Hippocampus Duality: Memory and Novelty Detection Are Subserved by Distinct Mechanisms

Emmanuel J. Barbeau [1]*, Patrick Chauvel,[2,3,4] Christopher J.A. Moulin,[5] Jean Regis,[2,3,4] and Catherine Liégeois-Chauvel[2,3,4]

ABSTRACT: The hippocampus plays a pivotal role both in novelty detection and in long-term memory. The physiological mechanisms underlying these behaviors have yet to be understood in humans. We recorded intracerebral evoked potentials within the hippocampus of epileptic patients ($n = 10$) during both memory and novelty detection tasks (targets in oddball tasks). We found that memory and detection tasks elicited late local field potentials in the hippocampus during the same period, but of opposite polarity (negative during novelty detection tasks, positive during memory tasks, ~260–600 ms poststimulus onset, $P < 0.05$). Critically, these potentials had maximal amplitude on the same contact in the hippocampus for each patient. This pattern did not depend on the task as different types of memory and novelty detection tasks were used. It did not depend on the novelty of the stimulus or the difficulty of the task either. Two different hypotheses are discussed to account for this result: it is either due to the activation of CA1 pyramidal neurons by two different pathways such as the monosynaptic and trisynaptic entorhinal-hippocampus pathways, or to the activation of different neuronal populations, that is, differing either functionally (e.g., novelty/familiarity neurons) or located in different regions of the hippocampus (e.g., CA1/subiculum). In either case, these activities may integrate the activity of two distinct large-scale networks implementing externally or internally oriented, mutually exclusive, brain states. © 2016 Wiley Periodicals, Inc.

KEY WORDS: event-related potential; human; intracerebral recording; oddball; patient

INTRODUCTION

The hippocampus plays a dual role in two key aspects of human cognition: detection of novel stimuli given their context (e.g., Halgren et al., 1995a,b; Knight, 1996) and long-term memory (e.g., Squire,

1992). This leads to a situation where the same brain region is apparently responsible both for detecting out-of-context stimuli and also for matching stimuli in the environment to stored representations. Each of these aspects of cognition is associated with frequently used experimental paradigms and robust electrophysiological signatures, but the anatomo-functional interaction between the two remains unclear in humans.

In novelty detection (oddball) paradigms, infrequent targets are randomly embedded in a series of task-irrelevant stimuli. Typical instructions consist of asking subjects to count targets mentally or press a button when targets are detected. Intracerebral recordings in epileptic patients have shown that targets elicit a large event-related potential (ERP) in the hippocampus with a peak latency between 300 and 600 ms. This hippocampal component has been termed "MTL P300" in reference to the P300, a positive scalp EEG component recorded in the same experimental conditions (Halgren et al., 1980, 1995a; McCarthy et al., 1989; Brazdil et al., 2001; Fell et al., 2005).

On the other hand, recognition of famous faces, familiar visual patterns, or previously learned words elicits a "hippocampal P600" (hP600), also a large component, culminating between 400 and 800 ms (Grunwald et al., 2003; Trautner et al., 2004; Barbeau et al., 2008). Its amplitude increases with successful memory recognition and is larger for known than for unknown stimuli (Trautner et al., 2004; Barbeau et al., 2008).

The fact that a high-amplitude P300 component can reliably be recorded from the hippocampus, and given the known role of the hippocampus in memory, suggests that novelty detection paradigms are somehow related to memory. Indeed, various authors have proposed that oddball tasks require memory processes, for example, to maintain the target stimulus or the context in memory, to identify novel events so that they can be stored, or to act as a comparator between previous experience and sensory information (Kumaran and Maguire, 2007; Polich, 2007; Ludowig et al., 2010). In contrast, there have also been many studies on the effect of novelty on memory (Tulving and Kroll, 1995; Poppenk et al, 2010). However, the link between both remains unclear and under debate (Verleger, 2008) and the intracerebral literature,

[1] Centre de recherche Cerveau et Cognition, Université de Toulouse, CNRS CERCO UMR 5549, Toulouse Cedex, France; [2] Faculté de Médecine, Institut de Neurosciences des Systèmes, Inserm UMR1106, Marseille, France; [3] Faculté de médecine, Aix-Marseille Université, Marseille, France; [4] Hôpital de la Timone, Service de Neurophysiologie clinique, Assistance Publique-Hôpitaux de Marseille, Marseille, France; [5] Laboratoire de Psychologie & Neurocognition, CNRS LPNC UMR 5105. Université Grenoble Alpes, Grenoble, France
*Correspondence to: Emmanuel Barbeau, Centre de recherche Cerveau & Cognition (CerCo), CNRS CERCO UMR 5549, Pavillon Baudot, CHU Purpan, BP 25202, 31052 Toulouse Cedex, France. Tel: (33)5-81-18-49-56. E-mail: emmanuel.barbeau@cnrs.fr

Patients Demographic Data and Epileptic Status

Patient	Sex	Age	Hand.	Lg. lat.	Epileptic focus	Etiology	Hippocampus recorded	Tasks
P1	M	23	R	L	R LTL	CD	L ant.	VOB, SAOB, LAOB, CVOB FF, VRM, ASSO MMN, COUNT
P2	M	36	R	L	R&L MTL	Unkn.	L post.	VOB, LAOB, voice OB FF, VRM, ASSO
P3	M	34	R	R	L MTL	HS	R post.	VOB FF, ASSO
P4	M	43	R	L	R LTL	Unkn.	R post.	VOB, LAOB, voice OB FF, VRM, ASSO
P5	M	42	L	L	R MTL	Unkn.	R ant.	VOB, LAOB, CVOB FF, ASSO COUNT
P6	F	24	R	L	L LTL-LO	Unkn.	L ant.	VOB, LAOB, voice OB FF, VRM, ASSO
P7	M	25	R	B	R MTL	Unkn.	R ant.	VOB FF
P8	F	25	R	Unkn.	R LTL	UnKn.	L ant.	FF Mixed
P9	M	43	R	Unkn.	R LTL-MTL	Heterotopia	R ant.	SAOB VRM MMN, COUNT
P10	M	31	R	Unkn.	R LTL-MTL	Gliosis	R ant.	SAOB VRM MMN

The tasks each patient underwent are summarized in the last column of the table. Hand: handedness. Lg. Lat: language lateralization. L: left; R: right. LTL: lateral temporal lobe; MTL: medial temporal lobe; LO: lateral occipital. CD: cortical dysplasia; HS: hippocampal sclerosis. Unkn.: unknown. ant: anterior. post: posterior. ASSO: associative memory task; COUNT: counting task; CVOB: categorical visual OB task; FF: famous faces recognition task; LAOB: long auditory OB task; MMN: mismatch negativity task; SAOB: short auditory OB task; VOB: visual oddball task; VRM: visual recognition memory task. All tasks are described in the Methods section.

allowing a precise spatio-temporal in vivo recording of the hippocampus, has never addressed the anatomo-functional relationship between these two processes in the same patients and in the same hippocampal site.

The question we address in this study is that of the relationship between the MTL-P300 and the hP600. Do they correspond to the activation of different hippocampal systems or circuits? Or are they related, in which case it might reveal a functional link between memory and odd-ball tasks? We undertook to compare intracerebral ERPs for different oddball and memory tasks conducted in the same patients. These ERPs were recorded from electrodes implanted in the temporal lobe of candidates for epilepsy surgery.

MATERIALS AND METHODS

Patients and Recordings

Ten patients (age: 23–43, two females, one left-hander; Table 1 for details) with drug-resistant epilepsy undergoing

presurgical investigations were included in this study. Four had an epileptogenic zone outside the medial temporal lobes. In the remaining MTL epileptic patients, except for one patient (P3) no hippocampal sclerosis or other structural abnormality of the hippocampus was observed as ascertained by magnetic resonance imaging (MRI). The absence of hippocampal sclerosis was evaluated as follows: (1) no visual atrophy, (2) no signal change either in 3D fluid-attenuated inversion-recovery sequences nor in a T2-weighted sequence, and (3) no loss of digitation of the head of the hippocampus. Epochs contaminated with abnormal electrophysiological activity were rejected before ERPs were computed (see below). The morphology, amplitude, and latencies of the hippocampal ERPs recorded from this series of patients did not differ from studies from other groups (e.g., McCarthy et al., 1989; Dietl et al., 2005).

Stereoelectroencephalographic (SEEG) recording was performed to localize the epileptogenic zone (Talairach and Bancaud, 1973). The choice of electrode location was based on pre-SEEG clinical and video-EEG recordings and was made independently of this study. This study did not add any invasive procedure to depth EEG recordings. ERP recordings were part of the functional mapping procedure carried out in each
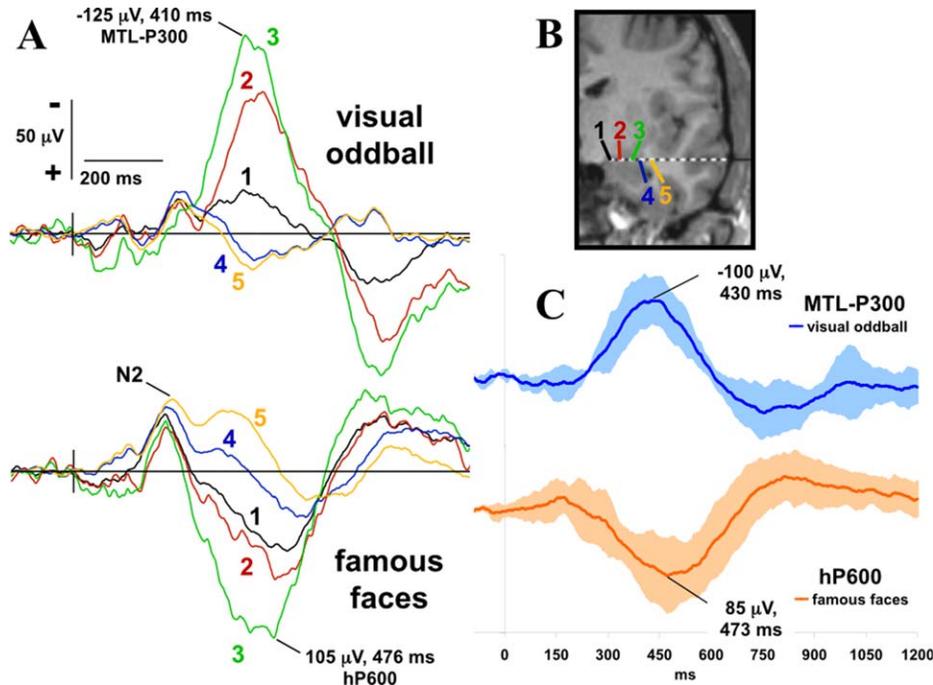
FIGURE 1. (A): ERPs of a single patient (P1) recorded from the hippocampus for both tasks. The ERP on contact 3 shows opposite polarity between the two tasks, negative in the OB task (average over 51 trials, for rare stimuli), positive in the famous faces task (average over 48 correct trials, for correct famous faces recognition). Note that the negativity is upward. The large ERPs recorded on contact 3 disappear on adjacent contacts 4 and 5, also on both tasks, suggesting that these are located outside the hippocampus. See text for detailed explanation. (B): The insert shows the electrode track reconstructed in patient P1 MRI. Contacts are in white. Contacts 1-3 are in the hippocampus, contacts 4-5 outside. The color of the contacts corresponds to the color of the ERPs in A. (C): Grand averages MTL-P300 to rare stimuli in the visual OB task and hP600 to famous faces in the famous/nonfamous memory task. For each task, averages were taken across the same seven patients (P1–P7). The light colors indicate one standard deviation above and below mean. [Color figure can be viewed at wileyonlinelibrary.com]

subject with the aim of assessing the functionality of the hippocampus through correct characterization of the hippocampal ERPs. All subjects were fully informed about the aim of investigation before giving consent. This study was approved by the Institutional Review Board of the French Institute of Health (agreement nos. IRB0000388). Subjects had from 6–10 intracerebral electrodes implanted stereotaxically and were typically approximately orthogonal to the brain midline (example in Fig. 1B). Each electrode was from 33.5 to 51 mm long, had a diameter of 0.8 mm and contained from 10 to 15 contacts 2 mm long separated by 1.5 mm (Alcis, Besançon, France). All electrode implantations in these patients were made by the same neurosurgeon (J.R.). Anticonvulsant therapy was reduced or withdrawn during the SEEG exploration to facilitate seizure occurrence. However, no subject had seizures in the 12 h before ERP recordings.
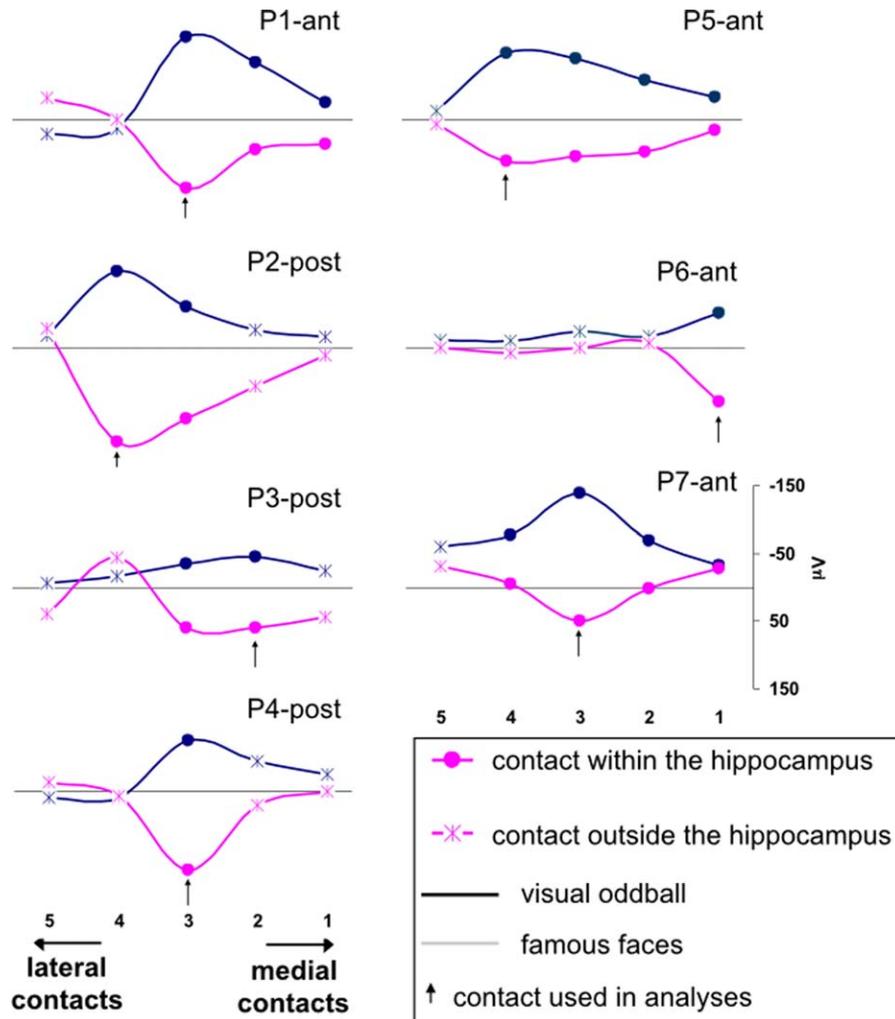
Tasks

The tasks are described in further detail when necessary in the Results section. The tasks each patient underwent are listed in Table 1. Stimuli presentation and behavioral recordings were monitored using Eprime v1.1 (Psychology Software Tools Inc., Pittsburgh, PA).

Oddball Tasks

General procedure. Single stimuli were presented one after the other, and participants had to mentally count the rare, target stimuli, which appeared randomly among distractors. They reported the number of targets they had counted after the end of the task.

The visual Oddball task (OB) consisted of 250 trials (20% targets), the duration of the presentation of each stimulus was 400 ms, and the interstimulus interval (ISI) varied between 1000 and 1600 ms. The target and distractor were the same throughout the task and were abstract pictures difficult to verbalize. In the categorical OB task, targets (23%, 261 trials in total) were different pictures of animals and the distractors were different pictures of objects from other categories (clothes, tools, fruits, and vegetables). Duration of the stimuli and ISI were the same as in the visual OB task.

The auditory OB tasks were set up in a similar way. The sounds were delivered through loudspeakers. The ISI was fixed at 1,200 ms for each. In the short auditory OB task, targets (23%, 230 trials in total) were pure tones at 1 kHz interspersed with tones at 500 Hz, length of the stimuli is 50 ms. In the long auditory OB, stimuli were the same but the length of the stimuli was 400 ms. In the voice OB task, targets (20%,

FIGURE 2. Amplitude profiles across electrode contacts for each of the seven patients included in Fig. 1C. Patient P1 corresponds to the patient detailed in Fig. 1. Each patient shows opposite polarity for both tasks on the same contact. Contacts located outside of the hippocampus show no ERP (amplitude close to 0), implying that the ERPs recorded in the hippocampus originate from within this structure. ERPs for the rare stimuli of the visual oddball task and famous faces in the famous/unknown recognition task. [Color figure can be viewed at wileyonlinelibrary.com]

250 trials in total) were human sounds (400 ms duration) interspersed with various other natural sounds. All sounds were different in this task.

Memory Tasks

In the face recognition memory task, patients viewed 48 faces of celebrities in grey-scale and 48 faces of unknown people displayed on a screen for 396 ms with an ISI between 1300 and 2000 ms (for a full description and examples of stimuli, see Barbeau et al., 2008). They had to say for each whether they knew the face or not. This procedure was not intended to assess how the patients recognized the faces (e.g., by familiarity or naming). The task was run in one block and without any study phase since pictures of celebrities were used.

In the visual recognition memory task (described with examples in Barbeau et al., 2008), patients viewed 15 trial-unique abstract pictures during an explicit encoding phase. The recognition phase took place after a 3 min delay. The patients were asked to say whether the stimulus presented was old or new. All stimuli were single-trial and consisted of abstract pictures which were difficult to verbalize. Participants underwent 4–6 blocks depending on clinical availability. Each stimulus was displayed for 396 ms, and the ISI was 1,300–2,000 ms.

In the crossmodal associative memory task, names of concrete objects (e.g., a rabbit, $n = 15$) were shown during an explicit encoding phase. After a delay of 3 min, related pictures (e.g., of a rabbit) were presented among distractors (e.g., a picture of an object not shown as a name during the encoding phase) during the recall phase. The patients had to say whether

Hippocampus

the picture matched one of the previously presented names. The stimuli were displayed on a screen for 396 ms with an ISI between 1600 and 2400 ms. The patients underwent three to four blocks depending on clinical availability.

Other Tasks

For comparison purposes, some patients also underwent other tasks (see Table 1 for details).

- *Mismatch negativity task*: some participants listened to the short auditory OB task (same as described above), without having to count the targets (an equivalent to an auditory mismatch task). The purpose of this condition was to assess what would happen if the patients did not have to pay attention to the targets.
- *Counting task*: Some patients also underwent the visual OB task (same as described above) and were asked to count all stimuli. In contrast to the previous control task, the purpose of this condition was to assess the outcome if the patients paid attention to all stimuli.
- *Mixed task*: Finally, one patient underwent a specific OB task in which the target was a famous face (Angelina Jolie), while the distractors were other famous faces. The purpose of this control task was to mix an oddball design with well-known stimuli to assess if it would modify the polarity of the components that were recorded during the oddball tasks.

Signal Acquisition

Signal was acquired using SynAmps amplifiers and Neuroscan software (Compumedics, El Paso, TX). The sampling frequency of EEG depth-recording was 1,000 Hz with an acquisition filter band-pass of 0.15–200 Hz. Reference was a surface electrode located in Fz.

ERP Processing

Epochs were computed off-line using Brainvision v1.05 (Brain Products GmbH, München, Germany) between 0 and 1,200 ms with a prestimulus baseline of 150 ms. Visual inspection of the EEG and epochs as well as artefact rejection procedures enabled the rejection of epochs with interictal activities. Epochs from memory tasks were computed after rejection of errors (false alarms and omissions) separately for correct hits and correct rejection. Epochs for OB tasks were computed separately for infrequent targets and frequent distractors. Epochs were then averaged per condition and baseline corrected to obtain ERPs.

Statistical Analyses

A matched-pair two-tailed signed-rank Wilcoxon test on individual averaged ERPs was used to assess significant differences between conditions. Such a nonparametric test was chosen because it does not require the assumption of normality. Furthermore, paired comparisons allow the comparison of ERP amplitudes independently of amplitude variation among patients. Level of significance was set at $P < 0.05$. The Wilcoxon test was run on each millisecond in the 0–650 ms time window. As can be observed in Figures 1 and 4, most effects reported in this study were significant for more than 100 ms consecutively, which allows controlling for multiple comparisons.

Location of the Electrode Contacts

A routine postoperative CT-scan without contrast was performed to check for the absence of bleeding after electrode insertion. MRI with 3D reconstruction performed after removal of the electrodes allowed locating the trace of each depth probe in the brain. The fusion of the postoperative CT-scan with this MRI allowed precise anatomical localization of contacts.

RESULTS

We first compared the ERPs in an OB task in which patients had to mentally count visual targets (20%) appearing randomly in a set of distractors (80%) with those from a famous face recognition memory task. Figure 1A presents ERPs to OB targets and famous faces recorded along successive contacts of an electrode implanted in the hippocampus in Patient 1. Both tasks elicited a negative component culminating at 200 ms (N2). Its amplitude (larger for the famous faces task) and polarity did not vary across the successive contacts located in the hippocampus. A later negative component peaking around 400 ms was evoked by OB targets, while famous faces elicited a component of reverse polarity. To maintain nomenclature consistency through the literature (Guillem et al., 1999; Soltani and Knight, 2000; Polich, 2007) these components correspond to the MTL-P300 and hP600, respectively. Amplitudes varied gradually and symmetrically for both tasks along successive contacts (1-2 and 3) in the hippocampus. Amplitude of this component was maximal on contact 3. For each condition, this component dropped on the contacts 4-5 immediately adjacent to contact 3, indicating that the localization of its source was within the hippocampus (Figs. 1B and 2 for a schematic representation of the data for all subjects).

In every patient included in this part of the study ($n = 7$), the MTL-P300 elicited by oddball targets was negative in the hippocampus (mean amplitude of the peak: -100 ± 47 μV, mean latency: 430 ms poststimulus onset), while the hP600 elicited by famous faces was positive (same patients, amplitude: 85 ± 49 μV, latency: 473 ms) (Fig. 1C). The temporal course of these potentials produced this opposite pattern for more than 300 ms starting at 260 ms poststimulus onset (matched-pair two-tailed signed-rank Wilcoxon test, $P < 0.05$ during the 260–604 ms period). The hP600 peaked later than the MTL-P300 (mean intrasubject peak latencies difference $= 79$ ms $\pm$ 55 ms).
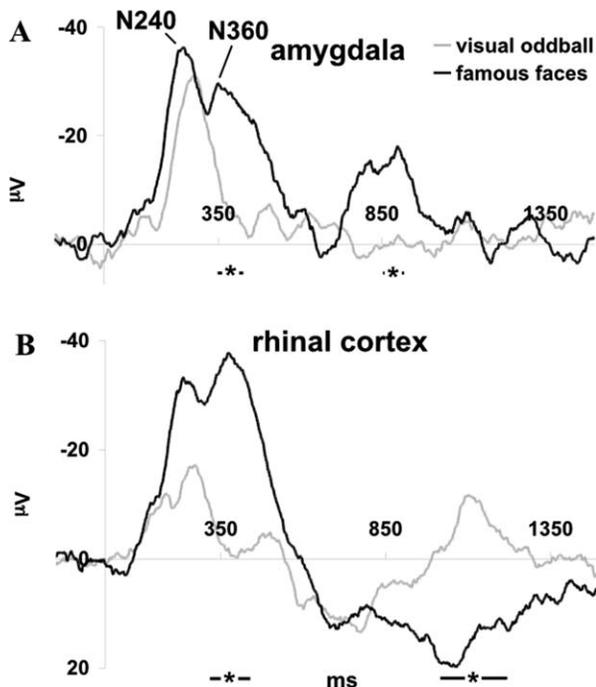
FIGURE 3. ERPs for the rare stimuli of the visual OB task and famous faces in the famous/unknown recognition task averaged across the same seven patients. ERPs were recorded from the amygdala (A) and rhinal cortex (B). A negative potential peaking at 240 ms (N240) followed by a second negative component at 360 ms (N360) could be recorded in both regions in response to famous faces. Rare stimuli in the OB task also elicited a negative response. Interestingly, no N360 was recorded in the oddball task.

Localization of the ERPs

The MTL-P300 and hP600 were local and had maximal negative or positive amplitude on the same contact within the hippocampus, a consistent finding in every patient (e.g., Fig. 1A). To check whether this pattern was focal, we first computed the matched-pairs percentage amplitude reduction of the potentials elicited by the OB targets and the famous faces on the medial and lateral contacts adjacent to the contact of maximum amplitude. Reduction rate was equivalent (Wilcoxon test, medial: 49% vs. 34%, $P = 0.25$; lateral: 70% vs. 73%, $P = 0.87$). We further studied the profile of ERP amplitudes for all patients. As can be seen from Figure 2, the contacts located immediately outside the hippocampus show small voltage amplitude, which is expected since these are usually located in the white matter laterally (for electrodes reaching the anterior hippocampus, e.g., contacts 4 and 5 in Fig. 1) and medially (for electrodes reaching the posterior hippocampus) from the hippocampus. A similar profile of increasing and decreasing amplitudes across contacts, but of opposite polarity, was observed in every patient, suggesting that the neural signatures of underlying processing of face recognition and target detection originate from the same hippocampal region (Figure 2). Furthermore, there were usually several electrode contacts within the hippocampus. If more than one hippocampal region had been at the origin of each late potential, the potential of

maximal amplitude would have been recorded from distinct contacts as a function of task.

The location of the contact of maximal amplitude within the hippocampus was ascertained through electrode reconstruction in the MRI of each patient and comparison with an atlas of the human hippocampus (Duvernoy, 2005). Contacts recording maximal amplitude were most likely located in the CA1 region in all patients (examples in Figs. 1B and 4B, see also Fig. 2 showing that the contact of maximum amplitude in the hippocampus was lateral, where the CA1 region is located in humans).

ERPs from Other Medial Temporal Lobe Structures

Although the oddball and memory tasks elicited ERPs in several brain regions other than the hippocampus (6–10 electrodes were implanted in each patient and areas sampled included recordings in the temporal as well as in parietal and frontal lobes), a similar pattern was not observed in any of the other brain areas from which recordings were available. For example, in the amygdala and rhinal cortex, regions adjacent, and closely related to the hippocampus, a double negative ERP (N240-N360) was recorded during memory tasks, while only a N240 was recorded during the OB tasks, in accordance with other studies (Fig. 3; Trautner et al., 2004; Barbeau et al., 2008; Ludowig et al., 2010).

ERPs for Other OB and Memory Tasks

To ascertain that these late components were reliably related to the type of task and that results did not depend on specific modalities or procedures used, we developed a series of OB and memory tasks with differing designs and materials. The tasks each patient underwent depended on clinical availability. In the OB tasks, we used both auditory and visual targets; short and long targets (e.g., 50 or 400 ms pure tones); repeated (e.g., same target to be detected throughout the task) or always different (e.g., detect trial-unique pictures of animals in series of trial-unique other objects) targets. We also used targets that could be detected using simple discrimination (e.g., high vs. low frequency sound) or targets that required higher cognitive processes such as categorization (detect trial unique human sounds among series of artificial sounds). Memory tasks were also purposefully diverse (see below). Despite these different conditions, all targets in the OB tasks elicited negative potentials in hippocampus, while all memory tasks elicited positive potentials at the same contact in each patient (Fig. 4). These results indicate that the type of task, rather than the type of materials and design, was critical to determine the polarity of the hippocampal MTL-P300/hP600 components.

Having found consistent differences in our OB and memory tasks, we were motivated to design a task where instruction alone, and not material differentiated the two tasks. To this end, we ran an OB task using famous faces. Patient (P8) had to count the occurrence of a famous face (Angelina Jolie) presented repeatedly at random among other famous faces. The
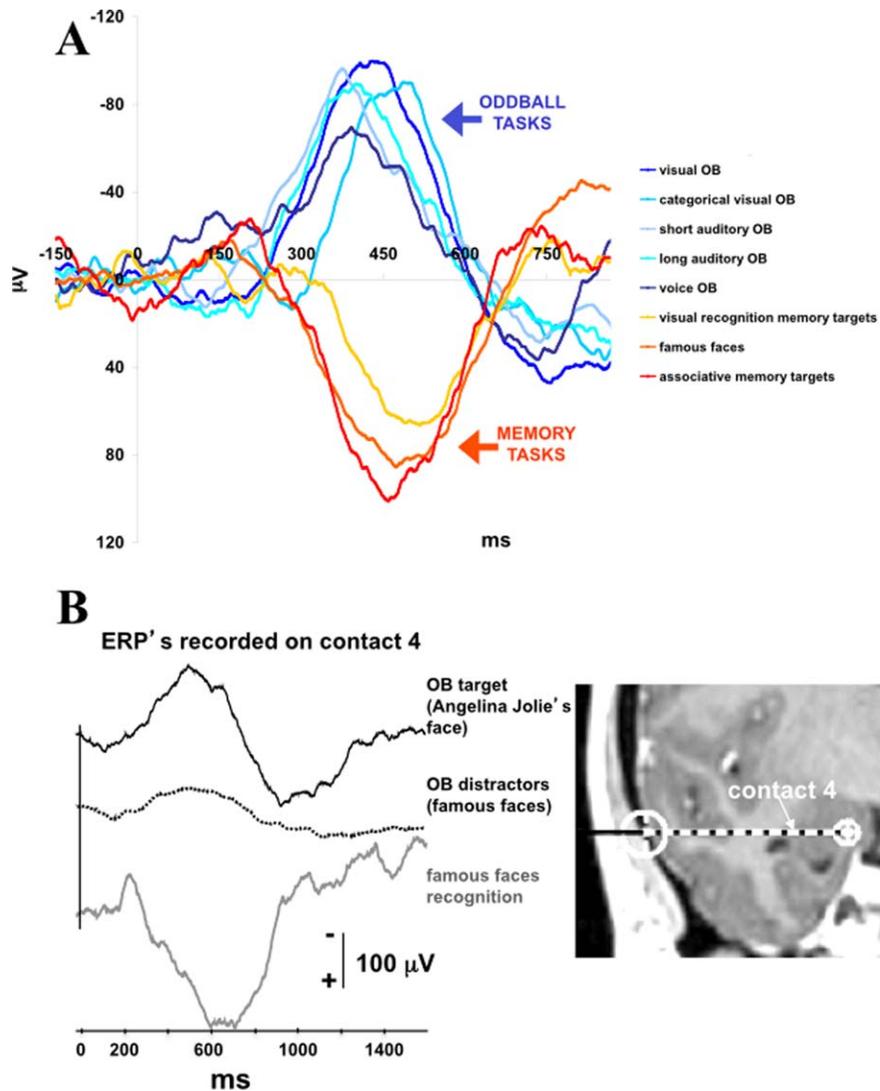
FIGURE 4. (A): Grand mean ERPs to different OB and memory tasks. The ERPs presented in Fig. 1C are also reported on this figure. ERPs for the rare stimuli in the oddball tasks and for correct old stimuli in the memory tasks. B: OB experiment in which a patient had to count the occurrence of a famous face (Angelina Jolie) among other famous faces. This ERP was negative (MTL-P300, plain black line). The ERP to irrelevant famous faces (distractors) in the OB task are also presented (dotted black line). This ERP did not have a positive polarity although all faces were famous. On the other hand, ERPs to famous faces that had to be recognized explicitly in a yes/no procedure had a positive polarity (hP600) in the same patient (grey line). All these ERPs were recorded from the same contact 4 located in CA1 as shown by the electrode reconstruction in the MRI of the patient. Contacts are in white. [Color figure can be viewed at wileyonlinelibrary.com]

ERP to the target famous face was compared to the ERP evoked by famous faces when they had to be recognized explicitly among unknown faces. The famous face in the OB task (Angelina Jolie) elicited a negative component, while famous faces in the recognition paradigm elicited a positive component (Fig. 4B). Furthermore, irrelevant famous faces (distractors) in the OB task elicited a negative ERP of weak amplitude.

Modulation of the Hippocampal Potentials

As expected, and as has been shown previously (Halgren et al., 1980; McCarthy et al., 1989; Grunwald et al., 1998; Grunwald et al., 2003; Trautner et al., 2004; Barbeau et al., 2008), the MTL-P300 and hP600 were modulated by the target/distractor or old/new status of the stimuli that were presented during the different tasks. Rare visual targets elicited potentials of much larger amplitude than frequent, behaviorally irrelevant, stimuli (Wilcoxon test, $n = 7$, $P < 0.05$, 241–587 ms poststimulus) (Fig. 5A). The targets that elicited a MTL-P300 in the auditory OB task did not elicit any potential when patients passively heard the same list of tones in a mismatch paradigm, indicating that task requirement and endogenous attention modulated the negative potential (Wilcoxon test, $n = 5$, $P < 0.05$, 267–563 ms poststimulus) (Fig. 5B).
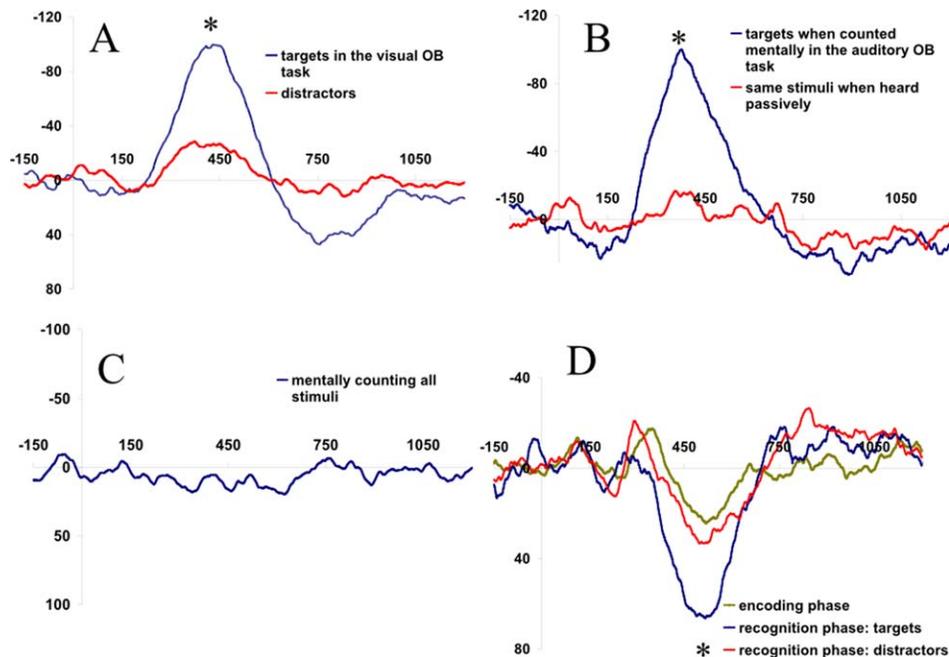
FIGURE 5. Grand average of MTL-P300 and hP600 were modulated by the target/distractor or old/new status of the stimuli that were presented during the different tasks. (A): Visual rare targets compared to frequent stimuli in the visual OB task. (B): The targets that elicited a MTL-P300 in the short auditory OB task did not elicit any potential when patients passively heard the same list of tones (i.e., in this case the patients did not have to count the stimuli). (C): Patients viewed blocks of trial-unique abstract pictures and had to count all of them mentally. This task did not elicit any potential within the hippocampus. (D): The hP600 was itself modulated by different factors related to memory, here between the old or new status of the stimulus. *Significant difference. [Color figure can be viewed at wileyonlinelibrary. com]

Three patients viewed blocks of trial-unique abstract pictures and had to count all of them mentally. This task did not elicit any potential within the hippocampus, demonstrating, in accord with the context updating theory (Polich, 2007), that it is a significant change in a current series of stimuli that is important to elicit an MTL-P300 rather than merely processing all targets or simply updating current counts of targets in working memory (Fig. 5C).

The hP600 was itself modulated by different factors related to memory. Although encoding phases also elicited positive potentials, recognition phases elicited potentials of significantly larger amplitude (Fig. 5D; Wilcoxon test, $n = 6$, $P < 0.05$, 351–595 ms post stimulus). In addition, the recognition of targets (hits) elicited an hP600 of higher amplitude than the correct rejection of distractors (Fig. 5D, $n = 6$, $P < 0.05$, 459–490 and 510–567 ms poststimulus). We used a variety of memory tasks ranging from prelearned general-knowledge like materials (famous faces) to experimentally presented words and images of everyday objects. Interestingly, the positive potential was larger for tasks which placed higher demands on episodic memory than for tasks that could rely merely on familiarity. In this study, one task used a yes/no visual recognition memory method that could be performed principally relying on familiarity. In turn, we also used a crossmodal associative memory task that relied more on episodic memory. In this task, names of concrete objects (e.g., a rabbit) were shown during the encoding phase whereas related pictures were shown among distractors during the recall phase. Hence, recall relied less on perceptual familiarity with the stimulus due to the crossmodal nature of the task; the recognition decision was based on access to a representation which was not a mere perceptual overlap with the previously presented stimulus. Moreover, the critical recognition decision was based on reference to having encountered the stimuli in a specific study phase, rather than identifying a famous face as someone familiar. The positive potential elicited by the targets in the crossmodal associative memory task showed significantly higher amplitude than the potential to the targets in the visual recognition memory task (Fig. 4, Wilcoxon test, $n = 5$, $P < 0.05$, 354–488 ms poststimulus).

Stimulus Novelty

Stimulus novelty did not change the polarity of the potentials per se. Stimuli were all novel (trial-unique) during the voice and categorical OB tasks, in which case the polarity was negative (Fig. 4A). Some were novel during memory tasks (during encoding and during recognition of distractors) and they elicited a positive polarity (Fig. 5D). Finally they were all novel during a task during which all stimuli had to be counted, in which case there was no obvious ERP (Fig. 5C). It is thus the nature of the task, rather than the novelty/familiarity

characteristic of the stimulus, which influences the polarity of the potential.

Task difficulty

We used different OB and memory tasks with different levels of difficulty. The level of difficulty of the task did not change the polarity of the potentials although it is known that it can affect amplitude or latency (Kim et al., 2008).

DISCUSSION

Our results show different activation patterns between 400 and 600 ms in response to OB and memory tasks in the same hippocampal region: whereas a negativity akin to the novelty P300 was recorded in oddball tasks, a positivity which resembled the hippocampal P600 was recorded during memory tasks. Strikingly, there was a similar temporal course but of opposite polarity observed for the two tasks. The polarity inversion between these two late components was robust, being observed for all versions of the tasks tested in each patient and consistent from one patient to another.

Neither the other medial temporal structures nor neocortical areas displayed the same phenomenon. In addition, these components disappeared as soon as contacts were located outside the hippocampus indicating that these late components were generated within the hippocampus. It did not seem to depend on whether the components were recorded in the anterior or posterior hippocampus (Poppenk et al., 2013). Our findings are in agreement with the collated picture from studies which report positive potentials for memory tasks and negative potentials for OB tasks from the human hippocampus in similar recording conditions (Halgren et al., 1980; Halgren et al., 1998; Fernandez et al., 1999; Trautner et al., 2004; Fell et al., 2005; Barbeau et al., 2008; Axmacher et al., 2010). Despite the fact that it had been known that OB and memory tasks reliably induced large hippocampal components, our study is the first to provide data strongly suggesting that their intra-hippocampal circuitry is different.

Our results suggest that OB and memory tasks are processed within a similar time window in the same hippocampal region but in different ways. The polarity of the potentials did not depend on the novelty of the stimuli or on the difficulty of the tasks. Furthermore, the hippocampal activation is clearly task-dependent and not stimulus-dependent. Famous faces evoke large positive potential in the hippocampus in the context of memory tasks (Trautner et al., 2004; Dietl et al., 2005; Barbeau et al., 2008). However a famous face, when processed as a target in the context of an OB task, evoked a large negative potential (Fig. 4B). Thus, the class of task (OB vs. memory), rather than stimuli per se, determines the polarity of the potentials, suggesting that it may be the same cell population activated through two different pathways, which generates the MTL-300 and hP600.

What are the mechanisms underlying this reverse pattern of activation? Because polarity reversal is localized strictly in the same site whatever the task, the first hypothesis is that both activities are generated by a single neuronal population, probably CA1 pyramidal cells. Pyramidal neurons in CA1 have a remarkable size due to their long apical dendritic arborization of up to ~1.5 mm (Duvernoy, 2005). CA1 is also the largest field in the human hippocampus and contains the highest number of pyramidal neurons (Amaral and Lavenex, 2007; Malykhin et al., 2010). The entorhinal cortex conveys information to CA1 via the monosynaptic (Temporo-Ammonic) and trisynaptic pathways, coming from entorhinal layer III and layer II, respectively (Van Strien et al., 2009). They reach the pyramidal cells of CA1 at different levels of their dendritic tree: the monosynaptic at the apical level (stratum lacunosum moleculare) and the trisynaptic at the basal level (stratum radiatum). The synaptic activity (increased ionic permeability) at a given site of the somato-dendritic arborization leads to a sink-source dipolar configuration in the extracellular field. Activation of apical synapses creates a local current sink (negative) and consequently a current source (positive) close to the soma (Lopes da Silva, 2010). Activation of basal dendrites produces a reverse sink-source configuration. Our data are in accordance with such mechanism, hence generating the hypothesis of an involvement of one or the other pathway, depending on the task.

These two pathways carry distinct information to CA1. Whereas the monosynaptic pathway may convey inputs from sensory systems to CA1 and maintain a record of the current state of the world (McNaughton et al., 1989), the trisynaptic pathway and the autoassociative properties of CA3 is involved in memory retrieval (Rolls, 2010). These respective circuits could support OB and memory tasks as hypothesized above. McCarthy et al. (1989) have proposed that the negative potential evoked by OB tasks within the hippocampus could be due to depolarization of distal dendrites by excitatory inputs from the entorhinal cortex. Recordings in the rat CA1 actually support such a pattern of sinks and sources (Speed and Dobrunz, 2009, their Fig. 1A). Furthermore, the trisynaptic pathway transfers to CA1 activities that are delayed compared to the monosynaptic pathway due to integration at each stage (Dudman et al., 2007). Accordingly, we found a delay of approximately 80 ms (mean peak difference across subjects) between ERPs to memory tasks and ERPs to OB tasks further supporting the interpretation that negative or positive ERPs reflect the activation of each pathway (note that it is difficult to estimate the onset time of hippocampal components, which is why we focused on the peak delay). Witter et al (2000) have however emphasized the complexity of entorhinal–hippocampal circuits with the idea of having both distinct pathways to the hippocampus from either the lateral or medial entorhinal cortex and also first, second and third order entorhinal representations following the activation of different entorhinal-hippocampal circuits. Interestingly, second-order representations could contribute to assessing the novelty of a new input. Thus, other

pathways or more complex interactions than simply the mono-synaptic or trisynaptic pathways could be considered.

An alternative hypothesis is that the activity of two distinct neuronal populations was recorded, one responding to OB and the other to memory tasks. Due to the variety of hippocampal subfields, several possibilities can be advanced. For example, Rutishauser et al. (2015) using microwire electrodes implanted within the human anterior hippocampus and amygdala identified two populations of neurons, one selective for given categories of objects, the other signaling either novelty or familiarity (see also Rutishauser et al., 2006). These authors suggested that these neurons could possibly be morphologically or physiologically different. The very similar profile of polarity reversal along the successive contacts of the electrode as well as the similar amplitude for both potentials recorded in the two tasks (Fig. 2) raises however the question of the location of these two classes of neurons. Another possibility in line with the idea of two distinct populations of neurons was presented by Valero et al. (2015) who showed a different participation of deep and superficial CA1 pyramidal cells to sharp-wave ripples, as they showed opposite membrane polarization. These authors discussed the possibility that the hippocampal pyramidal cells were not functionally uniform and depended on brain states (Senior et al., 2008; Mizuseki et al., 2011). A third possibility is that the polarity reversal we observed could be achieved by CA1 pyramidal cells on the one hand, and the dentate gyrus granule cells or another sector of CA on the other. Modeling and recordings of the rat hippocampus has indeed shown that the curved configuration of granule cells layer may induce local field potentials much larger at some distance from the synaptic sites (Fernandez-Ruiz et al., 2013).

However, it is evident that the spatial resolution of the depth electrodes that are used in epileptic patients cannot analyze current source densities at the microscale level and thus cannot disambiguate between these different hypotheses. This study thus calls for further studies combining macroelectrodes/microelectrodes and state of the art MRI reconstruction to view hippocampal subfields (Yushkevich et al., 2010) or to specific time-frequency and coherence analyses that could help distinguishing the neural circuitry or neuronal activation underlying the MTL-P300 and hP-600. Finally, both MTL-P300 and hP600 potentials may be related to increased BOLD response suggesting it may be difficult to observe using fMRI the same phenomena that we report using intracerebral recordings (Axmacher et al., 2008).

From a broader perspective, memory (Halgren et al., 1994a,1994b; Nyberg et al., 2000; Steinvorth et al., 2006) and target detection (Corbetta and Shulman, 2002; Yamaguchi et al., 2004; Crottaz-Herbette et al., 2005; Mantini et al., 2009; Vanni-Mercier et al., 2009) are supported by the activity of two different large-scale neocortical networks. Hippocampal functional circuitry could shift according to the subject's implication in one or the other class of task. Interestingly, it has been shown that the activity of self-oriented or goal-directed behavior networks are anticorrelated (Fox et al., 2005), which may map upon how memory and target detection tasks are

respectively processed in the hippocampus. In line with the idea that some brain areas may work under modes that are exclusive of others, a model of hippocampal theta rhythms suggests that encoding and retrieval may take place at different phase of the theta rhythm and that these cannot overlap (Separate Phases of Encoding and Retrieval model, Hasselmo and Stern, 2014). Allan and Allen (2005) experimentally showed that retrieval from memory transiently interfered with encoding (for about 450 ms). In short, the hippocampus could participate in the transition between two neocortical large-scale mutually exclusive networks (Tang et al., 2012), one involved in memory, the other in target detection, the functional reason for their respective exclusiveness being that oddball tasks require attention to external stimuli, while memory tasks require attention to internal representations.

In conclusion, we report that the large potentials evoked by memory or OB tasks have similar temporal course but opposite polarity in the human hippocampus. Activation of the direct and indirect entorhinal–hippocampal CA1 pathways would subserve novelty detection and recognition memory, respectively. Their final common target in CA1 would integrate activities of two distinct large-scale networks implementing externally or internally oriented, mutually exclusive, brain states.

ACKNOWLEDGMENT

REFERENCES

Allan K, Allen R. 2005. Retrieval attempts transiently interfere with concurrent encoding of episodic memories but not vice versa. J Neurosci 25:8122–8130.

Amaral D, Lavenex P. 2007. Hippocampal neuroanatomy. In: The Hippocampus Book. Andersen P, Morris R, Amaral D, Bliss T, O'Keefe J, editors. New-York: Oxford University Press. pp 37–114.

Axmacher N, Elger CE, Fell J. 2008. Memory formation by refinement of neural representations: The inhibition hypothesis. Behav Brain Res 189:1–8.

Axmacher N, Cohen MX, Fell J, Haupt S, Dumpelmann M, Elger CE, Schlaepfer TE, Lenartz D, Sturm V, Ranganath C. 2010. Intracranial EEG correlates of expectancy and memory formation in the human hippocampus and nucleus accumbens. Neuron 65:541–549.

Barbeau EJ, Taylor MJ, Regis J, Marquis P, Chauvel P, Liegeois-Chauvel C. 2008. Spatio temporal dynamics of face recognition. Cereb Cortex 18:997–1009.

Brazdil M, Rektor I, Daniel P, Dufek M, Jurak P. 2001. Intracerebral event-related potentials to subthreshold target stimuli. Clin Neurophysiol 112:650–661.

Corbetta M, Shulman GL. 2002. Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 3:201–215.

Crottaz-Herbette S, Lau KM, Glover GH, Menon V. 2005. Hippocampal involvement in detection of deviant auditory and visual stimuli. Hippocampus 15:132–139.

Dietl T, Trautner P, Staedtgen M, Vannuchi M, Mecklinger A, Grunwald T, Clusmann H, Elger CE, Kurthen M. 2005. Processing of famous faces and medial temporal lobe event-related potentials: A depth electrode study. Neuroimage 25:401–407.

Dudman JT, Tsay D, Siegelbaum SA. 2007. A role for synaptic inputs at distal dendrites: Instructive signals for hippocampal long-term plasticity. Neuron 56:866–879.

Duvernoy H. 2005. The human hippocampus: Functional anatomy, vascularization and serial sections with MRI, 3rd ed. Berlin: Springer Verlag.

Fell J, Kohling R, Grunwald T, Klaver P, Dietl T, Schaller C, Becker A, Elger CE, Fernandez G. 2005. Phase-locking characteristics of limbic P3 responses in hippocampal sclerosis. Neuroimage 24:980–989.

Fernandez-Ruiz A, Munoz S, Sancho M, Makarova J, Makarov VA, Herreras O. 2013. Cytoarchitectonic and dynamic origins of giant positive local field potentials in the dentate gyrus. J Neurosci 33:15518–15532.

Fernandez G, Effern A, Grunwald T, Pezer N, Lehnertz K, Dumpelmann M, Van Roost D, Elger CE. 1999. Real-time tracking of memory formation in the human rhinal cortex and hippocampus. Science 285:1582–1585.

Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. 2005. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci USA 102:9673–9678.

Grunwald T, Lehnertz K, Heinze HJ, Helmstaedter C, Elger CE. 1998. Verbal novelty detection within the human hippocampus proper. Proc Natl Acad Sci USA 95:3193–3197.

Grunwald T, Pezer N, Munte TF, Kurthen M, Lehnertz K, Van Roost D, Fernandez G, Kutas M, Elger CE. 2003. Dissecting out conscious and unconscious memory (sub)processes within the human medial temporal lobe. Neuroimage 20 Suppl 1:S139–S145.

Guillem F, Rougier A, Claverie B. 1999. Short- and long-delay intracranial ERP repetition effects dissociate memory systems in the human brain. J Cogn Neurosci 11:437–458.

Halgren E, Marinkovic K, Chauvel P. 1998. Generators of the late cognitive potentials in auditory and visual oddball tasks. Electroencephalogr Clin Neurophysiol 106:156–164.

Halgren E, Squires NK, Wilson CL, Rohrbaugh JW, Babb TL, Crandall PH. 1980. Endogenous potentials generated in the human hippocampal formation and amygdala by infrequent events. Science 210:803–805.

Halgren E, Baudena P, Heit G, Clarke JM, Marinkovic K, Clarke M. 1994a. Spatio-temporal stages in face and word processing. I. Depth-recorded potentials in the human occipital, temporal and parietal lobes. J Physiol Paris 88:1–50.

Halgren E, Baudena P, Heit G, Clarke JM, Marinkovic K, Chauvel P, Clarke M. 1994b. Spatio-temporal stages in face and word processing. 2. Depth-recorded potentials in the human frontal and Rolandic cortices. J Physiol Paris 88:51–80.

Halgren E, Baudena P, Clarke JM, Heit G, Liegeois C, Chauvel P, Musolino A. 1995a. Intracerebral potentials to rare target and distractor auditory and visual stimuli. I. Superior temporal plane and parietal lobe. Electroencephalogr Clin Neurophysiol 94:191–220.

Halgren E, Baudena P, Clarke JM, Heit G, Marinkovic K, Devaux B, Vignal JP, Biraben A. 1995b. Intracerebral potentials to rare target and distractor auditory and visual stimuli. II. Medial, lateral and posterior temporal lobe. Electroencephalogr Clin Neurophysiol 94:229–250.

Hasselmo ME, Stern CE. 2014. Theta rhythm and the encoding and retrieval of space and time. Neuroimage 85:656–666.

Kim KH, Kim JH, Yoon J, Jung KY. 2008. Influence of task difficulty on the features of event-related potential during visual oddball task. Neurosci Lett 445:179–83.

Knight R. 1996. Contribution of human hippocampal region to novelty detection. Nature 383:256–259.

Kumaran D, Maguire EA. 2007. Which computational mechanisms operate in the hippocampus during novelty detection?. Hippocampus 17:735–748.

Lopes da Silva F. 2010. EEG: Origin and measurement. In: EEG-fMRI: Physiological Basis, Technique, and Applications. Mulert C, Lemieux L, editors. Berlin, Heidelberg: Springer Verlag.

Ludowig E, Bien CG, Elger CE, Rosburg T. 2010. Two P300 generators in the hippocampal formation. Hippocampus 20:186–195.

Malykhin NV, Lebel RM, Coupland NJ, Wilman AH, Carter R. 2010. In vivo quantification of hippocampal subfields using 4.7 T fast spin echo imaging. Neuroimage 1549:1224–1230.

Mantini D, Corbetta M, Perrucci MG, Romani GL, Del Gratta C. 2009. Large-scale brain networks account for sustained and transient activity during target detection. Neuroimage 44:265–274.

McCarthy G, Wood CC, Williamson PD, Spencer DD. 1989. Task-dependent field potentials in human hippocampal formation. J Neurosci 9:4253–4268.

McNaughton BL, Barnes CA, Meltzer J, Sutherland RJ. 1989. Hippocampal granule cells are necessary for normal spatial learning but not for spatially-selective pyramidal cell discharge. Exp Brain Res 76:485–496.

Mizuseki K, Diba K, Pastalkova E, Buzsáki G. 2011. Hippocampal CA1 pyramidal cells form functionally distinct sublayers. Nat Neurosci 14:1174–1181.

Nyberg L, Persson J, Habib R, Tulving E, McIntosh AR, Cabeza R, Houle S. 2000. Large scale neurocognitive networks underlying episodic memory. J Cogn Neurosci 12:163–173.

Polich J. 2007. Updating P300: An integrative theory of P3a and P3b. Clin Neurophysiol 118:2128–2148.

Poppenk J, Köhler S, Moscovitch M. 2010. Revisiting the novelty effect: When familiarity, not novelty, enhances memory. J Exp Psychol Learn Mem Cogn 36:1321–30.

Poppenk J, Evensmoen HR, Moscovitch M, Nadel L. 2013. Long-axis specialization of the human hippocampus. Trends Cogn Sci 17:230–40.

Rolls ET. 2010. A computational theory of episodic memory formation in the hippocampus. Behav Brain Res 215:180–196.

Rutishauser U, Mamelak AN, Schuman EM. 2006. Single-trial learning of novel stimuli by individual neurons of the human hippocampus-amygdala complex. Neuron 49:805–813.

Rutishauser U, Ye S, Koroma M, Tudusciuc O, Ross IB, Chung JM, Mamelak AN. 2015. Representation of retrieval confidence by single neurons in the human medial temporal lobe. Nat Neurosci 18:1–12.

Senior TJ, Huxter JR, Allen K, O'Neill J, Csicsvari J. 2008. Gamma oscillatory firing reveals distinct populations of pyramidal cells in the CA1 region of the hippocampus. J Neurosci 28:2274–2286.

Soltani M, Knight RT. 2000. Neural origins of the P300. Crit Rev Neurobiol 14:199–224.

Speed HE, Dobrunz LE. 2009. Developmental changes in short-term facilitation are opposite at temporoammonic synapses compared to Schaffer collateral synapses onto CA1 pyramidal cells. Hippocampus 19:187–204.

Squire LR. 1992. Memory and the hippocampus: A synthesis from findings with rats, monkeys, and humans. Psych Rev 99:195–231.

Steinvorth S, Corkin S, Halgren E. 2006. Ecphory of autobiographical memories: An fMRI study of recent and remote memory retrieval. Neuroimage 30:285–298.

Talairach J, Bancaud J. 1973. Stereotaxic approach to epilepsy. Methodology of anatomo-functional stereotaxic investigations. Progr Neurol Surg 5:297–354.

Tang YY, Rothbart MK, Posner MI. 2012. Neural correlates of establishing, maintaining, and switching brain states. Trends Cogn Sci 16:330–337.

Trautner P, Dietl T, Staedtgen M, Mecklinger A, Grunwald T, Elger CE, Kurthen M. 2004. Recognition of famous faces in the medial temporal lobe: An invasive ERP study. Neurology 63:1203–1208.

Tulving E, Kroll N. 1995. Novelty assessment in the brain and long-term memory encoding. Psychon Bull Rev 2:387–90.

Valero M, Cid E, Averkin RG, Aguilar J, Sanchez-Aguilera A, Viney TJ, Gomez-Dominguez D, Bellistri E, de la Prida LM. 2015. Determinants of different deep and superficial CA1 pyramidal cell dynamics during sharp-wave ripples. Nat Neurosci 18:1281–1290.

Van Strien NM, Cappaert NLM, Witter MP. 2009. The anatomy of memory: An interactive overview of the parahippocampal-hippocampal network. Nat Rev Neurosci 10:272–282.

Vanni-Mercier G, Mauguiere F, Isnard J, Dreher JC. 2009. The hippocampus codes the uncertainty of cue-outcome associations: An intracranial electrophysiological study in humans. J Neurosci 29:5287–5294.

Verleger R. 2008. P3b: Towards some decision about memory. Clin Neurophysiol 119:968–970.

Witter MP, Naber PA, van Haeften T, Machielsen WC, Rombouts SA, Barkhof F, Scheltens P, Lopes da Silva FH. 2000. Cortico-hippocampal communication by way of parallel parahippocampal-subicular pathways. Hippocampus 10:398–410.

Yamaguchi S, Hale LA, D'Esposito M, Knight RT. 2004. Rapid prefrontal-hippocampal habituation to novel events. J Neurosci 24:5356–5363.

Yushkevich PA, Wang H, Pluta J, Das SR, Craige C, Avants BB, Weiner MW, Mueller S. 2010. Nearly automatic segmentation of hippocampal subfields in in vivo focal T2-weighted MRI. Neuroimage 53:1208–1224.