages were then grand averaged (Figure 6B). The mean ($\pm$ SD) fast and slow RTs for the patient group were, respectively, 341 ms (± 39) and 505 ms (± 111); for the controls, these values were 317 ms (± 37) and 445 ms (± 90).

³Thanks to an anonymous reviewer who suggested we consider this possibility.

Collectively, these results demonstrate (Figure 6A and 6B) that, aside from differences in amplitude (smaller for longer RTs) and latency (somewhat longer for slower RTs), the within-subject as well as between-subject P3 data show a high degree of morphological consistency between the fast and slow RT subgroupings.

In summary, P3a and P3b amplitudes did not differ between LAMTL patients and controls. By contrast, relative to controls, both P3a and P3b were less positive in the RAMTL data, particularly over central sites, most likely due to an overlapping negative-going activity in the RAMTL patients. However, this was specific to targets and novels, as the overlapping negativity did not differ reliably between RAMTL patients and controls when measured in the standard ERPs. Additionally, the number of prescribed anti-convulsant medications did not appear to be a contributing factor to the genesis of the overlapping negativity, nor did P3 latency variability at the individual or group level. Most important, novel repetition engendered a decrement in P3a amplitude for controls (Friedman, Kazmerski, & Cycowicz, 1998), but not LAMTL or RAMTL patients.

4. DISCUSSION

The aim of the present investigation was to determine whether we would observe, in groups with precisely defined left- and right-AMTL excisions, the reduction in novelty P3 amplitude originally described by Knight, (1996) in patients with lesions presumably confined to the posterior hippocampus. Moreover, because Knight, (1996) demonstrated lack of habituation to novel events using only a peripheral nervous system measure, we wished to extend his finding to a central nervous system index of the orienting response, the scalp-recorded P3a. We were, however, unable to demonstrate an overall reduction in novelty P3 magnitude over fronto-central scalp regions in Left AMTL patients compared to controls (see discussion below for right AMTL patients). Nonetheless, we observed reliable habituation to the repetition of the identical novel sounds in the controls but not in either of the patient groups, adding to the evidence of the essential role of the hippocampus in the habituation of the orienting response (Knight, 1996).

One possibility for the lack of habituation in the patients could be that, due to potential memory deficits, the patients did not notice the repetitions of the novel sounds and, therefore, processed them in the same fashion as first presentations⁴. However, based on the results of the recency/recognition task this seems unlikely. LAMTL and RAMTL patients did not differ reliably from each other or the controls, suggesting relatively spared episodic memory function in the patients, at least based on this paradigm. Moreover, this conclusion is bolstered by the fact that the two patient groups scored within the average range on the standard assessments of episodic memory.

At this juncture, it is important to note the methodological differences between our investigation and that of Knight, (1996), which most likely account for the disparity in the patients' novelty P3a findings. One critical variation is that Knight, (1996) had little control over the size and extent of the infarct-induced lesions in his patient sample. Hence, abnormalities in the novelty P3 over frontal scalp sites could have been due to tissue damage that extended beyond the posterior hippocampus, a possibility that was noted by Knight (1996). However, due to the variability among patients in the extent and sites of extrahippocampal damage, it would have been difficult to determine how this might have impacted systematically the results he reported. Nevertheless, the fact that we recorded, at least in left-AMTL patients, a relatively intact novelty P3 over fronto-central scalp sites (i.e., statistically indistinguishable from that of controls, Figure 3), suggests that unilateral

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⁴We thank an anonymous reviewer for pointing out this possibility.

removal of the entire hippocampus seems to have had little effect on the magnitude (and scalp topography) of the ERP sign of the orienting response. On the other hand, the orienting response in right-AMTL patients was dramatically reduced over fronto-central scalp locations, ostensibly due to a long-duration negative-going activity that overlapped with the novelty P3, thereby reducing its positive magnitude. We return to a discussion of this neural event below. Hence, had we averaged our data across left- and right-AMTL patients, as Knight, (1996) had for his posterior hippocampal patients, we too would have demonstrated a reduction in the P3a at fronto-central midline sites in the patient group when taken as a whole.

One of the other key findings of Knight, (1996) was that, by contrast with the abnormal orienting response at frontal sites in posterior-hippocampal patients, his patients evinced relatively intact P3b components in response to deviant targets. Here, as well, left- and to some extent, right-AMTL patients demonstrated relatively intact, decision-related, target P3b components when measured at parietal scalp locations (Figure 1). Collectively, these data join those of others in suggesting a clear distinction in the cognitive processes reflected by the target P3b and the novelty P3a (Friedman, et al., 2001; Polich, 2007; Ranganath & Rainer, 2003; Squires, et al., 1975), and confirm the target P3 findings reported by Knight, (1996). Hence, the scalp-recorded target P3b appears to receive little in the way of direct contributions from the AMTL, including the hippocampus, thereby supporting the findings of others who have studied this phenomenon (Johnson, 1988; 1994; Polich & Squire, 1993; Rugg, Pickles, Potter, & Roberts, 1991).

However, as noted above, the overlapping negativity undoubtedly distorted the novelty P3a as well as the target P3b in the right-AMTL patient group, causing a reduction in P3a and P3b amplitudes. Hence, because it is difficult to disentangle the two overlapping activities, we cannot determine unequivocally whether the novelty P3 and/or the target P3b are truly unaffected (or abnormal) in patients who have had their right AMTL removed. Additional research will be necessary to understand this phenomenon, for example, by attempting to manipulate the central negativity independently from the P3 activity with which it overlaps.

The processes reflected by the overlapping negative-going activity observed only in the waveforms of the RAMTL participants are unknown at this time. Negative-going activity with a highly-similar scalp focus and timing has been observed in older relative to young adults in the brain's response to pre-instructed targets though, here too, the processes it reflects are not known with certainty (Friedman, Kazmerski, & Fabiani, 1997). The presence of the negativity is not due to one or two outliers as, on visual inspection, the majority of right-AMTL participants showed evidence of this activity. Another possibility is that the negative-going activity could have been due to the older mean age of the RAMTL patients relative to LAMTL patients and controls (though this difference was not significant; Table 1). However, this seems unlikely, as the typical difference between young and older adults in age-related investigations of the novelty oddball is on the order of 40 to 50 years. Nonetheless, the relatively small mean age difference of approximately 9 years cannot be ruled out definitively as a contributing factor⁵. Other factors that appear to *not* contribute to the presence of the negativity are medication status and P3 latency variability. The two patient groups did not differ reliably in the number of anticonvulsive medications being administered at the time of testing. Moreover, analysis of within- as well as between-participant P3 latency variability (based on fast and slow RT distributions to which P3 is coupled -- Johnson, et al., 2011) did not reveal morphological differences in any of the three

⁵To determine if age influenced the results unduly, analyses of covariance (ANCOVAs) were employed with age as the covariate. All of the ANOVAs reported in the results section were recomputed using ANCOVA. Age did not have an effect on the data as the ANCOVAs returned the same results as those observed in the original ANOVAs

groups including, critically, the RAMTL group (Figure 6A and 6B). Hence, several factors can be ruled out as influencing the presence of the centrally-oriented negativity in RAMTL patients. On the other hand, what remain to be determined are the processes that do play a role in modulating the negative-going activity.

One possibility is that, because attentional as well as mnemonic processes are undoubtedly engaged by the deviant events, the negativity could reflect an attentional mechanism that is recruited exclusively by RAMTL patients in the service of maintaining task performance. Unfortunately, there are no data, to the very best of our knowledge, that speak to this issue, making this a highly speculative proposal. Moreover, as can be observed in Figures 2 and 3, this activity had a very early onset (~50 ms), making it less likely that it could have reflected a volitional, attentional-control mechanism. Thus, until more data are collected, the processes that this negativity reflects in target and novelty detection remain quite unclear.

It is also possible that the AMTL findings reported here could have been due to secondary degenerative and/or compensatory processes in brain regions outside the AMTL. For example, it is known that anatomical abnormalities extend to areas beyond the AMTL prior to surgical intervention (e.g., Bell, Lin, Seidenberg, & Hermann, 2011; McDonald et al., 2008). There is also some evidence that reorganization in white matter tracts occurs following AMTL surgery (Yogarajah et al., 2010). Nonetheless, these kinds of data are quite sparse. Furthermore, had compensatory brain mechanisms been recruited, we would have expected habituation of the P3a to have occurred in the patient groups; this was not the case. Collectively, these data suggest that the extent to which such extra-MTL changes might have impacted the results reported here remains equivocal.

The prefrontal cortex and the hippocampus are richly interconnected and their interaction appears necessary in generating a fully intact scalp-recorded orienting response (Daffner, et al., 2000; Daffner et al., 2003; Knight, 1984; Knight, 1996; Yamaguchi, Hale, D'Esposito, & Knight, 2004). Importantly, an fMRI investigation of habituation of the brain's novelty response indicates that hippocampal activation is reduced *bilaterally* as more unique and unexpected novel events are experienced (Yamaguchi, et al., 2004). Moreover, in confirmation of the contributions of *both* the hippocampus and prefrontal cortex to the orienting response, the superior middle frontal gyrus also showed bilateral diminution of activity as more novel events were presented (Yamaguchi, et al., 2004). Hence, the fact that we observed reliable habituation to the repetition of the identical novel sounds in the controls but not in either of the patient groups adds to the evidence, initially provided by Knight, (1996) and Yamaguchi, et al., (2004), and reinforced by the findings of Bidet-Caulet, et al., (2009) and Strange & Dolan, (2001), that bilaterally intact AMTLs are necessary for a biologically-primitive, repetition-induced memory to occur (Sokolov, 1990).

To conclude, neither the novelty P3a nor the target P3b appears to be markedly abnormal in patients with complete, unilateral removal of the AMTL, including resection of the entire hippocampus. By contrast, left- or right-unilateral AMTL removal has a dramatic effect on habituation of the orienting response. That is, in controls, the P3a showed the expected diminution in amplitude with repetition, but neither left-nor right-AMTL patients exhibited this ubiquitous sign of the orienting response (Sokolov, 1990). In accord with recent hemodynamic findings (Yamaguchi, et al., 2004), these data suggest that bilaterally intact hippocampi are essential for habituation of the orienting response to be recorded over the fronto-central regions of the human scalp.

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Neuropsychologia Highlights

- The cortical sign of the orienting response, the P3a, habituates to novel repetition.
- The hippocampus contributes to this scalp-recorded potential.
- We studied P3a habituation in patients with unilateral removal of the entire hippocampus.
- Normal controls, but not patients, showed reliable P3a habituation.
- We conclude that bilaterally intact hippocampi are critical to show P3a habituation.

Figure 1. T2-weighted coronal, sagittal and axial MR images at the level of the hippocampus for an exemplar LAMTL patient. The entire hippocampus and amygdala in the left hemisphere have been removed. The images are depicted in radiological convention, with L = left and R = right.

Figure 2. Grand-mean waveforms averaged across subjects within each of the control, LAMTL and RAMTL groups. The ERPs elicited by target events in standard oddball blocks are depicted. Arrows mark stimulus onset with timelines every 300 ms. The spherical-spline maps (right-hand column) were computed using the averaged reference on the averaged voltages in the 350–400 ms time window for each of the groups (Picton et al., 2000). Dots indicate the electrode locations.

Figure 3. Grand-mean waveforms averaged across subjects within each of the control, LAMTL and RAMTL groups. The ERPs elicited by all first-presentation novel sounds in novelty-oddball blocks are illustrated. Arrows mark stimulus onset with timelines every 300 ms. The spherical-spline maps were computed on the 265–315 ms time window for each of the groups. Dots indicate the electrode locations.

Figure 4. Grand-mean waveforms averaged across subjects within each of the control, LAMTL and RAMTL groups. The waveforms elicited by first and second novel presentations are superimposed separately for controls, LAMTL patients, and RAMTL patients. Arrows mark stimulus onset with timelines every 300 ms.

Figure 5. Grand-mean ERPs to standards (at Cz) during the first two standard-oddball blocks averaged across subjects within each of the control, LAMTL and RAMTL groups. Arrows mark stimulus onset with timelines every 300 ms.

Figure 6.

A. Grand-mean, within-subject ERPs associated with fast and slow reaction times based on the median RT for each participant. The data are depicted for controls, LAMTL and RAMTL patients. Arrows mark stimulus onset with timelines every 300 ms. **B.** Grand-mean, between-subject waveforms associated with fast and slow reaction times based on the median between-subject RT. The data are shown for control, LAMTL and RAMTL patient groups. Markers and timelines are the same as in Figure 6A.

Table 1 Mean ($\pm$ SD) Demographic and Neuropsychological measures for control and patient groups.

	Controls (N=16)	LAMTL (N=8)	RAMTL (N=8)	P
Age	35.2 (9.0)	33.0 (9.2)	42.5 (6.3)	ns
Education	15.5 (1.8) ²	14.8 (2.6)	15.9 (2.6)	ns
Digits Forward	6.9 (1.3) ²	6.5 (0.8)	7.4 (1.1)	ns
Digits Backward	5.0 (1.6) ²	4.8 (1.4)	6.1 (1.0)	ns
Laterality Quotient [¶] (EHI)	90.7 (17.4) ²	45.4 (70.1)	45.2 (50.2)	<0.05
WAIS-III verbal IQ	114.3 (10.2) ²	101.7 (13.4) ^I	112.1 (12.0)	ns
WAIS-III performance IQ	102.0 (19) ²	116.4 (21.2) ^I	104.9 (17.0)	ns
Controlled Oral Word Association Test (FAS)	0.6 (0.3)	0.5 (0.3)	0.6 (0.3)	ns
Percent Correct Recognition Memory	64.7 (16.1) *	69.2 (12.3) **	61.3 (10.5)	ns
Percent Correct Recency Memory	49.4 (10.8) *	55.2 (5.9) **	49.5 (8.1)	ns
Logical Memory I	NA	32.0 (25.0)	42.6 (23.1)	ns
Logical Memory II	NA	33.4 (26.6)	43.9 (22.4)	ns
Visual Reproduction I	NA	86.5 (26.3)	70.7 (17.9)	ns
Visual Reproduction II	NA	87.2 (19.7)	46.0 (24.1)	<0.009

Notes.

^I N=7;² N=15; ns = not significant;[¶] EHI = Edinburgh Handedness Inventory (Oldfield, 1971); +100 = completely right-handed; -100 = completely left-handed; WAIS: Wechsler Intelligence Scale III (Wechsler 1997);

* N = 15;

** N = 7. For Logical Memory I and II, post-surgical percentile scores were available for 7 LAMTL and 7 RAMTL participants; for Visual Reproduction I and II, post-surgical percentile scores were available for 6 LAMTL and 6 RAMTL participants. NA = not applicable.

Table 2

Mean ($\pm$ SD) percent accuracy for Targets and false alarm (FA) rates for Standards and Novels and RTs (in ms) in control and patient groups.

	Controls (N=16)	LAMTL (N=8)	RAMTL (N=8)
Standard Oddball Blocks			
Targets Correct	99.7 (1.1)	99.5 (1.5)	99.0 (1.9)
Standard FA rate	0.1 (0.3)	0.1 (0.2)	0.6 (1.0)
RT Correct	381 (93.7)	435 (95.6)	411 (140.6)
Novelty Oddball Blocks			
Targets Correct	97.8 (2.4)	98.6 (3.5)	97.4 (4.8)
Standard FA rate	0.2 (0.1)	0.09 (0.2)	0.2 (0.3)
Novel 1 FA rate	5.7 (7.6)	2.0 (3.3)	7.8 (10.0)
Novel 2 FA rate	0.6 (1.7)	0.0 (0.0)	3.18 (5.0)
RT Correct	481 (91.8)	488 (96.8)	503 (140.8)