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Sensory Gating in the Human Hippocampal and Rhinal Regions: Regional Differences

N.N. Boutros,[1]* R. Mears,[1] M.E. Pflieger,[2] K.A. Moxon,[3] E. Ludowig,[4] and T. Rosburg[4]

ABSTRACT: To further explore the roles of medial temporal structures in mediating sensory gating of incoming irrelevant or redundant auditory input, twenty-seven patients with intractable epilepsy with depth electrodes implanted in the medial temporal lobe for presurgery evaluation underwent evoked response recording to auditory paired-stimuli (S1–S2). Seventeen subjects were diagnosed with left medial temporal lobe epilepsy (MTLE) and 10 with right MTLE. Only data from the nonlesion side were included. Twenty-three records from rhinal and anterior hippocampal regions, and 21 from posterior hippocampal regions were included in the analysis. The rhinal region had two prominent components (a negativity peaking around 200 ms followed by a positivity peaking around 400 ms). Both the anterior and posterior hippocampal regions exhibited a dominant negative potential peaking around 400 ms. These components were all composed predominantly of slower frequencies. In contrast, a negativity in the posterior hippocampus at around 100 ms was composed of slow and fast frequencies. All components but the early rhinal negativity were attenuated by stimulus repetition. This is the first report documenting that different regions of the medial temporal area are differentially involved in the processing of auditory input, most likely reflecting separate steps of processing. The data support the need for further exploration of the contribution of these regions to sensory gating. This information helps to increase our understanding of this basic but important and complex function. © **2007 Wiley-Liss, Inc.**

KEY WORDS: auditory evoked response; habituation; P50; N100

INTRODUCTION

The ability of the CNS to inhibit or suppress responses to incoming redundant sensory input is a fundamental protective mechanism that prevents the flooding of higher cortical centers with irrelevant information (Venables, 1964). The circuitry that mediates this vital function has yet to be fully described, however, it has been proposed that the hippocampus plays a central role (Freedman et al., 1991; Moxon et al., 1999).

In humans, direct evidence for an involvement of the hippocampus in sensory gating is difficult to obtain due to the closed neuronal field configuration, which strongly attenuates the electrically generated hippocampal signal detectable from a distance such as from the scalp (Klee and Rall, 1977). However, the occasional need to implant intracranial electrodes during the presurgical evaluation of patients with medically intractable focal epilepsies makes it possible to record event-related potentials (ERPs) directly from the human hippocampal formation and cerebral cortex. Our group recently recorded neocortical and hippocampal responses to paired clicks with the aim of determining the extent to which different regions of the human brain contribute to sensory gating.

Our initial exploration revealed that P50 responses were recordable in two distinct regions, namely the temporo-parietal region (Brodmann's areas 22 and 2), and the prefrontal cortex (Brodmann's areas 6 and 24) (Grunwald et al., 2003). No P50 equivalent was detected in hippocampal recordings, but a later, much broader response with negative polarity and a peak latency of about 250 ms was observed. This late hippocampal response was strongly reduced by stimulus repetition. Activities in the hippocampus, and the rhinal regions in response to pairs of clicks were again examined in a second study (Boutros et al., 2005). Similar to the earlier investigation, a major negative component was identified in recordings obtained from the hippocampus while a major positive deflection was noted in rhinal region recordings. Both rhinal and hippocampal components attenuated strongly with repetition. In our most recent publication (Rosburg et al., 2007), additional components were identified: an earlier negative component in the rhinal region peaking around 200 ms (rhinal component #1/RH1), followed by the previously described major positivity peaking around 400 ms (rhinal component #2/RH2). Hippocampal recordings revealed one main negativity peaking between 300 and 400 ms (hippocampal component #1/HC1).

Given the aforementioned closed nature of the hippocampal field (Klee and Rall, 1977), activity recorded in medial temporal lobe (MTL) is not reflected in ERPs recorded from the scalp (Boutros et al., 2005; Rosburg et al., 2007). However, MTL activity might contribute to the function of sensory gating via some yet uncharacterized circuitry, thus indirectly influencing scalp-generated responses to repeating stimuli.

[1] **Department of Psychiatry and Behavioral Neurosciences, School of Medicine, Wayne State University, Jefferson, Detroit, Michigan;** [2] **Source Signal Imaging, Inc., San Diego;** [3] **Drexel University, School of Engineering;** [4] **Department of Epileptology, University of Bonn, Germany**

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*Correspondence to: Nash Boutros, M.D., Wayne State University, School of Medicine, UPC-Jefferson, 2751 E. Jefferson, Suite 401, Detroit MI, 48207, USA. E-mail: nboutros@med.wayne.edu

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Examination of the frequency content of the evoked responses in MTL structures should increase our understanding of their function in sensory gating and their relation to scalp-recorded activity. Our prior work (Boutros et al., 2005) revealed that evoked components recorded from MTL structures are predominantly of low frequency composition and strongly gated. In contrast, gating of scalp ERP components, seemed to be evident in both lower frequency components (Jansen et al., 2002), and higher frequency components (Clementz and Blumenfield, 2001).

In the current study, we intended to characterize the responses to repeating identical auditory stimuli in the rhinal cortex, but also in anterior and posterior hippocampus. Such a differentiation of ERPs recorded in the anterior and posterior hippocampus has turned out to be helpful for a deeper understanding of hippocampal functions, as recently shown for memory processes by Ludowig et al. (in press). In addition, we aimed to further characterize the frequency composition of the recorded components in a larger sample of patients with depth electrodes. To our knowledge, there are no previous studies comparing sensory gating occurring in the rhinal cortex and these two hippocampal regions.

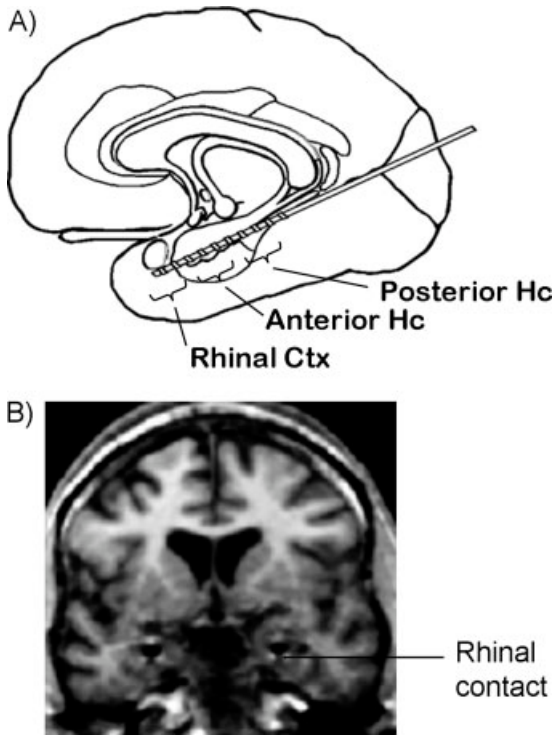

FIGURE 1. A: In each patient electrode contacts in the medial temporal lobe were classified on bases of MR scans as being located in the rhinal cortex, anterior hippocampus and posterior hippocampus. B: Exemplary MR data with electrode contacts in the rhinal cortex. Only data of the nonaffected hemisphere was analyzed in the current study.

MATERIALS AND METHODS

Twenty-seven patients with depth electrodes implanted in both hippocampi participated in the study and were exposed to a paired-click auditory stimulation paradigm. Six of the patients were included in a prior study (Boutros et al., 2005). All patients underwent invasive presurgical evaluation because the localization of the primary epileptogenic area could not be determined by noninvasive procedures. All subjects included in this study had a focal unilateral lesion (overwhelmingly hippocampal sclerosis), with no seizures recorded from the other side. Catheter-like, 1-mm thick silastic depth electrodes were implanted via the longitudinal axis of the medial temporal lobe from an occipital approach and contained 10 cylindrical contacts of a nickel-chromium alloy (2.5 mm) every 4 mm. Electrodes were implanted with the most anterior contacts reaching the rhinal cortex of the parahippocampal gyrus anterior to the amygdala, and the more posterior contacts targeting the hippocampal body (Van Roost et al., 1998). Consequently, we determined the anatomical location of the electrode by MR images obtained after implantation (Fig. 1). On an average the electrodes 1–3 were located in the rhinal cortex, electrodes 4–6 were located more anteriorly in the hippocampal body, and electrodes 7–10 in the more posterior hippocampal regions. When an identified region was represented by more than one electrode, we selected the electrode with the largest evoked potential.

All patients gave informed consent, and the study was approved by the Institutional Review Board of both Bonn and Wayne State Universities.

All subjects underwent scalp recording using the paired-click paradigm before implantation, then simultaneously from scalp, subdural and depth electrodes after implantation and the clinical monitoring phase. In a paired-click paradigm, 100 pairs of two identical clicks (S1 and S2; sinusoidal waves, frequency 1500 Hz, Gaussian envelope, duration 4 ms, onset and decay phases of 1.2 ms each) were presented via headphones with a short interstimulus interval of 500 ms and a long interpair interval of 8 s (Zouridakis and Boutros, 1993). Patients were asked to listen to the clicks without performing any additional task. Intracranial evoked responses were recorded and referenced to linked mastoids. EEG was collected using a high-pass filter (0.2 Hz, 12 dB/octave) and segmented related to stimulus S1 with a segment length of 2,000 ms including a prestimulus baseline of 500 ms. The EEG was inspected thoroughly for epileptic activity and all suspicious segments were rejected.

According to the MR-images, electrodes were grouped into contacts in the rhinal cortex, anterior hippocampus, and posterior hippocampus (as determined by one collaborator E.L., blind for the ERPs). Only data recorded from the nonlesion side were analyzed (17 left and 10 right). Averages were calculated for each patient for the rhinal and the hippocampal contacts separately. Signal was then band pass filtered between 0.2 and 50 Hz. Artifact-rejection was performed with thresholds of -300 to 300 μV and visual inspection of spikes and artifacts. For each electrode, averages of artifact-free trials were computed (usually at least 80 out of 100 trials after artifact-rejection). EEG signals were further filtered off-line in the P50 frequency

TABLE 1.

Amplitudes of Identified Components (Means ± Standard Deviations) to S1 and S2 Stimuli, as well as the Suppression Measures (S2/S1 Ratio and S1–S2 Difference)

Component	S1 Amp [μV]	S2 Amp [μV]	S2/S1 [%]	S1–S2 [μV]	Significance *P*
Rhinal cortex					
RH1	10.7 ± 8.2	9.2 ± 6.3	98 ± 70	1.5 ± 8.9	n.s.
RH2	15.7 ± 17.0	6.6 ± 6.2	46 ± 50	9.1 ± 15.7	$P < 0.001$
Anterior hippocampus					
HC1	18.7 ± 15.8	6.9 ± 10.9	35 ± 45	11.8 ± 9.6	$P < 0.0001$
Posterior hippocampus					
pHC1	9.5 ± 6.0	6.1 ± 10.0	60 ± 80	3.3 ± 10.7	$P < 0.05$
HC1	20.6 ± 15.6	10.2 ± 10.9	50 ± 40	10.4 ± 12.6	$P < 0.01$

P values refer to the comparison of S1 and S2 values.

range (10–50 Hz, 12 dB/octave) for the higher frequency components and in the range from 0.2 to 10 Hz (12 dB/octave) for the lower frequency components. Grand averages were calculated, applying the two kinds of band-pass filtering.

Amplitudes of the ERPs were quantified for 50 ms bins (area under the curve, AUC). encompassing a baseline bin (−50 to 0 ms) and 50 ms bins following 0–500 ms after the first tone. Both the grand averages and AUCs guided the choice of the different components following S1 stimuli. Identification of components following S2 stimuli was guided by the latency of the S1 component ±30 ms. If no component with a similar polarity was seen in this latency window, the component was considered to have been completely attenuated.

Initial repeated measures analyses of variance (ANOVAs) were performed to ascertain if there were overall main effects of S1 stimuli in each of the three areas examined. One set of post-hoc, Dunnett *t*-tests were performed comparing each post-stimulus AUC bin with the baseline bin for the three areas examined: rhinal, anterior hippocampus, and posterior hippocampus on both sides separately. As no significant differences were found between left and right hemispheric electrodes, data of both hemispheres were collapsed. The peak to baseline (50 ms prestimulus) amplitudes and latencies of each identified component in response to S1 and S2 stimuli were determined. A 2-way ANOVA was performed with both component (S1 vs. S2), and location (only one component was seen in more than one location; HC1), as within subjects variables. The S2/S1 ratios and the S1–S2 differences for the identified components of each of the three examined MTL regions are provided in Table 1. Once a main effect of component was detected, *t*-tests were performed to determine which of the components attenuated with stimulus repetition.

RESULTS

Recordings from the right (15) and left (8) rhinal, right (15) and left (8) anterior hippocampal, and right (14), and left (7) posterior hippocampal regions were included. Based on the MRI, not every included subject had electrodes that were definitely in all three anatomical regions, hence the difference between the number of enrolled subjects and the number of averages examined per location.

Statistical analysis of the effects of S1 stimuli was based on AUC calculations as provided further below. To ascertain if there is a main effect of bin, repeated measures ANOVA was performed for the eleven 50 ms bins. Significant main effects were observed for all regions (rhinal: $F(10.220) = 4.65$, $P < 0.01$, anterior hippocampus: $F(10.220) = 3.47$, $P < 0.01$, posterior hippocampus: $F(10.200) = 2.11$, $P < 0.05$), indicating a significant variation of the brain signal in response to the stimulation. Figure 2 shows the AUCs for the response to S1 stimuli.

Figure 3 shows the grand averages for the rhinal, anterior and posterior hippocampal regions following S1 and S2 stimuli. For the rhinal region, an early negativity was seen peaking around 200 ms (RH1) followed by a larger positivity peaking around 400 ms (RH 2). This later positivity returned back to baseline by 500 ms. For the anterior hippocampal (AH) region the grand average was dominated by a large negativity peaking around 400 ms (HC1), returning back to baseline after onset of S2. In addition to the HC1 component (the same or a very similar component to HC1 recorded from AH), posterior hippocampal (PH) contacts showed an earlier negativity peaking around 100 ms (posterior hippocampus component #1/pHC1).

A 2-way ANOVA revealed an over all significant effect of condition (S1–S2) ($F(1.11) = 22.05$, $P < 0.001$). There were no effects of location or condition X location. *T*-tests comparing the mean amplitudes of the responses to S1 and S2 stimuli for each of the identified rhinal and hippocampal components showed significant attenuation of all ERP components except RH1. Table 1 provides the mean amplitudes of S1 and S2 responses of all components, the S2/S1 ratios and the S1–S2 differences as well as the significances observed.

In all anatomical locations examined, the major activity was in the slower frequency range (0.2–10 Hz) with hardly any activity seen in the higher frequency ranges. The notable excep-

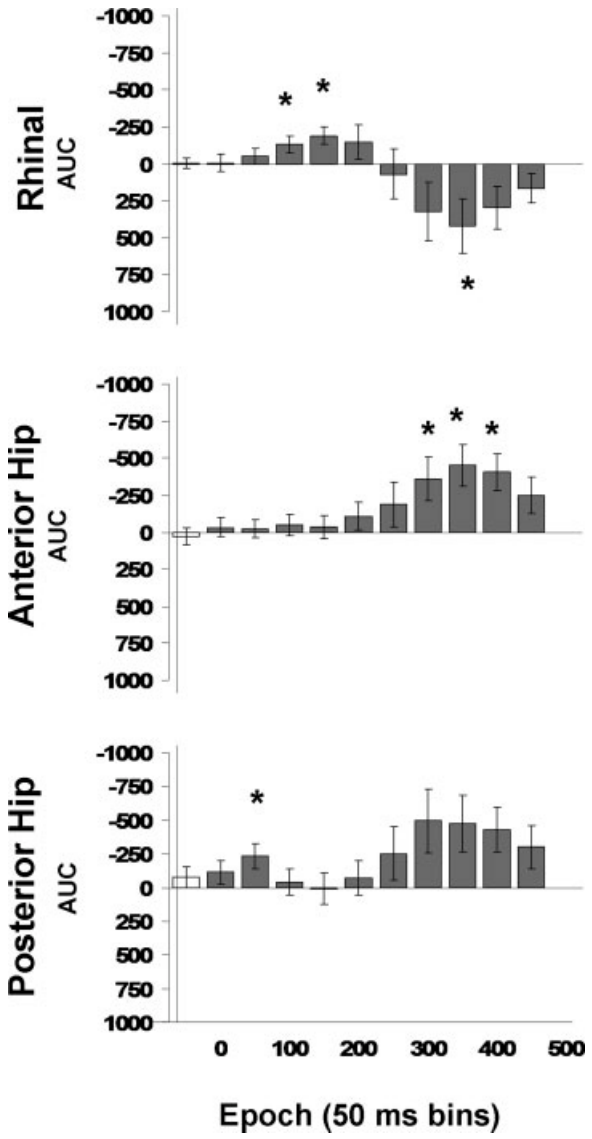

FIGURE 2. Local field potential activity for each electrode was averaged across all trials in the recording session, and absolute area information was integrated in 50 ms intervals from 50 ms before to 500 ms after the first tone-click. The bars represent mean area under the curve (AUC, microvolts * 50 ms) with standard error of the mean marked for each bin. After one-way ANOVA for each region, post-hoc repeated measures *t*-tests were used to compare each poststimulus bin with the baseline bin before the first tone-click ($P < 0.05$*, $P < 0.01$). Data obtained with a 0.2–50 Hz band pass filter.**

tion was the posterior hippocampal component (pHC1) which contained low and high frequency signals (Fig. 4).

Grand averages were produced for scalp electroencephalographic activity recorded from the Cz position of patients with included data from the right ($n = 17$) or left ($n = 10$) MTL structures (Fig. 5). The averages reflect the common configuration of the mid-latency responses, with very similar configuration for right or left MTL epilepsy patients.

DISCUSSION

In the current study intracranial recordings from the rhinal cortex, as well as anterior and posterior hippocampus in response to pairs of clicks were recorded. The ERP in each region was characterized by a different pattern of deflections. In the rhinal cortex, a negativity peaked at ~200 ms (RH1) and was followed by a positive deflection at ~400 ms (RH2). Both hippocampal regions exhibited a dominant negative potential peaking ~400 ms (HC1). These components were all composed predominantly of slower frequencies. In contrast, the negativity in the posterior hippocampus at ~100 ms (pHC1)

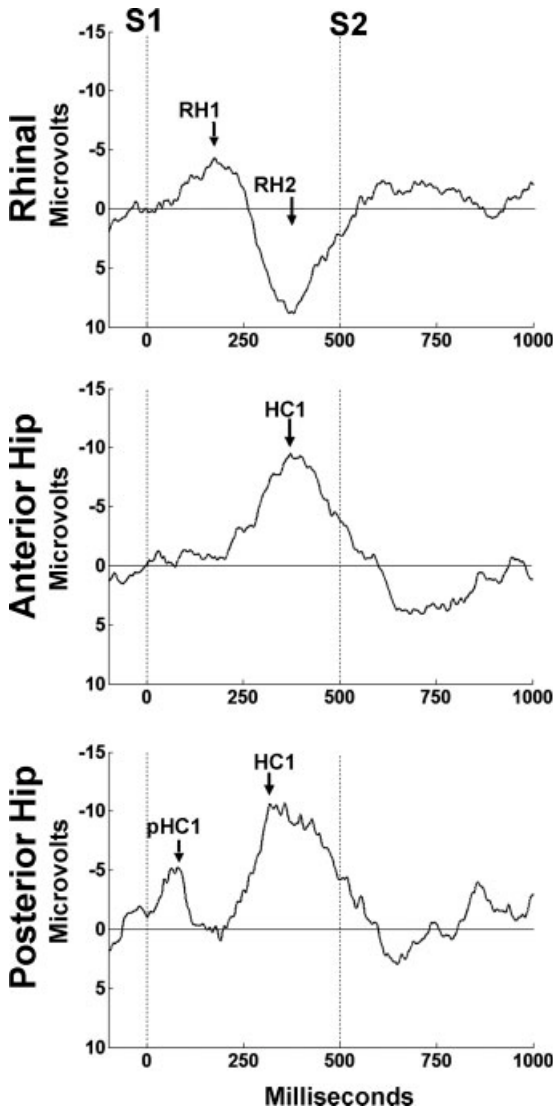

FIGURE 3. Grand averages were produced for a) rhinal cortex ($n = 23$), b) anterior hippocampus ($n = 23$), and c) posterior hippocampus ($n = 21$). The dotted lines in the graphs indicate the times of the first and second tone-clicks at 0 and 500 ms. Averages and grand averages were obtained with a 0.2–50 Hz band pass filter.

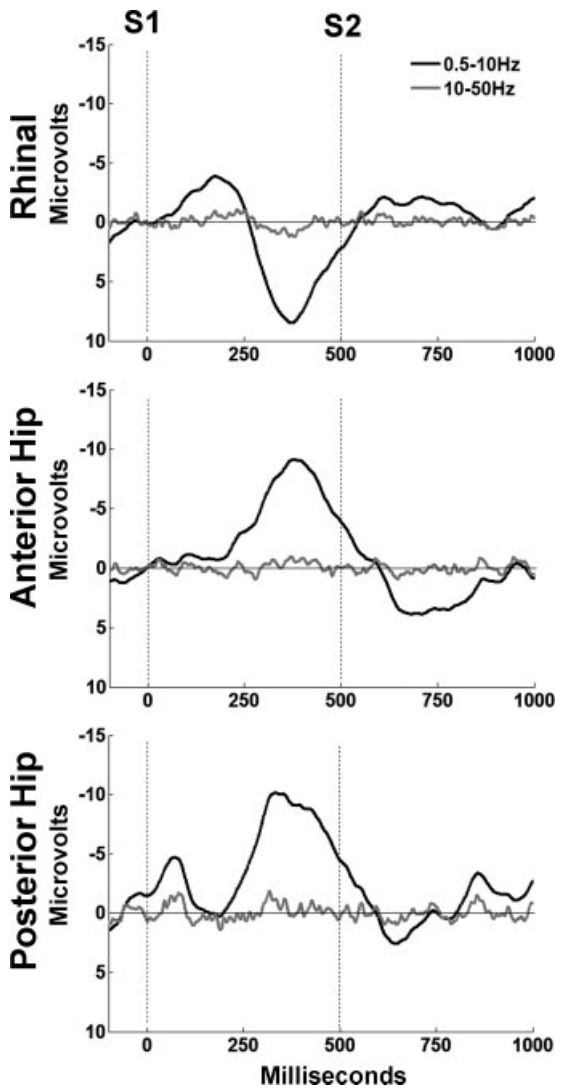

FIGURE 4. To determine the power contributed from different frequency bands, grand averages were separated by low and high band-pass filters. Low band frequencies (0.2–10 Hz, black trace) represented a majority of the power for peaks at long latencies after the first and second tone-clicks. High band frequencies (10–50 Hz, red trace) represented much less power from the wide band grand average except for a small early latency peak in posterior hippocampus.

was composed of slow and fast frequencies. All components but RH1 were attenuated by stimulus repetition.

To our knowledge, the above data represent the first suggestion that the anterior and posterior hippocampus may be contributing differently to the gating out of incoming redundant sensory input. It is worth noting that in the Goff graphs (1980) an early negativity (of a latency about 100 ms) was seen similar to the pHC1 component described in the current study. Responses to S2 varied between components suggesting different involvement in the gating process. While the early rhinal component did not attenuate with repetition, in line with a previous study of our group (Rosburg et al., 2007), all other recorded components did. The role of regions that do not exhibit gating in mediating the inhibition of incoming irrelevant or redundant sensory input (i.e., sensory gating), has not been investigated. On a superficial level of analysis it may be suggested that they are not involved in this particular function. On the other hand, it could be proposed that the few cortical regions not exhibiting gating are essential for the proper working of the system, as the system must know about the nature of the input in order to decide to suppress it.

In contrast to the neocortically generated P50 responses with a frequency content of about 10−50 Hz (Clementz et al., 1997), the noted hippocampal or rhinal responses were mainly in the lower frequency range (0.2–10 Hz). The one mixed frequency component noted in our recordings came mainly from the posterior hippocampal region. While very speculative, the recording of a mixed frequency component in relative proximity to the early gating phase (represented at the scalp by the P50), suggests that this region of the hippocampus may be involved in mediating this phase of auditory sensory gating. The evidence suggesting that different regions of the hippocampus mediate different neural functions was reviewed by Moser and Moser (1998). Indeed evidence has accumulated from animal work showing that different segments of the longitudinal axis of the hippocampal formation differ in terms of input and output (Swanson and Cowan, 1977; Contreras and Swanson, 1992). Functional imaging of humans during successful encoding of word lists has demonstrated significantly more activation of the posterior hippocampus as compared to the anterior parts of the structure (Fernandez et al., 1998).

Interpretation of the observed reversal of polarity between rhinal and hippocampal regions (the major rhinal component being of positive and the major hippocampal component being of a negative polarity; Fig. 3) is not straight forward (Liegeois-Chauvel et al., 2004). While the data may suggest that the generator sources for the activity is somewhere between these two areas, such phase reversal can be seen in rhinal contacts that touch the hippocampal border. Moreover, the two waveforms (RH2 and HC1) are not identical further suggesting that they are not reflecting a common source in the middle. Finally, if the source was indeed somewhere between the rhinal and anterior hippocampal regions, we would expect a larger amplitude of HC1 in the AH than in the PH region given the referential montage arrangement. This is not the case as seen in figure three, further supporting the possibility that the two components are independent. It should be noted that the initial negativity seen in the rhinal area was not mirrored by an initial positivity in the anterior hippocampal region, suggesting that significant differences may exist between these components and deserve further examination.

The idea of a hippocampal involvement in P50 generation stems from animal research. In rats the N40, which was thought to be equivalent to the human P50, (Boutros et al., 1997), occurs simultaneously in scalp and intrahippocampal recordings (Bickford-Wimer et al., 1990). Via extrapolation, from animal to human data, the hippocampus was also considered central to the gating of the human P50. However, in our

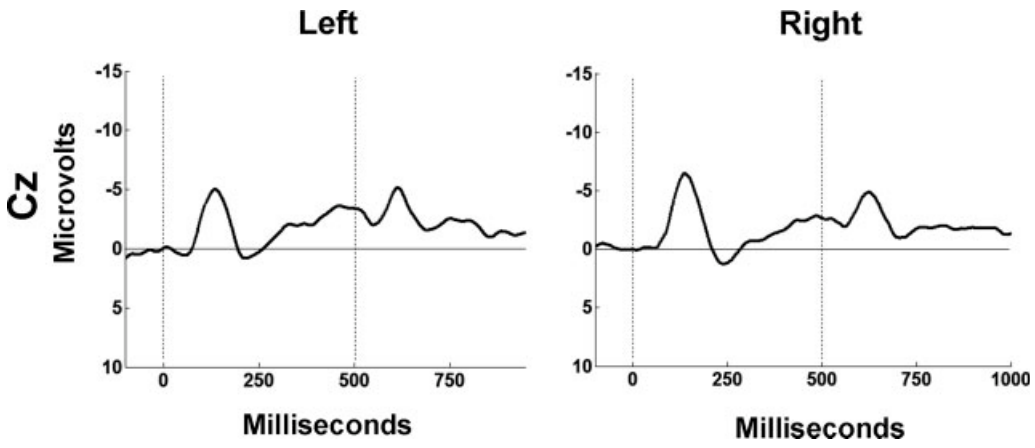

FIGURE 5. Grand averages were produced for electroencephalogram activity recorded from Cz position on patients with electrodes in right (n = 17) or left (n = 10) medial temporal lobes.

last two studies (Grunwald et al., 2003; Boutros et al., 2005), we found no evidence of hippocampal activation coinciding with the early or P50 phase of gating. A less frequently discussed component of the rat mid-latency response is the P20 seen preceding the N40 (Mears et al., 2006). Recently, strong parallels have been drawn between the human scalp-recorded P50 and the rodent P20 (Siegel et al., 2005; Phillips et al., 2007). The rodent P20 has also been recorded from the hippocampus (Maxwell et al., 2004). It is worthwhile noting that both the P20 component in rats (de Bruin et al., 2001), and mice (Connolly et al., 2004) and the pHC1 attenuate with repetition. We now suggest that the P20 may be a correlate of the pHC1. The observations that both the scalp-recorded P50 and hippocampus-recorded pHC1 are comprised of mixed frequencies (whereas all other hippocampal components are comprised of low frequencies) and that both components attenuate with stimulus repetition raise the possibility that these two components are elements of an early gating system in the two species. While the timing of the pHC1 suggests that it is unlikely to be significantly contributing to the generation of the scalp P50, it may be contributing to its gating. Further research is obviously needed to establish any parallels or correlations between the hippocampal/frontal recorded P20 in rodents, and the human pHC1 component and gating of the scalp P50.

The observation that not all cortical regions gate or gate to the same degree is not surprising. The occurrence and the degree of sensory gating vary between different brain regions. Functional animal studies have demonstrated that auditory gating is primarily observable in regions of the nonlemniscal pathway, such as the brain stem reticular formation (Moxon et al., 1999) and the medial septum (Miller and Freedman, 1993). In contrast, sensory gating did not take place in the medial geniculate nucleus (Bickford-Wimer et al., 1990). A modulatory action of septal nuclei (themselves exhibiting gating) on hippocampal pyramidal cell and interneuron activity has been demonstrated, and could contribute to auditory sensory gating in this region (Vertes and Kocsis, 1997). As more information accumulate about brain regions that exhibit gating and the degree to which they do so, a more complete picture of the system or systems that mediate this complex function will begin to immerge. As mentioned above, the role of brain regions not exhibiting gating in mediating the gating function remains entirely unexplored.

The results described above have a number of limitations. One is the large degree of variability between the subjects, both with regard to the morphology of the mesio-temporal ERP, as well as with regard to the exact electrode location. This variability may have masked additional differences between the regions examined. It should be noted that choice of subjects and electrode placement were solely guided by medical considerations. Secondly, while the recorded MTL components have been consistent in our studies (Grunwald et al., 2003; Boutros et al., 2005; Rosburg et al., 2007), a confirmation of these findings by independent research groups remains lacking. With regards to the response suppression in these regions, the 500 ms ISI may have been too short so the ERP in response to S1 is still ongoing when stimulation with S2 starts, thus two ERPs are overlapping following S2 stimuli. Longer ISIs may reveal more clearly the S2 responses which would allow a more accurate assessment of the inhibitory effects of stimulus repetition. Finally, while we examined two hippocampal regions and referred to them as "anterior" and "posterior", we have not utilized functional or anatomical tests (other than relying on location of electrodes on the MRI) to verify if the two regions were indeed functionally distinct. Regional differences of paired-click responses within medial temporal lobe structures suggest different functional roles of these sub-regions within the total brain network responsible for sensory gating. These functional issues may be addressed in future empirical studies via observations from neurological patients with discrete MTL lesions (Knight et al., 1980), additional animal experiments, and with advances in our capabilitie for recording or inferring human hippocampal activity. Finally, we expect that computer simulation studies will be essential to further our understanding

of dynamic interactions between all structures—both cortical and subcortical—involved in the sensory gating network.

In conclusion, the data provided here extend our probing of the role of the medial temporal structures in the sensory gating function. Our initial exploration suggested that the hippocampal region may be involved in a later stage of sensory gating than the earlier stage represented by the P50 (surface or neocortically recorded) evoked response (Grunwald et al., 2003). However, data presented here showing the pHC1 peaking around 100 ms re-opens the possibility that some hippocampal structures may be contributing to earlier phases of auditory gating. We have earlier proposed an expanded model of sensory gating with different stages (early and late) (Boutros and Belger, 1999). Based on the data provided here we now propose that the later stage of gating involving the medial temporal structures may not be a single stage or a single function.

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