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ORIGINAL PAPER

Abnormal Cortical Network Activation in Human Amnesia: A High-resolution Evoked Potential Study

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Abstract Little is known about how human amnesia affects the activation of cortical networks during memory processing. In this study, we recorded high-density evoked potentials in 12 healthy control subjects and 11 amnesic patients with various types of brain damage affecting the medial temporal lobes, diencephalic structures, or both. Subjects performed a continuous recognition task composed of meaningful designs. Using whole-scalp spatiotemporal mapping techniques, we found that, during the first 200 ms following picture presentation, map configuration of amnesics and controls were indistinguishable. Beyond this period, processing significantly differed. Between 200 and 350 ms, amnesic patients expressed different topographical maps than controls in response to new and repeated pictures. From 350 to 550 ms, healthy subjects showed modulation of the same maps in response to new and repeated items. In amnesics, by contrast, presentation of repeated items induced different maps, indicating distinct cortical processing of new and old information. The study indicates that cortical mechanisms underlying memory formation and re-activation in amnesia fundamentally differ from normal memory processing.

Keywords Amnesia · Recognition memory · Encoding · Brain damage · Evoked potentials · Brain mapping · EEG · Spatiotemporal analysis

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Introduction

Evoked potential recordings have the temporal resolution to study the rapid activation of cortical networks during memory processing in humans. So far, most studies analyzed electrical voltage changes over select electrodes. In healthy subjects, two main components differentiating the processing of novel from familiar information were identified (Friedman and Johnson 2000; Tsivilis et al. 2001; Curran and Cleary 2003; Duarte et al. 2004; Woodruff et al. 2006): (1) an early component, often prevalent over left frontal electrodes from 300 to 500 ms (also termed the N4 (Halgren and Smith 1987; Domalski et al. 1991)), which is associated with stimulus familiarity; (2) a second component, starting at 420–490 ms, maximally over left parietal-occipital electrodes (also termed the P3 (Halgren and Smith 1987; Domalski et al. 1991) or late old/new effect), which is associated with episodic retrieval.

ERP studies with patients having non-degenerative amnesia are very rare (Smith and Halgren 1989; Lalouschek et al. 1997; Mecklinger et al. 1998; Olichney et al. 2000; Duzel et al. 2001). The studies were heterogeneous with regards to study design (single case, group study), etiologies, and test paradigms, so that results are difficult to compare between the studies. Nonetheless, a common finding emerged: independently of the etiology of amnesia,

there was absence or significant reduction of repetition effects between 300 and 600 ms or even beyond, which consistently reflected decreases of the late old/new effect (or P3), sometimes also lesser modulation of the N4 (which was not always mentioned in the studies).

A difficulty with interpreting such findings is that alterations over single electrodes, as determined in these traditional ERP studies, may reflect decreased modulation of similar cortical networks or activation of different networks. High-resolution electroencephalography and spatiotemporal analysis allow studying the activation of cortical networks (Michel et al. 2004). Using these methods, we found that normal memory processing during a continuous recognition task with meaningful pictures is characterized by the activation of a series of distinct cortical map configurations over time and that normal encoding and recognition are associated with modulation of similar cortical networks (Schnider et al. 2002; Lehmann et al. 2007). By contrast, a patient with post-anoxic amnesia performing the same task had a strikingly different activation pattern, which was characterized by monotonous cortical activity, with little modulation, starting 150 ms after stimulus onset: brain activation remained restricted to visual areas and failed to spread to anterior regions, contrasting with the rapidly distributed pattern expressed by the control group (Lehmann et al. 2007).

The present study was conducted to examine temporal and spatial characteristics of cortical network activation in amnesia and to see whether this principle—failure to rapidly activate distributed networks—generally applies to amnesia resulting from medial temporal or diencephalic damage. Subjects performed a continuous recognition task with meaningful pictures. The task is known to activate the medial temporal lobes in healthy subjects (Schnider et al. 2000); failure in the task is most consistently associated with medial temporal lesions (Schnider et al. 1996b; Schnider and Ptak 1999; Schnider 2008).

Methods

Participants

Eleven right-handed men presenting a severe amnesic syndrome were compared to a group of 12 right-handed control subjects (9 women, 3 men; similar group as in Lehmann et al. 2007), matched for age, with no history of neurological or psychiatric illness. All participants gave written informed consent. The study was approved by the Ethical committee of the University Hospitals of Geneva and Lausanne.

Control subjects underwent neuropsychological evaluation in order to exclude cognitive dysfunction (Table 1).

Amnesic patients had various non-degenerative etiologies of amnesia: three patients had hypoxia in the context of cardiac arrest; in these patients, neuroradiologic examination revealed no circumscribed brain lesion, but the association of this amnesia with damage of the hippocampus is well known (Zola-Morgan et al. 1986). Two patients had amnesia after rupture of an anterior communicating artery aneurysm; one of them had right perirhinal, posterior orbitofrontal and basal forebrain damage, the other had damage of the posterior orbitofrontal cortex and basal forebrain, the right anterior cingulum and the right hippocampus (due to spasms). Two patients had amnesia after traumatic brain injury, one with damage centered on the left medial temporal lobe and insula, the other with contusions involving the splenium and the left retrospenial cortex. The other patients had alcoholic Korsakoff syndrome ($n = 1$), left paramedian thalamic ($N = 2$) or combined left thalamic and medial temporal stroke ($n = 1$). Eight patients were hospitalized for neurorehabilitation at the time of testing, three were out-patients. All patients were beyond the confusional state: they had normal sleep-wake cycle, good sustained attention, and normal digit span. The hospitalized patients participated in the neurorehabilitation program. Neuropsychological results are summarized in Table 1. All patients had severe anterograde amnesia, which was evident in severely deficient delayed free recall (Squire and Shimamura 1986) in the California Learning Verbal Task (Delis et al. 1987). The best amnesic subject had a delayed recall performance of six words; recognition was variably affected (Table 1). Eight patients were correctly oriented for time, place and current circumstances; three patients presented chronic disorientation. Several patients also had moderate executive failures (Table 1), as is often the case in amnesic subjects (Papagno et al. 2003; Lim et al. 2004; Carrera and Bogousslavsky 2006).

Memory Task

Subjects performed a continuous recognition task (Fig. 1), composed of 78 line drawings of objects (Snodgrass and Vanderwart 1980). Thirty stimuli reappeared twice (60 repeated stimuli), six items reappeared once (6 repeated stimuli; end of the test run) during the test, yielding a total of 144 presented stimuli, among which there were 66 repetitions. Repetitions occurred after 9–14 intervening items (mean $\pm$ SD $= 11.77 \pm 1.33$). Stimuli appeared on a computer screen for 2000 ms, with an interstimulus interval of 1700 ms. Subjects had to indicate for each item whether they had already seen it within the test run, or not. The healthy subjects responded by pressing a key for "yes", another for "no" with their right hand. Patients responded verbally and responses were typed in by the experimenter. This procedure was chosen to assure that patients' responses

Table 1 Demographic data and neuropsychological test results of patients and healthy controls

Group	Amnesics Mean ± SD (Range)	Controls Mean ± SD (Range)	*t*-test
Age	57 ± 7.3 (44–68)	51 ± 6.3 (45–64)	N.S.
Education			
Basic	$N = 1$	$N = 4$	
Upper secondary	$N = 8$	$N = 6$	
Graduate	$N = 2$	$N = 2$	
CVLT[a] (Delis et al. 1987)			
Delayed recall	1.6 ± 1.9 (0–6)	15 ± 1 (13–16)	$P < 0.01$
Correct recognition	11.4 ± 3.6 (5–16)	15.7 ± 0.6 (14–16)	$P < 0.01$
False positives	6.1 ± 4 (1–14)	0.3 ± 0.5 (0–1)	$P < 0.01$
Rey–Osterrieth complex Figure (Osterrieth 1944)			
Copy; max. 36	30.7 ± 5.4 (20–36)	33.7 ± 1.8 (31–36)	N.S
Delayed recall	8.2 ± 4.4 (0–14)	20.1 ± 4.7 (14–31)	$P < 0.01$
Verbal fluency[b]			
Letter: "P"	10 ± 6.6 (1–19)	26.7 ± 7.7 (16–39)	$P < 0.01$
Semantic: "animals"	17.1 ± 10.3 (4–36)	33.2 ± 6.9 (19–43)	$P < 0.01$
Non-verbal fluency (Regard et al. 1982)	16.2 ± 9.2 (2–30)	30.9 ± 7.8 (18–42)	$P < 0.01$
Trail making test (Reitan and Wolfson 1985)			
A (sec)	75.4 ± 37.5 (26–157)	32.7 ± 7.2 (25–50)	$P < 0.01$
B (sec)	228.9 ± 120.6 (56–480)	75.6 ± 32.1 (45–157)	$P < 0.01$
Stroop (Regard 1981)			
Sec	48.1 ± 33.8 (26–137)	24.1 ± 5.1 (18–33)	$P < 0.01$
Orientation (Von Cramon and Säring 1982)			
Cut-off = 15 (max. 20)	15 ± 2.5		
Span (Spreen and Strauss 1998)			
Verbal	5.1 ± 1		
Non-verbal	4.6 ± 0.9		

[a] *CVLT* California Verbal Learning Test (16 items);
[b] Score = correct productions minus repetitions

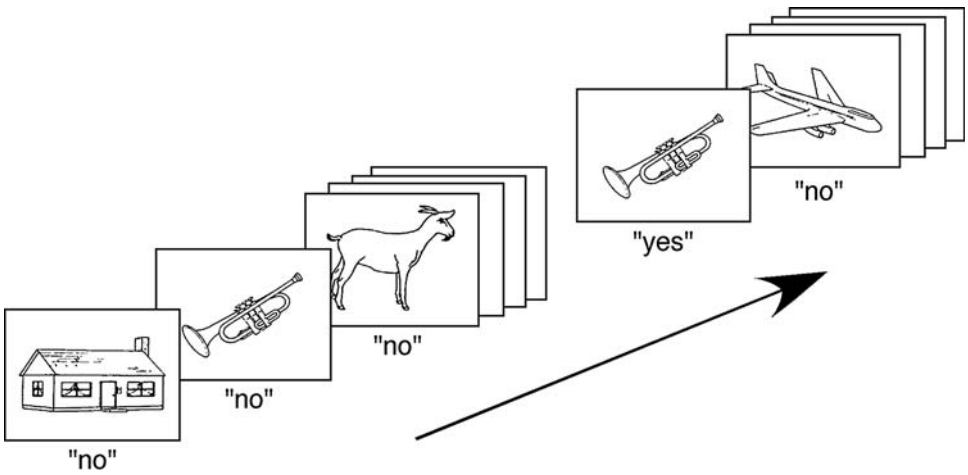

Fig. 1 Design of the task

truly reflected memory processing rather than their handling of a motor challenge. Also, the previous study by Lehmann et al. (2007) had shown that electrocortical differences between an amnesic patient and controls emerged at an early stage (>200 ms), long before motor preparation, although the patient had responded by button press.

ERP Analysis

The electroencephalogram (EEG) was recorded continuously using the Active—Two Biosemi EEG system (Biosemi V.O.F, Amsterdam, Netherlands) with 128 channels covering the entire scalp. Signals were sampled at 512 Hz in a bandwith filter of 0–134 Hz. As in our previous studies using a similar paradigm (Schnider et al. 2002; Murray et al. 2004; Lehmann et al. 2007), epochs of EEG starting at stimulus onset and ending 600 ms post-stimulus were extracted. The limitation to 600 ms was also decided because in our previous single-case study (Lehmann et al. 2007), the control group (identical with the present one) had mean reaction times around 720 ms, whereas the patient responded after 1200–1350 ms. This temporal dispersion of responses would preclude a comparison of the ERPs between controls and amnesics in terms of memory processing beyond 600 ms (presumed beginning of motor preparation in controls).

These epochs were visually scanned for eye-blinks and other artefacts higher than ±100 μV. Artifact-free epochs were averaged along each experimental condition. Before group averaging, individual data were recalculated against the average reference and bandpass filtered to 1–30 Hz. Only correct responses were analyzed (the number of false responses was too small to allow separate analysis).

Analyses were conducted using Cartool Software (http://brainmapping.unige.ch/Cartool.php), which contains the modules for ERP analysis, including waveform analysis and spatiotemporal analysis.

Waveform analysis was performed to allow comparison with earlier studies reporting traditional ERP analysis. Mean amplitudes were calculated across 3 time windows (0–200, 200–400 and 400–600 ms) at 10 electrode positions of the International 10–20 System (AF5, FT7, PO7, FPZ, Cz, Pz, Oz, AF6, FT8, PO8). ANOVA's were then performed to test for between-group (controls versus amnesic patients) and within-group differences (old/new effect).

For a more complete analysis of amplitude effects reflecting old/new distinction in the two groups, paired *t*-tests comparing ERP amplitudes in response to new and repeated items were computed for all electrode positions covering the whole period of interest (0–600 ms, with a test every 2 ms). This analysis concisely summarizes the entire data set without the observer-dependent assumption of picking electrode locations for statistical tests. Although there is, at present, no established statistical means to determine the spatial (i.e., over how many electrodes) or temporal (i.e., over how much time) extent over which a difference must be observed to be considered statistically robust, this analysis provides an estimate of the onset and offset of ERP effects and maintains the temporal resolution of the EEG methodology. In the present study, only differences extending over at least 10 time frames (20 ms) and 5 contiguous electrodes were retained, as described in an earlier study (Murray et al. 2004).

Spatiotemporal analysis was used to determine electrocortical configurations that represent encoding and recognition in normal and amnesic subjects. The controls' and amnesics' grand-mean ERPs for new and repeated items were segmented together, in order to determine time periods of stable electric field configurations (maps). Segmentation was performed using cluster analysis (Lehmann 1987; Michel et al. 2004). Appearance of maps in the individual data was then determined with a fitting procedure that allowed to establish how well these maps explained individual patterns of activity (GEV: global explained variance, a measure of how well a given map explains the data set; see computational details in Murray et al. (2008)) and their duration throughout different conditions. Fitting periods were defined on the basis of the results of the segmentation (Michel et al. 2004). Between-group effects were tested using repeated measures ANOVA, with group (control versus amnesic) as categorical factor, and item type (new versus repeated) and maps as dependant factors. Within-group repetition effects were tested using repeated measures ANOVAs, with item type (new versus repeated) and maps as dependant factors.

Spatial correlation between maps, a measure of the similarity of the spatial configuration of the voltage distribution over all electrodes, was calculated as described in detail by Brandeis et al. (1992) and summarized by Murray et al. (2008).

Pearson's correlations were performed between the GEV and duration of maps specific to amnesic patients (maps 6, 7, 9, 10) and scores of working and long-term memory task in order to explore whether the electrocortical configurations specific to patients were related to performance.

Results

Behavioural Results

Control participants detected 95.7 ± 5.6% of new items and 94.2 ± 5.0% of repeated items. Amnesic patients similarly well identified new items (90.2 ± 10.6%); false-positive responses were very rare. By contrast, they only recognized 72.4 ± 18.0% of item repetitions (comparison with controls, *t*-test: $t_{(21)} = -4.03$; $P < 0.01$).

After screening of the evoked potentials for artefacts, three patients were recorded again on a separate day to increase the number of analyzable responses. The analysis described below was thus based on the following number

of epochs: In controls, there were 68 ± 6 (range, 58–78) responses to new items and 57 ± 4.2 (range, 52–64) responses to repeated items. In patients, there were 73.4 ± 28.9 responses to new items (range, 37–127, the highest number recorded in two sessions) and 48.1 ± 25.7 in response to repeated items (range 18–118, the highest number from two recordings). The higher variance in the patients reflects the different degrees of amnesia.

ERP Results

Waveform Analysis

Figure 2 displays the results of the waveform analysis performed on 10 electrode positions during three time intervals. Repeated measures ANOVA conducted on mean amplitude of controls' and amnesics' grand average ERPs (including both new and repeated items) revealed between-group differences between 200 and 400 ms over FPz ($F_{(1,21)} = 4.94$; $P = 0.037$) and AF6 ($F_{(1,21)} = 5.49$; $P = 0.029$) (arrows in Fig. 2). There were no interactions of group (controls, amnesics) X stimulus type (new, repeated) over any electrode.

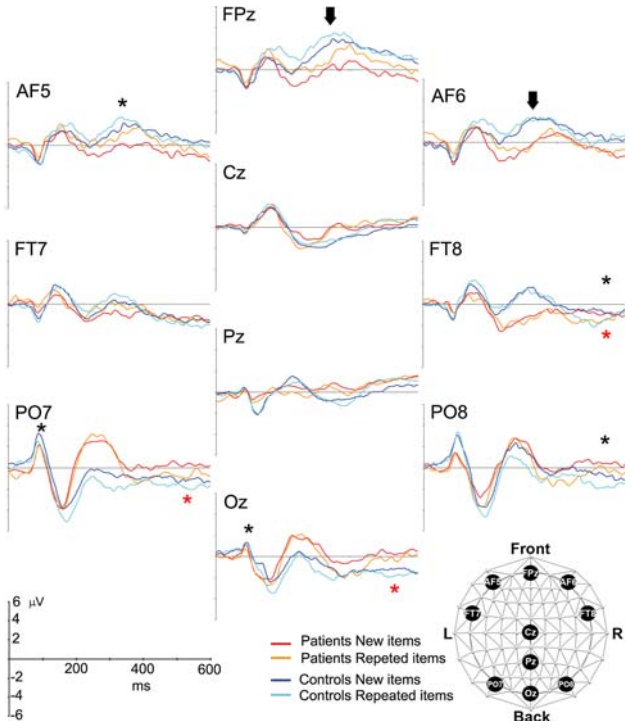

Fig. 2 Waveform analysis. Grand average ERPs evoked by old and new items for controls and amnesic patient groups at 10 electrode sites. Repeated-measures ANOVAs applied on the mean amplitudes were performed across 3 time windows: 0–200, 200–400 and 400–600 ms. Black arrows indicate between-group differences. Black asterisks (*) indicate periods of differences within the control group. Red asterisks indicate periods of differences within the patient group

When comparing the amplitudes between new and repeated items (old/new effects) within the groups and averaged in the three time windows 0–200 ms, 200–400 ms, and 400–600 ms, the following differences appeared: In the control group (black asterisks in Fig. 2), new and repeated items evoked higher amplitude responses (a stronger P100) over PO7 ($F_{(1,11)} = 9.71$; $P = 0.009$) and Oz ($F_{(1,11)} = 6{,}23$; $P = 0.029$) at 0–200 ms; over AF5 ($F_{(1,11)} = 5.69$; $P = 0.036$) at 200–400 ms; and over FT8 ($F_{(1,11)} = 9.01$; $P = 0.012$) and PO8 ($F_{(1,11)} = 14.25$; $P = 0.003$) at 400–600 ms.

Within the amnesic group (red asterisks in Fig. 2), differences between new and repeated items were found only at 400–600 ms over FT8 ($F_{(1,10)} = 9.19$; $P = 0.012$), PO7 ($F_{(1,10)} = 8.35$; $P = 0.016$), and Oz ($F_{(1,10)} = 9.6$; $P = 0.011$).

Figure 3 shows a more fine-grained within-group analysis (*t*-tests between new and repeated items), referring to all 128 electrodes and with a finer temporal grid (20 ms; see Methods). The analysis indicates spatially and temporally much more extended old/new effects than suggested by the analysis of the single traces selected for Fig. 2. In healthy subjects (Fig. 3b), amplitude differences occurred during four approximate time periods: (1) from 130 to 180 ms over occipital and left parietal electrodes; (2) from 190 to 250 ms over primarily right-sided fronto-temporal electrodes; (3) from 270 to 350 ms over bilateral parieto-occipital electrodes; and (4) from 470 to 560 ms over temporal, parietal and occipital electrodes predominantly on the right side.

In the amnesic group (Fig. 3c), responses differed between new and repeated pictures mainly during two time periods: (1) from 140 to 185 ms over right parieto-occipital electrodes; (2) from 365 to 460 ms over primarily left-sided parieto-occipital electrodes.

Thus, this summary analysis taking into account all 128 electrodes shows that, starting at 200 ms, amnesic patients expressed processing differences between new and repeated items in different time windows and over partly different groups of electrodes than healthy subjects.

Spatiotemporal Analysis

Segmentation applied to the grand-mean ERPs of the control and amnesic groups yielded 12 electrocortical map configurations over 600 ms after stimulus presentation (Fig 4a). Temporal succession of the maps is displayed in Fig. 4b.

Figure 4b shows that within the first 200 ms, both groups expressed maps 1, 2 and 3 in response to new and repeated ("old") items. Repeated measures ANOVA revealed a significant Repetition X Map interaction in terms of GEV ($F_{(2,42)} = 7.7$; $P = 0.001$), but no Group

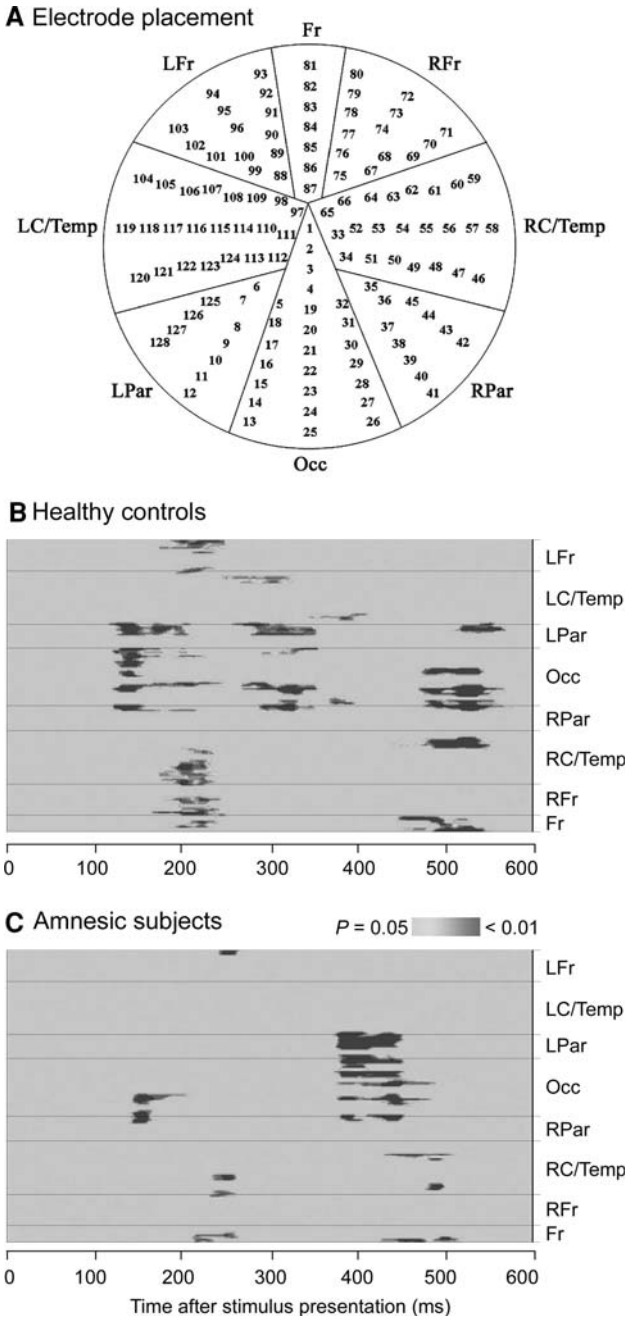

Fig. 3 Analysis of amplitude modulations. **a** Distribution of 128 electrodes according to the Biosemi system. *Fr* frontal, *RFr* right frontal, *RC/Temp* right central and temporal, *RPar* right parietal, *Occ* occipital, *LPar* left parietal, *LC/Temp* left central and temporal, *LFr* left frontal. **b** and **c** Paired *t*-tests comparing amplitudes of traces in response to new versus repeated items for all electrode positions over 600 ms (see Methods), for **b** controls subjects and **c** amnesic group

effect. Map 1 was more representative of new items ($t_{(22)} = 6.1$; $P = 0.021$), whereas map 3 was more representative of repeated items ($t_{(22)} = -9.7$; $P < 0.01$). (Attentive readers may observe a somewhat different sequence of maps in the control group in Lehmann et al. (2007), although this was the same control group. Indeed, spatiotemporal analysis as performed here searches for the maps that best explain the whole data set—controls and patients; new and repeated items. Thus, the maps retained as salient in the data of the controls is also influenced by the patients' data entering the analysis.)

From 200 ms on, processing significantly differed between control subjects and amnesic patients. Between 190 and 345 ms, the control group expressed two different maps (maps 4 and 5 in Fig. 4b) in comparison with the amnesic group (maps 6 and 7). Repeated measures ANOVA revealed a significant Map X Group interaction in terms of GEV ($F_{(3,63)} = 3.4$; $P = 0.02$) and map duration ($F_{(3,63)} = 3.8$; $P = 0.01$). Map 4 was more present in healthy than in amnesic subjects (GEV: $t_{(22)} = 3.3$; $P < 0.01$; map duration: $t_{(22)} = 2.9$; $P < 0.01$). Also map 5 was significantly more present in the healthy subjects (map duration: $t_{(22)} = 2.2$; $P = 0.03$). Inversely, maps 6 and 7 had higher GEV (map 6, $t_{(44)} = -2.2$, $P = 0.03$; map 7, $t_{(44)} = -2.0$; $P = 0.05$) and were more present (map duration: map 6, $t_{(44)} = -2.1$, $P = 0.04$; map 7, $t_{(44)} = -2.2$, $P = 0.03$) in the amnesic group than in the control group.

Maps which were specific to the amnesic group within the 190–345 ms time interval had a very similar configuration as visual P1 map, as evident in Figure 4a (comparison of maps 1, 6, and 7): indeed, map 6 spatially correlated at 65% and map 7 at 81% with map 1. In contrast, maps 4 and 5, which were specific to the control group, respectively correlated at 32% and −14% with map 1.

In the subsequent period (305–440 ms), healthy subjects expressed the same map (map 8) in response to new and repeated items. By contrast, amnesic patients not only had a different electrocortical configuration in response to new items (map 9, configuration in Fig. 4a), but they also expressed a different map in response to repeated items (map 10). In terms of GEV, there was a significant Repetition X Map X Group interaction ($F_{(2,42)} = 3.4$, $P = 0.04$), and a Repetition X Group interaction for map 10 ($F_{(1,21)} = 5.3$, $P = 0.03$). In the control group, there was no significant Repetition X Map interaction for map 8. In the amnesic group, a significant Repetition X Map interaction was found in terms of GEV ($F_{(1,10)} = 8.0$; $P = 0.02$) and map duration ($F_{(1,10)} = 6.6$; $P = 0.03$). Post-hoc comparisons determined that map 10 had higher GEV ($t_{(10)} = -2.8$; $P = 0.02$) and longer duration ($t_{(10)} = -2.6$; $P = 0.02$) when processing repeated items.

Apparent differences between groups in the period beyond 440 ms (map 11 in controls, map 12 in amnesic subjects) were non-significant. However, in the control group, an effect of repetition was observed on the duration of map 11, in favour of repeated item processing ($t_{(11)} = -2.6$; $P = 0.03$).

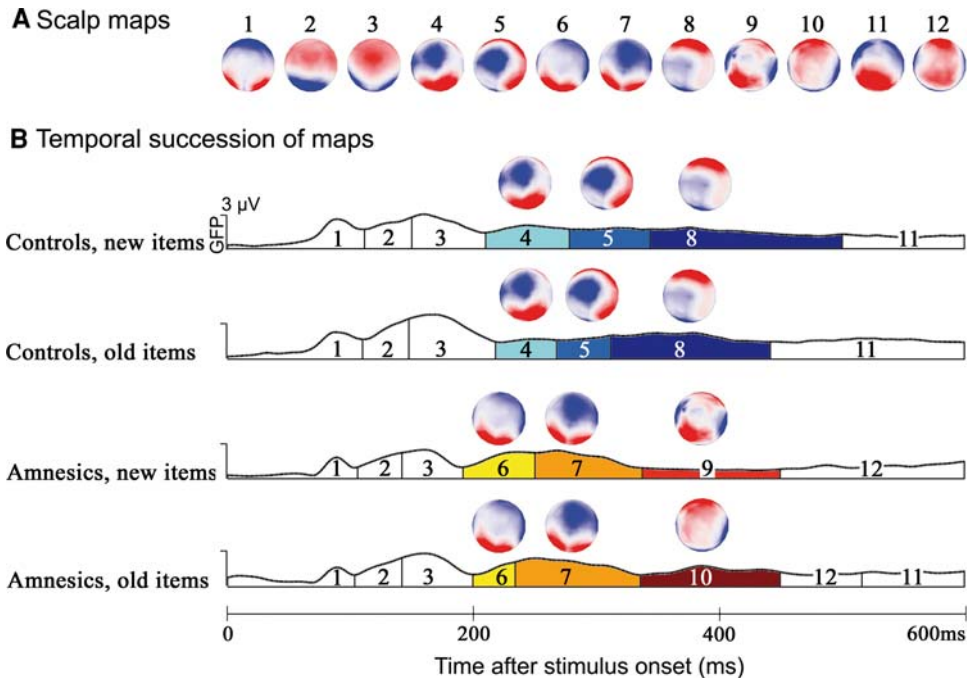

Fig. 4 Spatiotemporal analysis. **a** Electrocortical maps (scalp maps) identified by segmenting ERPs of control and amnesic groups in response to correctly recognized new and old (repeated) items. Red indicates positive, blue indicates negative voltage. **b** Temporal succession of the dominant maps in the control and amnesic groups, in response to new and old (repeated) items

Among the maps specific to the amnesics, the GEV of map 10 significantly correlated with verbal ($r = 0.78$, $P = 0.004$) and non-verbal span (r = 0.64, $P = 0.03$), but not with measures of long-term memory.

Discussion

The present study using spatiotemporal analysis of high-resolution evoked potentials provides significantly refined interpretation of cortical information processing in amnesia over studies using traditional trace analysis. Similar to earlier studies using trace analyses of ERPs in amnesia (Smith and Halgren 1989; Lalouschek et al. 1997; Mecklinger et al. 1998; Olichney et al. 2000; Duzel et al. 2001), we found attenuated amplitude modulations between new and repeated stimuli in amnesic patients. In our patient group, the analysis of 10 electrode sites yielded repetition effects during a unique time window, between 400 and 600 ms, whereas they occurred over three time intervals in the control group (Fig. 2).

A detailed comparison of our findings with previous studies is difficult for several reasons. First, only very few ERP studies have been performed with amnesic patients, probably due to the attentional requirements of such studies, which make recruitment of patients difficult. Second, every study used a separate paradigm and none used a similar paradigm as ours. Nonetheless, a general finding emerged from these studies: amnesic patients had attenuated or absent late repetition effects (late old/new effects, P3), an abnormality starting—depending on the paradigm used—at 300–500 ms. Although the traditional waveform analysis in this study (Fig. 2) is in agreement with these earlier findings, a more fine-grained analysis of amplitude modulations (Fig. 3) considerably refines them: we found that amnesic subjects did have amplitude modulations in the late time window (Fig. 3c), which, however, differed from healthy subjects in their temporal, partially also their spatial extension (Fig. 3b). This difference with earlier studies may be due not only to the different sensitivity of the analysis, but also to the use of different experimental paradigms.

We used a paradigm (a continuous recognition task with pictures), which is known to depend on the medial temporal lobes: lesions of subjects failing on this task had a strong overlap on the medial temporal lobes (Schnider et al. 1996a; Schnider and Ptak 1999; Schnider 2003); healthy subjects performing this task had strong activation of the medial temporal lobes (parahippocampal gyrus) bilaterally, as determined with H_2[15]O-PET (Schnider et al. 2000). In addition, the task used in the present study has the advantage of low strategic demands, so that even severely amnesic patients may perform above chance (Schnider et al. 1996b). In that sense, the task constitutes a "pure" measure of learning and recognition, independent of strategic efforts during encoding and retrieval (Squire and Shimamura 1986). The use of this paradigm in association with spatiotemporal analysis of the potential field over the whole scalp considerably extends the interpretation of waveform analyses, because it allows the exploration of the activity of whole networks (Michel et al. 2004).

We obtained three main findings, all temporally consistent with the waveform analysis (Figs. 2, 3). First, up to approximately 200 ms, there was no difference in electrocortical map configuration between controls and amnesic subjects and between new and repeated items (Fig. 4b). Thus, the amplitude differences observed in the waveform analysis (e.g., a stronger P100 in the controls) in this early period reflect intensity differences of similar networks, rather than the activity of different networks.

The second finding was that, starting at about 200 ms, distinct brain networks were involved in the amnesic patients' memory processing (Fig. 4a, b, maps 6 and 7) with respect to the control group (Fig. 4a, b, maps 4, 5, and 8). The observation is in agreement with our previous study on a single patient with post-anoxic amnesia, who also activated different maps than the controls in this period while performing the same task as in the present study. In his case, activation remained restricted to posterior cortical areas, an activation which contrasted with rapid distributed processing in the controls (Lehmann et al. 2007). The present study suggests that the failure to rapidly activate normal distributed networks may be a characteristic of learning in amnesia in general, irrespective of etiology. This view is compatible with the rare imaging studies using [18]FDG-PET (positron emission tomography) in amnesic subjects, which reported extended hypometabolism in multiple structures critical for memory (Fazio et al. 1992; Kuwert et al. 1993; Reed et al. 1999; Reed et al. 2003).

The third finding concerns the processing of new as opposed to repeated items. Similar to earlier studies with young, healthy test subjects (Schnider et al. 2002; James et al. 2008), the controls in the present study had modulation of identically configured, but differently intense, maps in response to new and repeated items around 300–500 ms (Fig. 4b, map 8). The finding is consistent with functional imaging studies, which demonstrated activation of similar networks during encoding and retrieval (Schacter et al. 1999; Greicius et al. 2003).

In contrast to the normal modulation of similar networks, as it occurred in the controls, electrocortical activation patterns strikingly differed between new and repeated items within the amnesic group at about 350–450 ms. Indeed, the two maps had inversed polarity (Fig. 4, map 9 versus 10). The observation indicates that patients activated different neuronal networks while processing repeated as opposed to new items. A recent study using functional imaging in a single patient with amnesia due to Wernicke–Korsakoff syndrome also concluded on an abnormal activation pattern (Caulo et al. 2005).

The reason for this fundamental processing difference between healthy subjects (modulation of similar networks) and amnesic patients (activation of different networks) is up for speculation. As discussed above, amnesics already had abnormal activation patterns when first learning the pictures (Fig. 4b, amnesics, new items). It is therefore likely that their remaining recognition capacity depended on other processes than in healthy subjects, who had normally encoded the information under the normal influence of the MTL. The fact that the GEV of map 10 correlated with measures of working memory would be compatible with this interpretation. An obvious candidate process underlying preserved recognition in amnesics is repetition priming (Tulving and Schacter 1990). Indeed, a very recent ERP study with healthy subjects showed that correct guessing in a recognition task ("unconscious recognition") was associated with a distinct electrocortical configuration, which differed from conscious recognition between 200 and 400 ms after stimulus presentation (Voss and Paller 2009), a time window corresponding to the one differing new and repeated item processing in the amnesics of the present study. Another study described electrocortical modulations during perceptual priming in the same time range (Doniger et al. 2001). Thus, our present findings provide an electrophysiological basis to the well-known observation of intact priming in amnesia (Squire and Zola 1997) and help to explain our observation that even patients with maximally severe amnesia after bilateral medial temporal destruction may have significant recognition performance in this type of a continuous recognition task (e.g., patient described in Schnider et al. (1995), who also participated in the study by Schnider and Ptak (1999)).

The study has technical and theoretic limitations. A potential technical limitation is that controls responded manually, while patients responded verbally. This compromise was chosen to assure that the patients' responses reflected their processing of the memory task rather than a motor challenge. Apart from the considerations explained in the methods section (in particular the expected late reaction times in amnesics), the finding that amnesics had different electrocortical maps starting already after 200 ms (but not beyond 550 ms) and especially that they had different maps in response to new and repeated items at around 350–450 ms would be difficult to explain by their verbal response mode. A further caveat with the present study is that—similar to Olichney et al.'s (2000) study—the group of patients was heterogeneous, having diverse lesions affecting not only the MTL but also diencephalic areas connected with the MTL. The inclusion of these patients—essentially based on the presence of typical amnesia—allowed arriving at the patient sample necessary for the type of analysis proposed here. It is possible that patients having damage to a specific site might yield partly different results. Nonetheless, the present study indicates that amnesics with diverse etiologies, in contrast to healthy subjects, not only fail to rapidly activate distributed cortical networks during initial encoding of new information, but

that they also rely on different processes—presumably priming—when re-encountering the information.

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