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Neural Transition From Short- to Long-Term Memory and the Medial Temporal Lobe: A Human Evoked-Potential Study

Clara James,¹ Stéphanie Morand,¹ Sandra Barcellona-Lehmann,¹
 Christoph M. Michel,² and Armin Schnider^{1*}

ABSTRACT: Recent studies indicated that the human medial temporal lobe (MTL) may not only be important for long-term memory consolidation but also for certain forms of short-term memory. In this study, we explored the interplay between short- and long-term memory using high-density event-related potentials. We found that pictures immediately repeated after an unfilled interval were better recognized than pictures repeated after intervening items. After 30 min, however, the immediately repeated pictures were significantly less well recognized than pictures repeated after intervening items. This processing advantage at immediate repetition but disadvantage for long-term storage had an electrophysiological correlate: spatiotemporal analysis showed that immediate repetition induced a strikingly different electrocortical response after 200–300 ms, with inverted polarity, than new stimuli and delayed repetitions. Inverse solutions indicated that this difference reflected transient activity in the MTL. The findings demonstrate behavioral and electrophysiological dissociation between recognition during active maintenance and recognition after intervening items. Processing of novel information seems to immediately initiate a consolidation process, which remains vulnerable during active maintenance and increases its effectiveness during off-line processing. © 2008 Wiley-Liss, Inc.

KEY WORDS: consolidation; evoked potentials; immediate recognition; long-term memory; medial temporal lobe; short-term memory

INTRODUCTION

Although the critical role of the human medial temporal lobe (MTL) for long-term memory is generally accepted, its role for short-term memory—the ability to temporarily retain information for processing (Fuster, 1995; Baddeley, 2003; Jonides et al., 2008)—is more controversial. In contradiction to earlier studies (Cave and Squire, 1992), recent studies found that amnesic subjects with proven or suspected MTL damage also displayed difficulty in short-term memory tasks involving the retention of spatial relations between items (Hannula et al., 2006; Olson

et al., 2006; Hartley et al., 2007). Imaging studies showed MTL activation in such a task (Hannula and Ranganath, 2008) and during active maintenance of faces (Ranganath and D'Esposito, 2001).

These studies suggested that MTL activation—which is undoubtedly essential for long-term-memory—may be beneficial for short-term memory, too, and be involved in the processing of information during active maintenance. But it is unclear whether these MTL contributions to memory would be independent from each other, additive, or competitive. In the present study, we explored the interplay between short- and long-term memory for simple visual stimuli. Subjects performed a continuous recognition task while brain activity was recorded using high-density evoked potentials, allowing spatiotemporal analysis with very high temporal—albeit limited spatial—resolution (Michel et al., 2004). We compared the behavioral effects and electrocortical correlates of immediate stimulus repetition as opposed to delayed stimulus repetition and tested the effect of these manipulations on delayed recognition after 30 min.

MATERIALS AND METHODS

Participants

Fifteen healthy, paid subjects (5 men, 10 women; 28.3 ± 4.3 years) gave written informed consent to participate in the study, which was approved by the Ethical committee of the University Hospital of Geneva.

Learning Task

Subjects performed a continuous recognition task composed of 120 concrete black on white line drawings (Snodgrass and Vanderwart, 1980), all of which were repeated once, either immediately following a two-seconds stimulation-free interval after the initial presentation (one-back items, $N = 60$) or after nine intervening items (ten-back items, $N = 60$). Stimuli were presented on a 17 in. monitor for 1000 ms, at the size of 8° of visual angle, with an interstimulus interval of 2000 ms filled with a fixation cross. Subjects had to indicate new pictures by pressing one button, picture recurrences by pressing another button with the right hand.

¹ Division of Neurorehabilitation, Department of Clinical Neurosciences, University Hospital and University of Geneva, Geneva, Switzerland;

² Functional Brain Mapping Laboratory, Department of Basic Neurosciences, University of Geneva, Geneva, Switzerland

C.J. and S. M contributed equally to this work.

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*Correspondence to: Armin Schnider, Service de neurorééducation, Hôpitaux Universitaires de Genève, 26, av. de Beau-Séjour, CH-1211 Geneva 14/Switzerland. E-mail: armin.schnider@hcuge.ch

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Delayed Recognition Task

Thirty minutes after termination of the learning task, participants performed a delayed recognition task containing all pictures from the learning task and 120 new pictures in random order. Presentation parameters were similar to the learning task. Subjects had to indicate pictures they recognized from the learning task by pressing one button, new pictures by pressing another button with the right hand.

Control Task

As will be shown below (Results section), the behavioral analysis of the delayed recognition task raised the question as to whether immediate picture repetition during learning was beneficial or detrimental for delayed recognition in comparison to single picture presentation (no repetition). We therefore conducted a control experiment with a separate group of 14 healthy subjects of similar age as the main subject group. The control learning task had a similar design as the main learning task except that 60 additional pictures were included which were not repeated during the run. The control delayed recognition task, performed 30 min after the control learning task, had a similar design as the main delayed recognition task, except that it contained more stimuli: 60 pictures that had been presented only once during the control learning task (single presentation items), 60 that had been immediately repeated (one-back items), 60 that had been repeated after nine intervening items (ten-back) and 90 new items. Subjects had to indicate pictures they recognized from the learning task by pressing one button, new pictures by pressing another button with the right hand.

EEG Acquisition

EEG was continuously recorded during the learning task with an Active-Two Biosemi EEG system (BioSemi Active-Two, V.O.F., Amsterdam, The Netherlands) with 128 scalp electrodes. Signals were sampled at 512 Hz and filtered at a bandwidth of 0–134 Hz. Epochs from 50 ms prestimulus to 800 ms poststimulus onset were averaged along each stimulus type and for each subject to calculate the event-related potential (ERP). Only correct trials were retained. In addition to an automated artifact criterion of $\pm 100 \mu\text{V}$, data were visually inspected to reject epochs with blinks, eye movements and other sources of transient noise. Baseline was defined as the 50 ms period prior to stimulus onset. ERPs were then bandpass-filtered to 1–30 Hz and recalculated against the average reference before group averaging. The filtering was carried out with second order Butterworth Low and High pass with -12 dB/octave roll-off filters. After filtering, a baseline correction was computed, using a 50 ms period prior to stimulus onset. Finally ERP data were group-averaged.

ERP Waveform Analysis

At six commonly reported electrodes (Fz, Cz, Pz, Oz, T7, T8), amplitude differences between stimulus types were tested

using point-wise paired t -tests over 800 ms following stimulus onset. Because these amplitude measurements are not independent in time and space, a Bonferroni correction for multiple comparisons would be inadequate (Guthrie and Buchwald, 1991; Murray et al., 2008). To reduce the risk of false-positive effects, we only considered effects as significant ($P < 0.05$, uncorrected) if they persisted over at least 40 ms (20 time points) as proposed by previous authors (Rossell et al., 2003).

Spatio-Temporal ERP Analysis

Amplitude variations of ERP traces may reflect activation of different networks (with different electrocortical fields) or modulation of similar networks (Michel et al., 2004). To make this distinction, we applied spatiotemporal segmentation to the ERPs recorded over the 128 electrodes in search for segments of stable electric field configurations (Maps), as previously described (Pascual-Marqui et al., 1995; Michel et al., 2001; Michel et al., 2004). In brief, segments were determined using a spatial k means cluster analysis in the group-averaged ERPs for each stimulus over 800 ms. The optimal number of cluster maps was determined by cross validation. The cluster maps identified in this grand mean were then fitted in the individual ERPs to determine how well the maps explained individual patterns of activity (global explained variance, GEV) and their duration (Michel et al., 2004; Michel et al., 2001). Individual values were subjected to repeated-measure ANOVAs with map and stimulus type as factors. Based on an initial inspection of spatio-temporal analysis (see below, Results), two time windows of analysis were chosen: 180–310 and 310–650 ms. The limitation of the analysis to these time windows allows verifying whether maps appearing in the grand mean (which show only the dominant map in any given period) are statistically more strongly present in the respective time window, independently of their potential presence outside this time window.

Source Estimation

Neural generators for each condition were estimated by applying a distributed linear inverse solution based on weighted minimum norm (WMN) model (Grave de Peralta Menendez and Gonzalez Andino, 1998; Hämäläinen and Ilmoniemi, 1994), using a 3D realistic head model with a solution space of 3005 nodes (Spinelli et al., 2000). Current density distribution was referred to the grey matter of the brain template of the Montreal Neurological Institute (MNI). Source estimation was limited to the time period in which spatiotemporal analysis of scalp ERP demonstrated significantly different map topographies between stimulus types (as results below will show, this period was 180–310 ms). Within this period of interest, the WMN inverse solution was averaged across time for each subject and condition (15 subjects \times 3 conditions). We then used statistical parametric mapping (SPM) to compute paired t -tests for the three contrasts between the three stimulus types for

TABLE 1.

Behavioral Results

New	Accuracy (% correct)			New	RT (ms)		
	Single	One-back	Ten-back		Single	One-back	Ten-back
(a) Learning task							
96.3 ± 3	N/A	98.3 ± 2	93.5 ± 7	785 ± 84	N/A	683 ± 66	782 ± 84
(b) 30-min Recognition							
94 ± 4.5	N/A	77 ± 13	86 ± 11	620 ± 236	N/A	1206 ± 433	836 ± 146
(c) Control learning task							
96 ± 2.5	94 ± 4	97 ± 3	95 ± 4	740 ± 81	752 ± 90	661 ± 56	734 ± 71
(d) Control task, 30-minute recognition							
94 ± 4	53 ± 18	66 ± 17	85 ± 12	766 ± 111	803 ± 128	800 ± 163	742 ± 102

each node of the solution space using across-subjects variance, with activation considered if $P < 0.05$, Bonferroni corrected by the number of electrodes [In distributed EEG/MEG inverse solutions, the number of independent measures corresponds to the number of recording sensors on the scalp rather than the number of solution points (Grave de Peralta Menendez et al., 2004; Michel et al., 2004; Murray et al., 2008)].

The area displaying significantly different current density in this analysis (left medial temporal area) was then selected for a region-of-interest analysis to verify the time course of current density differences between the three stimulus types. To this end, the solution space was spatially smoothed by averaging the 3005 solution points within 50 regions of interest (ROI), defined according to the MRIcro macroscopic anatomical parcellation of the MNI template (Rorden and Brett, 2000; Tzourio-Mazoyer et al., 2002). Using SPM again, uncorrected paired t -tests between experimental groups were then computed for the 50 ROIs. Because of multiple statistical testing (50 ROIs), only periods for which this topographic test exceeded a 0.005 alpha criterion for at least 40 consecutive ms (supplementary time constraint) were considered significantly different.

RESULTS

Learning Task, Behavioral Results

Subjects performed well, with differences between the types of items (Table 1a). Immediate repetitions (one-back items) were recognized more rapidly than new items ($F_{1,14} = 81$, $P < 0.0001$) and both more accurately ($F_{1,14} = 8$, $P = 0.013$) and more rapidly ($F_{1,14} = 57$, $P < 0.0001$) than ten-back items.

Delayed Recognition Task

In the delayed recognition task 30 min after the learning task, subjects recognized new items very accurately and rapidly (Table 1b). Recognition of one-back and two-back items differed significantly, but in the opposite sense to the learning run

(Table 1b): now, ten-back items were recognized significantly more accurately ($F_{1,14} = 18.6$; $P = 0.001$) and faster ($F_{1,14} = 12.4$; $P = 0.003$) than one-back items. That is, items repeated after nine intervening items during the learning run were better recognized than items that had been immediately repeated.

Control Task

The control task was conducted because the result of the delayed recognition task left open the possibility that immediate item repetition was even detrimental to long-term consolidation. Similar to the first learning task with a different group of subjects, one-back items were recognized more rapidly than ten-back items ($F_{1,13} = 50$; $P < 0.0001$) during the control learning task; accuracy did not differ (Table 1c). The main question was to know in what way recognition of one-back items would differ after 30 min from items presented only once during the learning run. As in the main delayed recognition task (see above, Table 1b), one-back items were recognized less accurately ($F_{1,13} = 58$, $P < 0.0001$) and less rapidly ($F_{1,13} = 7.9$, $P = 0.02$) than ten-back items. The main finding, however, was that one-back items were recognized equally rapidly and more accurately ($F_{1,13} = 22$, $P < 0.0001$) than Single presentation items (Table 1d). Thus, immediate repetition of pictures during learning prevented consolidation from being as solid as repetition after nine intervening items but had no retroactive detrimental effect on initial consolidation.

ERP Waveform Analysis

Figure 1 displays the event related potentials at six classically reported electrode positions (Fz, Cz, Pz, Oz, T7, T8), recorded during the main learning task. In contrast to new and ten-back items, one-back items evoked a strong positivity at frontal electrode Fz between 200 and 300 ms, and at central electrode Cz and posterior electrode Pz between 300 and 500 μ s. At temporal leads T7 (left) and T8 (right), polarity was inverted and one-back items selectively induced negative potentials between 300 and 450 ms. At occipital electrode Oz, a short negative

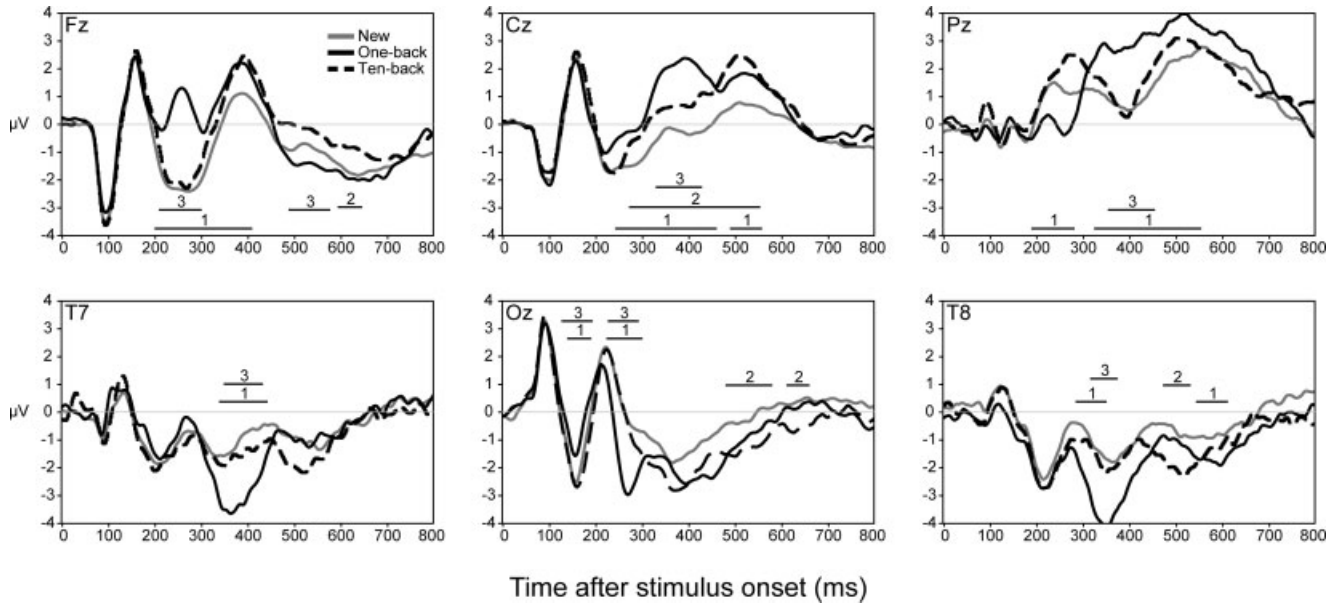


FIGURE 1. Waveform analysis at electrodes Fz, Cz, Pz, Oz, T7 and T8 in response to the three stimulus types (against average reference). Periods displaying significant amplitude differences between two stimulus types over at least 40 μ s are indicated with bars, where the numbers indicate the following comparisons: 1, new vs. one-back; 2, new vs. ten-back; 3, one-back vs. ten-back.

peak between 200 and 300 ms clearly dissociated responses to one-back items from those to the other items.

Spatio-Temporal Analysis

Spatio-temporal segmentation identified eight distinct scalp potential map configurations over 800 ms (Fig. 2a). Figures 2b-d shows the sequence and relative strength of the maps in response to the three item types. Six out of the eight maps appeared in the same order in response to all three item types. The main difference appeared between 200 and 300 ms, when one-back items proceeded through a configuration (Map 5) with opposite polarity than new and ten-back items (Map 4).

Maps appearing in this grand mean were then fitted in the individual ERPs and statistically tested for differences in GEV, a measure of how well a map configuration explains the individual data. Repeated-measures analysis of variance (ANOVA) revealed significant interaction between maps (Maps 3, 4, and 5) and conditions (three item types) in the 180–310 ms period ($F_{4,56} = 11.7$, $P < 0.00001$). Map 4 showed stronger GEV for new stimuli ($F_{1,14} = 27.2$, $P < 0.0001$) and for ten-back items ($F_{1,14} = 20$, $P = 0.001$) than for one-back items. In contrast, GEV of Map 5 was stronger in response to one-back items than new ($F_{1,14} = 16.6$, $P = 0.001$) and ten-back items ($F_{1,14} = 10$, $P = 0.006$). New and ten-back items induced no significantly different maps. Thus, from 200 to 300 ms, Map 4 was more representative of the processing of new and ten-back items, whereas Map 5 was more specific for one-back items, that is, the processing of immediate repetition.

Maps appearing in the 310–650 ms period (Maps 6 and 7) had no significant interaction, indicating that these maps did

not explain one condition better than the others. However, Map 6 showed stronger GEV for one-back ($F_{1,14} = 5.1$, $P = 0.04$) and ten-back items ($F_{1,14} = 5.9$, $P = 0.03$) than new items indicating that Map 6 was stronger in response to repeated than new items.

Source Estimation

Source analysis was performed for the period 180–310 ms, when one-back items induced a strikingly different scalp potential configuration than new and ten-back items (Fig. 2). Statistical parametric mapping of individual values of current density over all nodes, averaged over the period and separated by stimulus type, indicated that one-back items differed from new items (Figs. 3a,b), less so also from ten-back items (Figs. 3c,d), in that they were associated with significantly stronger activity ($P < 0.05$; corrected for the number of electrodes) in the left medial temporal area with extension into the anterior insula. By contrast, there was no significant difference of current density between new and ten-back items in this period of processing, agreeing with the observation that map configuration did not differ between these two item types (Fig. 2).

To verify the temporal specificity of this finding, the current density values over the nodes of the solution space situated in the left anterior medial temporal lobe—the area showing strongest difference of current density—were then analyzed over the 600 ms following stimulus presentation (Fig. 3e). This region-of-interest analysis yielded significant differences only in the period between 200 and 300 ms with higher current density in response to one-back items than both new and ten-back items. There was no significant difference in current density for

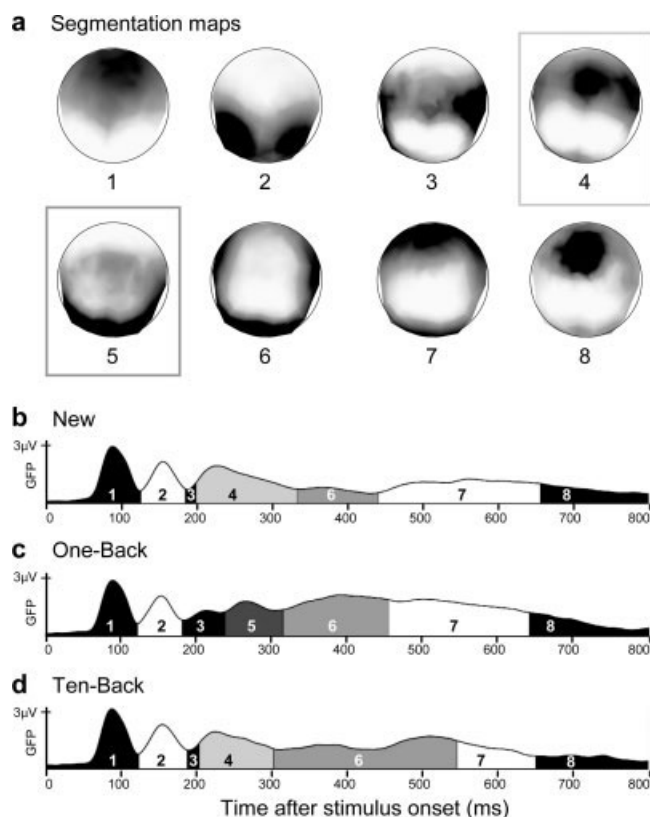


FIGURE 2. Spatio-temporal analysis. (a) Maps recognized in the ERPs by the segmentation procedure over all subjects and stimulus conditions occurring the first 800 ms following stimulus presentation. Black indicates negative voltage, white indicates positive voltage. Maps 4 and 5 appeared in the same period. (b-d) Sequence in which the maps appeared in response to new items (b), one-back items (c), and ten-back items (d). Statistical analysis confirmed that Map 4 better explained the response to new and ten-back items, whereas Map 5 occurred specifically in response to one-back items. Map 6 was stronger, but not specific, in response to repeated than new items. GFP, global field power.

this region-of-interest, not even transient, between new and ten-back items.

DISCUSSION

The study has three main results. A first, somewhat obvious, result is that pictures immediately repeated after a short, unfilled interval were better and faster recognized than pictures repeated after nine intervening pictures. A similar processing advantage for immediately repeated items has also been described in a continuous word recognition task (Kim et al., 2001) and priming tasks demanding specific decisions about pictures or words (Bentin and Moscovitch, 1988; Henson et al., 2004). Earlier studies showed that recognition during learning is similar for items repeated after only one item up to 32 intervening items (Friedman, 1990a,b; Kayser et al., 2003). Thus, behavioral data show that actively maintained information holds a special status in memory processing, which imme-

diately changes upon presentation of only one interfering stimulus.

The second result, much less trivial, is that stimuli that had been presented twice in immediate succession were less well recognized after 30 min than pictures that had also been seen twice during learning, but with intervening stimuli. The result is consistent with the common experience—studied more than

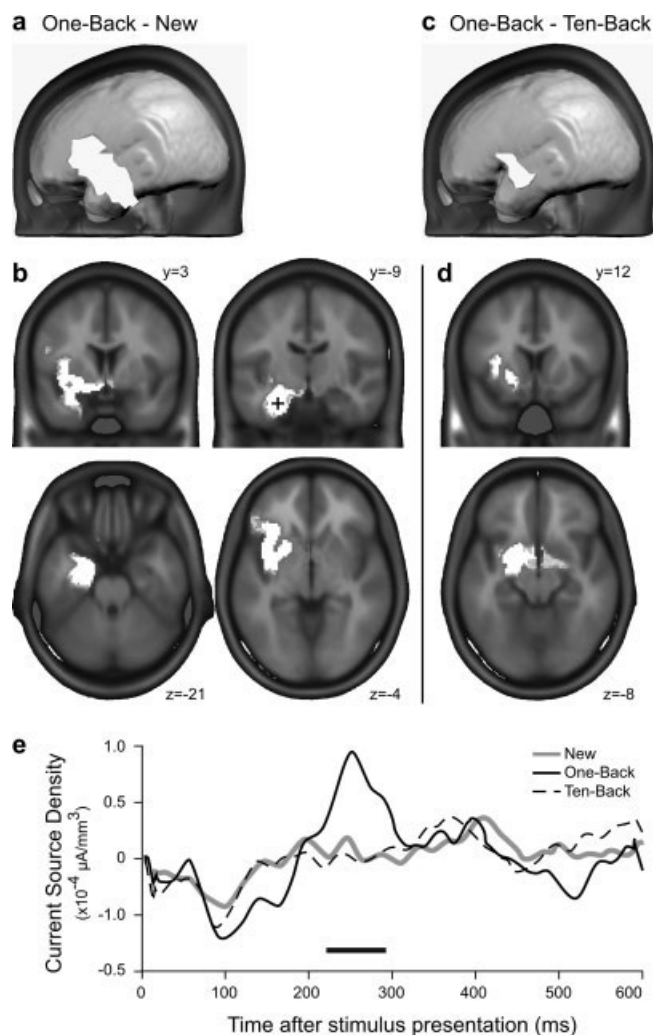


FIGURE 3. Differences in brain activation. (a-d) Statistical *t*-maps of Inverse solutions based on Weighted Minimal Norm (WMN) model are superimposed on slices of magnetic resonance imaging (MRI) brain templates for the time period of 230–310 ms. (a) Lateral projection of areas having different current density in the comparison of one-back—new items. (b) Coronal and axial brain cuts localizing these activity differences to the left medial temporal lobe and insula. (c) Lateral projection of areas having different current density in the comparison of one-back—ten-back items. (d) Coronal and axial brain cuts localizing these activity differences to similar, but less extended areas as in the comparison between one-back and new items. (e) Region-of-interest analysis of current density in the left medial temporal lobe. The region-of-interest is indicated by a cross in (b). The grey bar in the lower part indicates the only period of significant difference characterized by higher current density in response to one-back than both new and ten-back items.

a century ago (Ebbinghaus, 1885/1992)—that learning efficiency improves with delayed repetition, and is known as the spacing effect (Crowder, 1976; Greene, 1989). Thus, immediate repetition, while a stimulus is still actively held in memory, has the advantage of more rapid and accurate recognition, which comes at the price of less efficient long-term consolidation. This dissociation and the similarity of presentation of immediate and delayed repetition make an interpretation in terms of differently intense perceptual processing, as it is relevant to perceptual learning (priming) (Snodgrass and Feenan, 1990), unlikely. Our control experiment showed that immediately repeated items were still somewhat better recognized after 30 min than stimuli presented only once. Thus, immediate repetition seems to interrupt or slow down, but does not annihilate, an ongoing consolidation process.

The third result is that these effects had an electrophysiological correlate: Pictures presented after intervening stimuli induced essentially the same electrocortical response as new pictures, with differences limited to amplitude modulations between 400 and 600 ms. This finding is consistent with earlier studies using waveform analysis (Friedman, 1990a,b; Beisteiner et al., 1996; Schnider et al., 2002; Kayser et al., 2003) and whole-brain spatiotemporal analysis: the latter technique, also applied in the present study, indicated that these amplitude variations reflected modulation of similar networks (similar electrocortical map configurations) (Schnider et al., 2002). The finding also gives electrophysiological meaning to psychological interpretations of the spacing effect, namely, that delayed repetition, which induces very similar electrocortical activation as initial presentation, would create two memory traces differing with regards to contextual information (Greene, 1989), whereas immediate repetition would leave only one memory trace.

However, the most striking finding of this study was that immediate repetition induced a very different electrocortical response, with inverse polarity, than the other stimulus types (new and ten-back items) between 200 and 300 ms. Such early responses have previously been described in a perceptual priming task, as subjects started to recognize fragmented pictures (Doniger et al., 2001). Our task, however, did not involve demanding visual analysis, as the line drawings were unequivocal. In addition, there was amplitude modulation (with similar map configuration), more intense even than in response to delayed repetition items, between 400 and 600 ms, as previously described in a word recognition and a picture priming task (Kim et al., 2001; Henson et al., 2004). Thus, immediate repetition of information, while it is still actively held in memory, induces a strikingly different electrocortical response, reflecting a distinct processing stage, based on activity of different structures, than new stimuli or stimuli repeated after intervening items.

Source estimation indicated that this particular processing stage characterizing immediate repetition reflected transiently increased medial temporal activity in comparison to the other stimuli. The reliability of this finding is underscored by previous studies using simultaneous recordings of intracranial and scalp EEG in epileptic patients, which showed that medial-temporal activity can be reliably retrieved from scalp EEG by means of statistical distributed source reconstruction techniques

similar to the ones used in the present study (Lantz et al., 1997; Zumsteg et al., 2005).

There are different possible interpretations of the functional significance of this activity. One possibility would be that MTL activity was important for immediate recognition. This idea would be compatible with a recent study using intracranial recordings, which demonstrated coherent activation of the hippocampus with the prefrontal and lateral occipital cortex as subjects increasingly better recognized fragmented pictures in a perceptual learning (priming) task (Sehatpour et al., 2008). However, the task used in the present study was explicit and did not demand perceptual learning. Also, the line drawings used in the present study were unequivocal. Therefore, a perceptual learning effect seems to be an unlikely explanation for this MTL activity.

The idea of a role of the MTL for immediate recognition would also be compatible with recent studies claiming a role of the MTL in short-term memory (Hannula et al., 2006; Olson et al., 2006; Hartley et al., 2007; Hannula and Ranganath, 2008). However, these studies examined complex spatial processes during maintenance of information (Hannula et al., 2006; Hartley et al., 2007; Hannula and Ranganath, 2008), unlike simple picture recognition as in our study, or they tested patients with amnesia following anoxia (Hannula et al., 2006; Olson et al., 2006), where damage and dysfunction is rarely limited to the MTL (Lim et al., 2004; Schnider, 2008). Patients with circumscribed, even severe damage to the MTL do not normally fail in short-term memory tasks as simple as the immediate picture repetitions used in this study (Milner et al., 1968; Cave and Squire, 1992; Schnider et al., 1994; Stefanacci et al., 2000). But the debate is still ongoing.

Another possibility, which would explain both the immediate advantage and the long-term disadvantage of immediate repetition, is that the transient MTL activity reflects facilitated activation during an ongoing consolidation process. The higher accuracy and shorter reaction times in immediate recognition, as well as the less reliable late recognition of these items (but still better recognition than once-only presented items) are compatible with this interpretation. No matter what the precise role of the MTL in this task may be, our data clearly show that this activation, however beneficial it was for immediate recognition, weakened long-term consolidation; immediate repetition, even when associated with explicit recognition of the stimulus, does not induce as efficient consolidation as delayed repetition. This conclusion also means that the presentation of a new stimulus immediately initiates a consolidation process, whose neural basis involves the MTL.

Rapid, initial consolidation beyond an interfering stimulus may also be important for detailed information retrieval from memory and complex mental manipulations. Indeed, various medial temporal structures have been shown to be active even during speech comprehension and production (Awad et al., 2007). It is plausible that this capacity is crucial for producing a coherent, rich account of earlier experiences (Gilboa et al., 2004; Moscovitch et al., 2005), mentally retrieving and describing one's way around a city (Maguire et al., 2006), and for

constructing a coherent plan for the future (Addis et al., 2007; Hassabis et al., 2007). The rapid consolidation process indicated by the present study may help to explain the continued dependence of rich accounts of old memories and of ideas for the future on the medial temporal memory system.

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