HIPPOCAMPUS 21:689–693 (2011)

RAPID COMMUNICATION

Rapid Consolidation and the Human Hippocampus: Intracranial Recordings Confirm Surface EEG

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ABSTRACT: Diverse studies demonstrated that although immediately repeated stimuli are better and faster recognized than stimuli repeated after a delay, this comes at the price of less-efficient long-term retention. A recent-evoked potential study using source estimation of high-resolution scalp EEG indicated that while immediate repetition induced a strikingly different electrical activity than new items in the left-medial temporal lobe (MTL) after 200–300 ms, delayed repetition did not. In this study, we recorded evoked potentials in two epileptic patients with intracranial depth electrodes in diverse temporal and frontal areas as they performed the same task as in the previous study. We found that immediate repetition induced increase of neural activity specifically in the left MTL between 250 and 400 ms compared to new items and items repeated after a delay. The findings are important in two ways. First, they support our previous conclusion that novel information immediately initiates a consolidation process involving the left-hippocampal area, which remains vulnerable during active maintenance and increases its effectiveness during off-line processing. Second, they indicate that source estimation based on high-resolution scalp EEG correctly localizes the current source of electrical activity in midline structures like the MTL. © 2010 Wiley-Liss, Inc.

KEY WORDS: intracranial recording; depth electrodes; EEG; evoked potentials; spatiotemporal mapping; inverse solution; spacing effect; medial temporal lobe; hippocampus; short-term memory

INTRODUCTION

Although neuroimaging studies in healthy subjects have shown that the medial temporal lobe (MTL) contributes to both long-term (Milner et al., 1998; Pihlajamäki et al., 2003, Squire et al., 2004) and short-term memory (Ranganath and D'Esposito, 2001; Hannula et al., 2006; Axmacher et al., 2008), the nature of the specific MTL contributions to short- to long-term memory remains unclear. Recently, James et al. (2009) explored this question in a high-density event-related potentials (ERP) study, in which healthy subjects performed a continuous recognition task of meaningful drawings. All drawings were repeated once, either immediately or after nine intervening items. The findings showed that drawings immediately repeated after an unfilled interval were better recognized than drawings repeated after nine intervening items. Half an hour after the learning task, however, the immediately repeated drawings were significantly less well recognized than drawings repeated after intervening items, confirming that learning efficiency improves with delayed repetition (Ebbinghaus, 1885/1992), which is nowadays known as the spacing effect (Glenberg, 1979; Green, 1989). Spatiotemporal analysis of the ERP indicated that immediate repetition induced a strikingly different electrocortical response after ~200–300 ms, with inversed polarity, than new stimuli and delayed repetitions. Source localizations revealed that this difference reflected transient activity in the left MTL (Fig. 1).

The findings demonstrated behavioral and electrophysiological dissociation between recognition during active maintenance and recognition after intervening items. We concluded that novel information immediately initiates a consolidation process involving the MTL, which remains vulnerable during active maintenance and increases its effectiveness during off-line processing. In the case of the meaningful designs used in this task, this process appeared lateralized to the left MTL.

The method used by James et al. (2009)—inverse solutions calculated from high density surface EEG—has well-known high-temporal resolution. However, its ability to seize activity in deep midline structures like the MTL is debated (Lopes da Silva and van Rotterdam, 1993; Gaveret et al., 2004), despite demonstration of correct localization of epileptic activity in these areas in simultaneous intracranial and scalp

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Grant sponsor: Swiss National Science Foundation; Grant number: 320000-113436.

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Accepted for publication 29 March 2010
DOI 10.1002/hipo.20819
Published online 2 June 2010 in Wiley Online Library (wileyonlinelibrary.com).

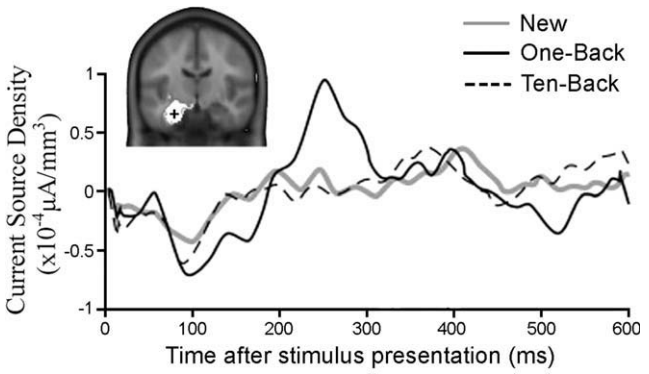

FIGURE 1. Activation observed in previous study. Region-of-interest analysis of current density in the left-medial temporal lobe calculated with inverse solutions on the basis of surface multichannels EEG (adapted from James et al., 2009, with permission). The region-of-interest is indicated by a cross in the coronal slide.

recordings (Zumsteg et al., 2005; Lantz et al., 2001). In this study, we had the opportunity to verify the findings of James et al. (2009) using intracranial depth electrode recordings in two patients performing the same memory task.

Both patients were evaluated for potential epilepsy surgery, and their legal representation gave written informed consent to participate in this study, which was approved by the institutional Ethics Committee.

Patient A.A. was a 16-year-old right-handed male, who suffered from refractory epilepsy with brief loss of consciousness since the age of 4 years after viral encephalitis. Seizure frequency was one per day. MRI revealed right-hippocampal sclerosis associated with discrete atrophy of the right temporal cortex. Treatment consisted of levitiracetam 2 g per day. Patient A.A. attended pubic high-school with no difficulty.

Patient B.B. was a 21-year-old right-handed man who suffered from refractory epilepsy since the age of 10 years. His seizures occurred at a frequency of five per day and were characterized by electrical sensations in the head and disordered speech comprehension. Treatment consisted of carbamazepine 1,200 mg per day. MRI revealed no apparent lesions. Patient B.B. had no school retardation and intended to enroll a business school. In both patients, seizures originate from the right-temporal lobe. Detailed neuropsychological evaluation showed no cognitive impairment. At the time of testing, both patients were free of medication.

Stereotaxic depth electrodes were used. A stereotactic headframe was affixed to the patients' skull with pins. A CT scan was performed after implantation and coregistered using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5) to the patients own brain MRI (which was Talairach normalized), allowing exact localization of each electrode contact. Electrodes (Fig. 2a) were placed in the right frontal lobe (10 electrode contacts in both patients), the left and right MTL, and the right anterior temporal lobe (six contacts in patient A.A. and eight contacts in patient B.B. for each sites). Patient B.B. additionally had an eight-contact electrode in the left-anterior temporal lobe.

Intracranial potentials were continuously recorded (Ceegraph XL, Biologic System Corp.) with a sampling rate of 1,024 Hz (bandpass 0.5–100 Hz). The reference electrode was an extracerebral scalp electrode located at position Cz of the 10–20 international EEG system.

The patients performed a continuous recognition task, which has been described elsewhere (James et al., 2009). In short, patients saw 120 meaningful drawings, all of which were repeated once, either immediately following a 2-s stimulus-free interval (One-back items, $N = 60$) or after nine intervening items (Ten-back items, $N = 60$). They had to indicate picture recurrences by pressing a button.

Thirty minutes after the termination of the learning task, participants performed a delayed recognition task containing all 120 pictures from the learning task plus 60 new pictures in random order.

Individual epochs were low-pass filtered using a 50-Hz cutoff. Single-trial intracranial-evoked potential epochs were analyzed offline using the Cartool software (http://brainmapping.unige.ch/Cartool.php). Epochs contaminated by epileptic spikes were removed (patient A.A.: 25%; patient B.B.: 39%). The remaining evoked potential epochs entered analysis for the three conditions (New, One-back repetition, Ten-back repetition) from 0 to 600 ms after stimulus onset. For all electrodes, the single-trial epochs were compared statistically at each time point (1 time point = 0.97 ms) with unpaired *t*-test for dependent samples. A difference between conditions was consid-

TABLE 1.

Behavioral Data from Patients A.A. and B.B. and from Controls Participants (Taken from James et al., 2009, with Permission)

		Accuracy (% correct)			RT (ms)		
	Stimulus type	A.A.	B.B.	Controls	A.A.	B.B.	Controls
Learning task	New 1	100	90	96 ± 3	920 ± 136	1409 ± 464	785 ± 84
	One-Back	100	95	98 ± 2	915 ± 143	1174 ± 481	683 ± 66
	Ten-Back	98	95	94 ± 7	945 ± 180	1293 ± 450	782 ± 84
Delayed recognition	New 2	94	76	94 ± 5	861 ± 108	1373 ± 515	620 ± 236
	One-Back	74	62	77 ± 13	847 ± 107	1233 ± 293	1206 ± 433
	Ten-Back	92	84	86 ± 11	800 ± 126	1096 ± 528	836 ± 146

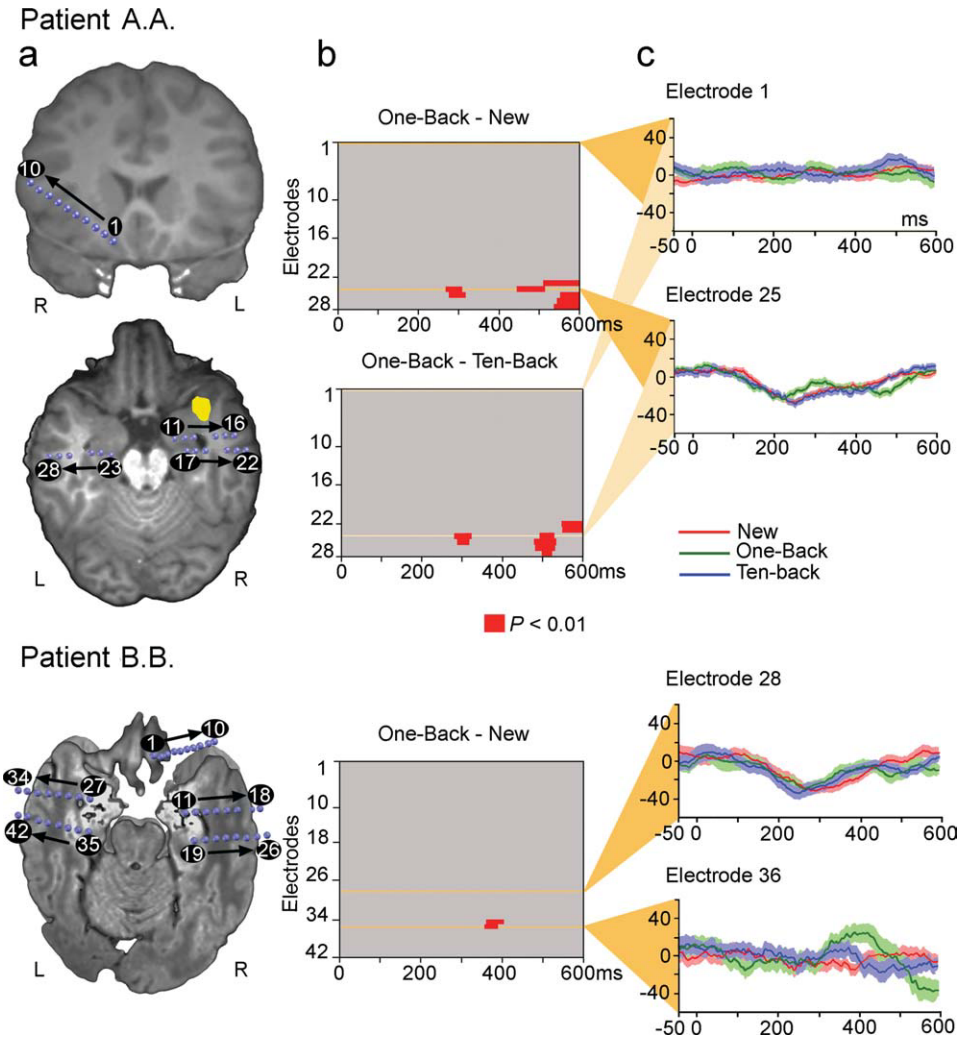

FIGURE 2. Results (a) Brain MRI slices of patient A.A. and patient B.B., showing the location of the electrodes. (b) Results of unpaired *t*-tests comparing the amplitude of One-back and New items, and of One-Back and Ten-Back items, from onset to 600-ms poststimulus at each electrode. Periods of statistical differences are depicted in red ($P < 0.01$). (c) ERP curves to each conditions from −50 ms to +600 ms recorded at electrodes 1 and 25 for patient A.A. and at electrodes 28 and 36 for patient B.B. The areas around the curves represent the standard error of the mean. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

ered statistically significant if $P < 0.01$ for at least 20 ms. Mean and standard deviation of all epochs for each condition were calculated for display purposes.

Table 1 indicates that both patients had comparable performance to a control group of young healthy subjects. Immediate repetitions were recognized more rapidly than New and Ten-back items, and both patients presented the expected spacing effect: items repeated after nine intervening items during the learning task were better recognized in the delayed recognition task than items that had been immediately repeated. Of note, patient B.B. (mean ± SD: 1,263 ± 480 ms) responded much slower on average than patient A.A. (mean ± SD: 881 ± 152 ms).

Figure 2b shows the results of unpaired *t*-tests on amplitude over all electrode contacts and over the whole period for the comparison between One-back and New items and between One-back and Ten-back items for both patients. This analysis revealed statistical differences over electrode contacts located in the left MTL. Figure 2c shows that in comparison with both Ten-back and New items, One-back items evoked positivity between ∼250 and 310 ms and negativity between 450 and 600 ms over the two electrode contacts in the hippocampal area (Talairach coordinates: $x = -25$, $y = -16$, and $z = -14$; $x = -30$, $y = -18$, and $z = -14$) in patient A.A.. In patient B.B, One-back items evoked positivity between ∼350 and 450 ms in contrast to New items over the two electrode contacts in the hippocampal area (Talairach coordinates: $x = -24$, $y = -20$, $z = -11$; $x = -29$, $y = -20$, $z = -12$). If the time period of analysis was extended to 800-ms poststimulus, One-back items evoked a negativity between 650 and 750 ms in contrast to New items over these two electrodes. Differences between One-back and Ten-back items just missed our

statistical threshold of significance; differences were found between 350 and 450 ms and between 650 and 750 ms as well over the hippocampal electrodes at $P < 0.05$ but not at $P < 0.01$.

No significant differences were found for other electrode positions in both patients (Fig. 2c). No statistical difference was found for the comparison between New items and Ten-back items on any electrode position in both patients.

Using intracranial recordings, this study confirms our finding obtained with inverse solution techniques applied to high-resolution surface EEG (James et al., 2009): immediate repetition of meaningful pictures elicits a different electrical response than New items and items repeated after a delay specifically in the left MTL. No other electrode position yielded any significant potential difference. In patient A.A., this immediate repetition effect was present around 250–300 ms, a latency compatible with our previous study (James et al., 2009). In patient B.B., the effect was delayed, probably corresponding to the slower reaction times both in comparison with patient A.A. and the young healthy subjects participating in James et al.'s (2009) study.

New and Ten-back items did not significantly differ from each other in any recording site. Studies using surface EEG had shown late-amplitude differences over temporal or parietal scalp electrodes (Friedman, 1990; Schnider et al., 2002; Kayser et al., 2003). According to spatiotemporal analyses, however, these amplitude differences appeared in the context of similar electrocortical patterns and hence reflected amplitude modulation of similar cortical networks rather than different generators (Schnider et al., 2002; James et al., 2009). The present findings obtained with depth electrodes confirm the latter interpretation.

Together with the different effects of immediate and delayed repetition on late recognition after 30 min, the results support our previous conclusion that novel information rapidly initiates a consolidation process involving the left-hippocampal area, which remains vulnerable during active maintenance and increases its effectiveness during off-line processing.

This study validates our previous finding of left-MTL activity obtained with distributed source reconstruction techniques applied to scalp EEG for estimation of the source of electrocortical activity (James et al., 2009). In that study, we used inverse solutions based on weighted minimum norm (Grave de Peralta Menendez and Gonzalez Andino, 1998; Hämäläinen and Ilmoniemi, 1994). Previous studies demonstrated that inverse solution models like low-resolution electromagnetic tomography or local autoregressive average can accurately identify the generators of evoked potential responses on the cortical surface (Pascual-Marqui et al., 1994; Grave de Peralta Menendez et al., 2004). The present data indicate that source estimation based on high-resolution scalp EEG probably also correctly localizes the current source of electrical activity in midline structures like the MTL, supporting earlier simulation (Attal et al., 2007), experimental (James et al., 2008), and clinical studies (Zumsteg et al., 2005; Lantz et al., 2001).

Acknowledgements

The Cartool software was developed by Denis Brunet, with support of the Center for Biomedical Imaging (CIBM) of Geneva and Lausanne.

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