Event-related potential evidence for a specific recognition memory deficit in adult survivors of cerebral hypoxia

Axel Mecklinger, D. Yves von Cramon and Gabi Matthes-von Cramon

Max Planck Institute of Cognitive Neuroscience, Leipzig, Germany

Summary

Transient global ischaemia due to cardiac arrest may lead to profound neuropsychological disorders. Recent research indicates that memory processes are particularly impaired after hypoxic brain injury. Visual recognition memory functions were examined in these patients by means of event-related potential (ERP) and performance data. Eight chronic hypoxic patients, matched with controls for sex and age, performed a visual recognition memory task requiring recognition judgements for either object forms or spatial locations and a visual classification (i.e. oddball) task that imposed negligible memory demands. Reliable P300 oddball effects were obtained both for patients and for controls, whereas the two groups differed in P300 latency and P300 scalp topography. In the memory task, old/new effects (i.e. larger ERP waveforms for previously studied than for unstudied items) were found for the controls. In contrast, in patients these old/new effects were absent or even inverted in polarity while recognition performance was well above chance level, except for one patient. These results suggest that recognition, based on the retrieval of an item’s study episode, is degraded in patients who have suffered a period of transient global ischaemia. In the light of the patients’ above-chance level of recognition performance and the outcome of post hoc analysis of practice-related changes in recognition performance, it is argued that the patients’ memory disorders are best characterized as a degradation of explicit memory functions such as episodic retrieval of a study episode. Implicit functions such as cognitive skill learning were intact.

Keywords: recognition memory; transient global ischaemia; event-related potentials; old/new effects; P300

Abbreviations: EOG = electrooculogram; ERP = event-related potential; WMS-R = Wechsler Memory Scale—revised

Introduction

Transient global ischaemia due to cardiac arrest may cause profound neuropsychological disorders. The deficits include impairments in memory and executive functions (Volpe et al., 1986), visuospatial deficits (Wilson, 1996) and even severe intellectual or other widespread cognitive impairments (Parkin et al., 1987). Although cognitive abnormalities are often defined simply as the inability to return to the prelesion occupation, there is increasing evidence for the view that transient global ischaemia leads to significant memory impairment and a variable degree of impairment of other cognitive abilities (Volpe et al., 1986; Kapur, 1988; Wilson, 1996). Wilson (1996) examined a group of 18 patients suffering from cerebral hypoxia and found a large variation in cognitive functioning, the largest group of patients (n = 6) showing deficits in memory and executive functioning. Hopkins et al. (1995) reported severe memory disorders and intact attentional functions in three hypoxic patients after coma of 10–14 days.

The functional characteristics of post-hypoxic amnesia were examined in more detail by Volpe et al. (1986) (see also Volpe and Petito, 1985; Hirst et al., 1986). These authors examined recognition and recall performance for high-frequency words in six patients with global hypoxic ischaemic injury and a group of age-matched controls. The patients had memory impairments without loss of general intelligence or sensorimotor functions, as revealed by the Wechsler Intelligence Score and the Wechsler Memory Quotient. Contrasting memory performance in recognition and recall tests at variable study—test delays, the authors found similar forgetting rates in patients and controls in the recognition memory test, but a more pronounced decay in recall performance in patients than in controls. A selective deficit in the patients’ recall performance was obtained even when they were given extra study time to attempt to equate their performance with that of the controls at the shortest study—
test delay. Intact recognition memory after hypoxic brain injury due to cardiac arrest has also been reported by Kapur (1988).

Selective decline in recall performance has been taken to support the view that recognition is reliant on perceptual processes that are preserved in post-hypoxic amnesic patients, whereas recall depends to a larger extent than recognition on other cognitive activities, such as the retrieval of an earlier study episode, which is selectively impaired in these patients. This view, however, is challenged by the fact that recognition also benefits from the processes assumed to contribute to recall performance. Also, the extent to which perceptual processes, such as judgements of an item’s familiarity, contribute to recognition performance is generally unclear.

In support of this latter notion, Haist et al. (1992) found that recall and recognition were impaired to the same extent in a group of 12 amnesic patients, some of whom became amnesic after hypoxic brain injury. These results, in contrast to those of Volpe et al. (1996), suggest that the processes underlying recall and recognition are functionally related and reliant on the integrity of the same brain structures (for similar arguments see Moscovitch, 1992). Some evidence for the latter view was also provided by a recent study (Knowlton and Squire, 1995) that examined recognition memory in amnesic patients using the R/K technique (Tulving, 1985). The subjects indicated whether they explicitly remembered a test item (R response) or simply knew that it was present without conscious recollection (K response) of the study episode. The patients were similarly impaired in the two types of response, suggesting that the memory processes contributing to both response types depend on brain structures damaged in amnesia.

Although it is unclear what accounts for the differential findings with respect to recognition memory impairments in amnesic patients, one possibility is the differences in the patients’ neuropathology. Aggleton and Shaw (1996) examined the extent of recognition memory deficits in 112 amnesics reported in the literature by grouping the patients according to their neuropathology. It was found that amnesic patients with multiple sites of brain pathology including the frontal lobes showed severe impairments on a standard recognition memory test, whereas patients with focal brain lesions, including those with hippocampal ischaemia, were only mildly impaired in a recognition memory test compared with controls. This indicates that patient groups with homogenous neuropathology and aetiology are required in order to examine the functional characteristics of memory disorders in amnesic patients.

Though transient global ischaemia is characterized by a large variety of neuropathological changes and can lead to localized and non-localized lesion patterns, certain human brain structures have been found to be selectively vulnerable to the lack of blood and oxygen supply. Transient global ischaemia regularly gives rise to brain damage in the hippocampus, cerebellum, striatum and neocortex. In the cortex, damage is accentuated over the boundary zones of the cerebral hemispheres (Brierley et al., 1969; Cervós-Navarro and Diemer, 1991; Auer and Benveniste, 1997). In a recent PET study (Kuwert et al., 1993), significantly reduced glucose consumption was found in the medial temporal cortex and thalamic projection zones in a group of seven patients whose hypoxia was due to cardiac arrest. No significant changes in glucose metabolism were obtained in frontal or parietal neocortical regions. Comparable metabolic changes in the medial temporal cortex following transient global ischaemia have been reported by Ruprecht et al. (1996).

More precise information on one crucial locus of brain damage was provided by post-mortem neuropathological analyses (Zola-Morgan et al., 1986; Rempel-Clower et al., 1996). Patient R.B., reported by Zola-Morgan et al. (1986), developed marked anterograde amnesia with little retrograde amnesia after ischaemic hypoxia. Neuropathological analysis after his death revealed selective neuronal loss in the CA1 field of the hippocampus with only minor pathological changes in other parts of the brain. A similar relationship between selective damage to the CA1 field within the hippocampus and anterograde amnesia was reported for patient G.D. after an assumed ischaemic episode due to cardiac arrhythmia (cf. Rempel-Clower et al., 1996). These results indicate that lesions to the hippocampus proper are sufficient to cause the memory impairments typically found after transient global ischaemia. Notably, like other amnesic patients, R.B. showed impaired memory performance in explicit memory tests, such as story recall or paired-associate learning, in combination with intact general intellectual capacities and implicit memory functions (i.e. word-stem completion). The view that ischaemic hypoxia leads to hippocampal damage and associated anterograde amnesia is also supported by animal data, which show, for instance, that experimentally induced ischaemia in rats causes selective damage in the CA1 region of the hippocampus and deficits in new learning abilities (Volpe et al., 1984; Davis et al., 1986).

The aim of the present study was to examine the functional characteristics of memory impairments by means of event-related potential (ERP) and performance measures in patients who have suffered a period of transient global ischaemia. While previous studies have used different tasks (i.e. recall and recognition) to infer selective post-hypoxic memory impairments, our approach was to examine memory impairments in these patients within the same task, i.e. a visual recognition memory task. ERPs are small-voltage oscillations measured at the scalp that are time-locked to the processing of external events. They involve a sequence of deflections (i.e. components) that mark the passage of information through the brain. Differences in the timing and scalp topography of ERP components allow inferences to be made about the temporal and spatial characteristics of brain activity involved in cognitive processing (Hillyard and Kutas, 1983; Mecklinger and Müller, 1996).

ERPs have been used extensively to examine recognition memory functions (for an overview see Rugg, 1995). A consistent finding of these studies is that repeated words or
figural stimuli evoke more positive ERPs than unrepeated (new) stimuli. These old/new effects start at ~300 ms and have a broad temporal and topographical extent. Old/new effects between 300 and 600 ms are also obtained across modalities, i.e. when items are studied in the auditory modality and tested in the visual modality (Feldstein et al., 1987). They have also been found to be larger when old items are correctly assigned to their study context than when old items are incorrectly assigned (Wilding et al., 1995). Based on these findings, a number of authors have suggested that old/new effects are evoked when recognition is accompanied by the retrieval of information formed at an item’s initial presentation, i.e. conscious recollection (Smith and Halgren, 1989; Paller and Kutas, 1992; Rugg, 1995; but see Potter et al., 1992). Since old/new effects in scalp-recorded ERPs are attenuated or diminished in patients with damage to the mediobasal temporal lobes (Smith and Halgren, 1989; Rugg et al., 1991; Johnson, 1995), these effects can be considered as an index of memory processes mediated by these brain structures (cf. Wilding and Rugg, 1996). Given these functional and neuroanatomical characteristics, ERP old/new effects appear to be a valuable method of examining the nature of recognition memory impairments caused by transient global ischaemia.

For the current study we employed a recently developed visual recognition memory task (cf. Mecklinger, 1998; Mecklinger and Meinshausen, 1998) in which the processes underlying recognition memory for object forms and object locations can be examined using the same study phase and test stimuli for both types of information. Subjects study familiar objects presented in various positions of a spatial matrix. Just prior to the test phase, a cue is presented indicating that recognition judgements for either object forms (object memory condition) or object locations (spatial memory condition) will be required. Previous experiments employing this paradigm have shown that there is a contribution from working memory processes in this task, in that rehearsal can be used to bridge the study–test intervals (Mecklinger and Meinshausen, 1998). In the present study, eight patients and age- and sex-matched control subjects performed both memory tasks while ERPs were recorded from 19 scalp sites. Two recognition conditions were employed in order to examine whether potential recognition deficits are information-specific (i.e. confined to either object forms or spatial locations) or rather reflect a general deficit in visual recognition memory functions.

Previous experiments employing this task used a randomized order presentation of the object and spatial conditions, such that subjects had to encode and rehearse both kinds of information until the cue was presented (cf. Mecklinger, 1998). To adapt to the needs of the brain-injured subjects, this experiment used a block presentation of the two conditions. We assumed that the extent to which the patients were able to retrieve either object forms or spatial locations from the study episode would be indexed by reliable ERP old/new effects. In contrast, the absence of old/new effects in either condition would be indicative of a selective deficit in retrieving either object forms or spatial locations from memory. Another modification concerned the delay between repetitions of items. This delay is usually not of major relevance in ERP studies on recognition memory and can vary from ~30 s (Rugg et al., 1991) to several minutes (Paller and Kutas, 1992). To ensure that the patients were able to perform the recognition task, we decided to use rather short intervals (20 s) between repetitions of items. Previous studies have shown that amnesic patients as well as monkeys with medial temporal lobe lesions perform well in memory tasks with very short retention intervals (<5 s) but are impaired at retention intervals of ~15 s (Sidman et al., 1968; Alvarez-Royo et al., 1992). This had led to the view that memory tasks in which information has to be retained for ~8 s mainly tap into short-term memory processes whereas tasks with retention intervals of ~15 s can be considered as long-term memory tasks (Alvarez-Royo et al., 1992). Given this, we considered a mean retention interval of 20 s as a good compromise that takes into account the patients’ memory deficits but still examines the retrieval from episodic long-term memory.

In order to ascribe possible changes in the ERPs evoked in the recognition task to memory deficits, ERPs were also recorded in a visual classification (i.e. oddball) task. In this task, subjects were presented with a series of standard and rare target events. The subjects’ task was to count the rare targets and to ignore the standards. It has been shown repeatedly that neurologically unimpaired subjects display a large, parietaledly focused P300 component to rare target events (i.e. the P300 oddball effect). Comparing the P300 oddball effect and the old/new effects in the recognition memory task in the patients and their age-matched controls would enable us to examine the extent to which transient global ischaemia has a general effect on ERP components evoked in cognitive tasks or can be ascribed to a particular memory deficit in these patients.

Method

Subjects

A group of eight patients, all of whom had suffered a period of transient global ischaemia due to cardiac arrest, and 24 controls participated in the experiment. The main clinical data and the medication applied at the time of the study are reported in Table 1A and B. The mean age was 42 years (range 19–60 years). Two female and six male right-handed patients participated. A selection of relevant neuropsychological data is displayed in Table 1C. Neuropsychological testing of the eight patients revealed a broad variance in cognitive performance. The difference between the WIP, a reduced version of the Wechsler Intelligence Scale (Dahl, 1996), and the Wechsler Memory Scale—revised score (WMS-R) provides an index of the severity of the patients’ memory impairment. In normal subjects the two scores are
Table 1 Individual patient information for the eight hypoxic patients under investigation

<table>
<thead>
<tr>
<th>Patient</th>
<th>22</th>
<th>32</th>
<th>92</th>
<th>51</th>
<th>14</th>
<th>2</th>
<th>67</th>
<th>160</th>
</tr>
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<tr>
<td><strong>(A) Main clinical data</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Age (years)</td>
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<td>46</td>
<td>46</td>
<td>19</td>
<td>60</td>
<td>43</td>
<td>39</td>
<td>37</td>
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<tr>
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<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>N</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Structural/functional causes</td>
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<td>DCM</td>
<td>CHD/MI</td>
<td>EI</td>
<td>CHD</td>
<td>Toxic</td>
<td>CHD/MI</td>
<td>CHD</td>
</tr>
<tr>
<td>Implementation of CPR</td>
<td>Delayed</td>
<td>Delayed</td>
<td>CHD/MI</td>
<td>El</td>
<td>CHD</td>
<td>Instantly</td>
<td>Unknown</td>
<td>Instantly</td>
</tr>
<tr>
<td>Time since cardiac arrest (months)</td>
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<td>12</td>
<td>36</td>
<td>5</td>
<td>9</td>
<td>31</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

**(B) Medication (mg) at time of study**

- Citalopram: ...
- Paroxetine: ...
- Valproic acid: ...
- Bromocriptine: ...
- Selectol: ...
- Pergolide: 2
- Sotalol: ...
- Enalapril: 10
- Captopril: ...
- Lisinopril: ...

**(C) Main neuropsychological data**

<table>
<thead>
<tr>
<th></th>
<th>WIP</th>
<th>WMS-R</th>
<th>Difference</th>
<th>Digit span</th>
<th>Visual span</th>
</tr>
</thead>
<tbody>
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<td>12</td>
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<tr>
<td>32</td>
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<td>50</td>
<td>−32</td>
<td>10</td>
<td>8</td>
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<tr>
<td>51</td>
<td>85</td>
<td>70</td>
<td>−15</td>
<td>6</td>
<td>6</td>
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<tr>
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<td>125</td>
<td>50</td>
<td>−75</td>
<td>6</td>
<td>8</td>
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<tr>
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<td>100</td>
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<td>−1</td>
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<td>10</td>
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<tr>
<td>160</td>
<td>95</td>
<td>83</td>
<td>−12</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

Part A: CHD = coronary heart disease; CPR = cardiopulmonary resuscitation; DCM = dilated cardiomyopathy; EI = electrical injury; MI = myocardial infarction; toxic = proarrhythmic drugs. Part C: Digit span, visual span = raw scores of the forward versions from the WMS-R; WIP = reduced version of the Wechsler Intelligence Scale (Dahl, 1986); WMS-R = Wechsler Memory Scale—revised.

equivalent. As is apparent from Table 1C, there was a pronounced difference between intelligence and memory scores in patients 22, 32, 51, 14, 2 and 160. Comparable scores, indicative of no selective memory impairments, were obtained for patients 92 and 67. Notably, for patient 92 the latter result arose from a low intelligence score, whereas for patient 67 memory and intelligence scores were on a similar, high level. The scores for digit and visual span, indicative of short-term storage capacity (Lezak, 1995), were between 12 and 6 and thus within the normal limits for all except one patient (patient 160). Patients 22, 32 and 92 were diagnosed as demented according to the guidelines of DSM IV (Sass et al., 1996).

There were 24 control subjects, all of whom were right-handed, with a mean age of 41 years (range 20–61 years). They were divided into four groups of six according to age, and each patient was then matched to one of these groups. Group A comprised six females with a mean age of 21 years (range 20–24 years) and served as a control group for patient 51. Group B included six males (mean age 39 years; range 34–43 years) and served as a control group for patients 2, 67 and 160. Group C comprised six males with a mean age of 47 years (range 43–53 years) and served as a control group for patients 22, 32 and 92. Group D included six males with a mean age of 59 years (range 55–61 years) and served as a control for patient 14. Each subject gave informed consent prior to participation in the study, which was approved by the ethics committee of the Max Planck Institute of Cognitive Neuroscience, Leipzig, Germany.

**Stimuli**

All stimuli were presented on a 17-inch VGA monitor under the control of a 486 computer. The stimuli of the visual oddball task were 16 geometrical figures (cross, circle, triangle, ring etc.). The stimuli in the memory task consisted of line drawings of 12 familiar and simple objects drawn from a standardized set of 260 line drawings (Snodgrass and Vanderwart, 1980). The objects were spectacles, pipe, key, hammer, table, scissors, sock, book, lamp, envelope, cup and hat. All objects were presented in one of 12 equally spaced squares of a $4 \times 3$ grid (dimensions 27.5 cm and 21.5 cm) in blue against a light grey background.

**Procedure**

Each subject was comfortably seated in an acoustically and electrically shielded, dimly lit chamber 0.9 m from a computer monitor, and held a small response box on his or her lap. Each subject performed in one session, which included the
oddball task and the object and spatial recognition memory tests. In the oddball task 300 objects were presented in the centre of the screen, each for 200 ms and with an interstimulus interval of 1200 ms. Twenty-five per cent of the objects were easily discernible through an opening (e.g. a ring) and the subject’s task was to count these particular objects. Next, the recognition memory tasks were performed, each of which consisted of 25 study–test blocks. In the study phases, four line drawings of familiar objects were presented sequentially with a duration of 500 ms and an interstimulus interval of 2000 ms at random positions of a 4 × 3 spatial matrix. The words ‘bitte warten’ (please wait) were presented for 3000 ms at an interval of 1000 ms after the end of the study phase. Thereafter a cue was presented for 1000 ms, which indicated whether in the following test phase, which started 1500 ms after the cue had been removed, object-based or spatial-based recognition judgements were required. The cues ‘Objekte’ and ‘Positionen’ were used to indicate the object and spatial recognition memory condition, respectively. The test phases in both conditions consisted of eight objects presented sequentially for 1000 ms at random positions of the spatial matrix. For each trial, in the object condition the subjects were required to indicate whether or not the object currently being presented was one already seen on the study list (irrespective of its spatial position in the spatial matrix), whereas in the spatial condition the subjects were required to indicate for each trial whether or not the object currently being presented was occupying one of the positions in the spatial matrix seen in the study list (irrespective of the object’s identity). In both conditions the same stimuli were presented and subjects pressed the left button to respond ‘old’ and the right button to respond ‘new’. Old and new responses were equiprobable in the two conditions and feedback was provided after each response (correct, false, no response). The maximum response time was 2500 ms. With this procedure the average delay between study items and their repetition in the test phases was 20 s. In the object condition, two of the four old/new objects were presented at positions that also occurred in the study phase; the other two old/new objects were presented at unstudied positions. However, old objects were never presented at exactly the same spatial positions as during the study phase. The same constraints were applied to the spatial condition. The four study list items and the eight test items within each block were presented with the restriction that spatial positions in the left and right half of the grid were equiprobable. The object condition was always performed first and four practice blocks were given to the subjects at the beginning of both the object condition and the spatial condition. Including electrode application and removal, each session lasted ~2.5 h.

**ERP recording**
The EEG activity was recorded with tin electrodes mounted in an elastic cap (Electrocap International) from the 19 electrode sites of the 10–20 system referenced to the left mastoid. The ground electrode was positioned 10% of the nasion–ion distance anterior to Fz. The vertical electrooculogram (EOG) was recorded from electrodes located above and below the right eye. The horizontal EOG was recorded from electrodes positioned at the outer canthus of each eye. Electrode impedance was kept below 5 kΩ. The EEG and EOG were recorded continuously in both tasks with a bandpass from DC to 70 Hz and were A–D converted with 16-bit resolution at a sampling rate of 250 Hz.

**Data analysis**
ERPs time-locked to rare and frequent objects (oddball task) and to correctly classified old and new items (memory conditions) were computed for each subject at all recording sites, with epochs extending from 200 ms before stimulus onset until 1000 ms thereafter. The average voltages in the 200 ms preceding the test items served as a baseline, i.e. its mean value was subtracted from each data point in the waveforms. Prior to averaging, each epoch was scanned for EOG and other artefacts. Whenever the SD in a 200 ms time interval exceeded 50 µV the epoch was rejected. The number of rejected trials did not differ between patients and controls. The subject average ERPs were digitally low-pass filtered at 12 Hz (cut-off frequency).

The P300 components in the oddball task were measured as mean voltages in the 300–600 ms time intervals. The peak latency was defined as the time point of the maximal positive deflection within this time interval. For technical reasons one patient (patient 14) did not perform the oddball task. Thus, the ERP analysis for this task will be restricted to seven patients and the respective three subgroups of controls. The time intervals for the quantification of the old/new effects were determined after visual inspection of the ERP waveforms and were based on previous studies (Mecklinger, 1998; Wilding and Rugg, 1996). The time windows were 300–600 ms in the object condition and 300–500 ms in the spatial condition. For statistical analysis of the ERP data, nine electrodes, including the three midline sites Fz, Cz and Pz as well as bilateral frontal (F3, F4), central (C3, C4) and parietal (P3, P4) recording sites, were selected. The ERP data were subjected to ANOVA (analysis of variance) with appropriate Huynh–Feldt corrections (Huynh and Feldt, 1970) for inappropriate degrees of freedom due to violations of the sphericity assumption. If not specified otherwise, post hoc comparisons were performed by means of a modified Bonferroni procedure (Keppel, 1991)

**Results**

**Oddball task**
The ERP waveforms evoked by target and standard stimuli for the hypoxic patients and all control subjects are displayed in Figs 1 and 2. One patient (patient 32) was unable to count the target objects but could discriminate between target and
standard objects. In both groups, the target stimuli evoked large P300 components which peaked earlier in the control group than in the patient group. The mean latencies of the target P300 at the Pz electrode for the two groups were 419 ms (SEM 5.47 ms) and 445 ms (SEM 7.99 ms), respectively. As revealed by a $t$ test for independent samples, this difference was highly significant [$t(21) = -2.56, P < 0.01$]. Though more pronounced in the control group, larger P300 amplitudes to targets than to standards (i.e. the P300 oddball effect) were obtained in both groups.

These observations were confirmed by statistical analysis. In a first step we examined whether the waveforms evoked by target and standard stimuli were different in the three control subgroups. An ANOVA with the between-subject factor subgroup (three levels) and the within-subjects factors electrode (nine levels) and stimulus type (target versus standard) revealed a main effect of stimulus type [$F(1,15) = 103.50, P < 0.0001$], and the interactions stimulus type $\times$ subgroup, [$F(2,15) = 8.44, P < 0.003$] and stimulus type $\times$ subgroup $\times$ electrode [$F(8,16) = 4.75, P < 0.004$]. Based on these interactions, separate ANOVAs (stimulus type $\times$ electrode) were performed for each of the subgroups. Stimulus type $\times$ electrode interaction was found for the young control subjects (i.e. subgroup A) ($P = 0.004$) but not for the two other subgroups ($P > 0.18$). This last result indicates that age had a systematic influence on the P300 scalp topography of the controls. In order to take these age-related changes in P300 scalp topography into account in the comparison of P300 in patients and controls, an analysis of covariance was performed with group (patients versus controls), stimulus type and electrode as factors and age as covariate. This analysis revealed a main effect of stimulus type [$F(1,22) = 36.41, P < 0.0001$], whereas the group $\times$ stimulus type interaction [$F(1,22) = 1.70, P < 0.20$] and the group $\times$ stimulus type $\times$ electrode

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**Fig. 1** Controls: oddball. Grand average ERPs for targets and standards in the visual oddball task. The vertical lines indicate the onset of appearance of the objects, which were presented for 200 ms. The vertical EOG (EOGV) is plotted in the upper left corner. Solid line = target stimuli; broken line = standard stimuli.
interaction \( F(8,176) = 1.30, P < 0.28 \) did not reach the significance level. These results suggest that the P300 oddball effect was statistically not different for patients and controls. Interestingly, a group \( \times \) electrode interaction \( F(8,176) = 2.98, P < 0.02 \) was obtained, suggesting that P300 scalp topographies for both targets and standards were different for patients and controls even when age effects on P300 topography were controlled for. The group \( \times \) electrode interaction was also significant when between-group differences in P300 amplitude were removed \( F(8,176) = 3.44, P < 0.02 \) (cf. McCarthy and Wood, 1985), indicating that the P300 components in the patients and controls arise from different neuronal sources.

The different P300 scalp topography in the control groups and the patients is further illustrated in Fig. 3, which displays the peak amplitude for the target P300 at the three midline electrodes for the patients and the subgroups of controls. To allow a better evaluation of topographical changes, P300 amplitudes in this figure were normalized by converting all P300 amplitudes to the percentage of the P300 at the Pz electrode (cf. Johnson, 1993). As is apparent from the figure, target P300s increased in amplitude from frontal to parietal recording sites for the three control groups; this topographic effect was substantially smaller for the two middle-aged groups than for the young control group (i.e. subgroup of patient 51). Notably, while the largest P300s were obtained at Pz for the three subgroups of controls, the P300 maximum for all patients was shifted from the parietal (Pz) to central (Cz) or frontal (Fz) recording sites.

**Memory task**

**Performance measures**

Mean reaction times, the proportion of correct responses, hit rates and false alarm rates for the eight patients and the four
Table 2 Performance results (reaction times/proportion of correct responses) in both memory conditions for all eight patients and the four control subgroups

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Patients</th>
<th></th>
<th></th>
<th></th>
<th>Controls</th>
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<tbody>
<tr>
<td></td>
<td>Proportion correct</td>
<td>Hits (%)</td>
<td>FA (%)</td>
<td>RT (ms)</td>
<td>Proportion correct</td>
<td>Hits (%)</td>
<td>FA (%)</td>
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FA = false alarm rate; Hits = hit rate; RT = reaction time. *Proportion correct differs significantly from chance performance (0.50).

The ERP waveforms of the control subjects evoked by old and new judgements in both tasks are displayed in Fig. 4 (object condition) and Fig. 5 (spatial condition). The corresponding ERPs of the patients are shown in Figs 6 and 7. Given that recognition memory performance was at chance level for patient 22 in both conditions and for patient 22 in the spatial recognition condition, the respective ERP
Fig. 4 Controls: object condition. Grand average ERPs evoked by old and new objects at the nine electrode sites also considered for statistical analysis. The vertical lines indicate the onset of appearance of the objects which were presented for 200 ms. The vertical EOG (EOGV) is plotted in the upper left corner. Solid line = old; broken line = new.

waveforms of these patients were excluded from Figs 6 and 7 and from further analysis. For the controls, the waveforms in both conditions started to get more positive for old responses than for new responses at around 300 ms. These old/new effects amounted to 2–3 µV and had a duration of ~300 ms in the object condition and of 200 ms in the spatial condition. While in the spatial condition the old/new effects were largest at parietal recording sites, they were more equally distributed across the scalp in the object condition. This latter result arose from a frontally focused negativity evoked by new objects peaking around 500 ms. In sharp contrast, these old/new effects were virtually absent in the patients’ ERPs.

The mean old/new effects for the patients and conditions in which recognition was different from chance level and their control groups in both recognition conditions are displayed in Fig. 8. The old/new effects in the object condition were either absent (patients 14, 22, 67, 92 and 160) or of much smaller magnitude (patients 51 and 2) than those of the controls. A similar pattern of results was obtained for the spatial condition: here the old/new effects were virtually absent (patients 67, 92 and 160) or substantially reduced in magnitude (patients 14, 51 and 2) compared with those of the controls.

In parallel to the ERP analysis in the oddball task, we first examined whether the ERPs in the memory task were different for the four control subgroups. The mean amplitude measures between 300 and 600 ms (object condition) and between 300 and 500 ms (spatial condition) were used for quantification of the old/new effects. The ANOVAs with the factors subgroup (four levels), response type (two levels) and electrode (nine levels) revealed main effects of response type
in the object condition \( F(1,20) = 43.51, P < 0.0001 \) and the spatial condition \( F(1,20) = 45.75, P < 0.0001 \) as well as interactions among response type and electrode (object condition: \( F(8,24) = 4.81, P < 0.02 \); spatial condition: \( F(8,24) = 7.33, P < 0.001 \)). However, no interactions involving the subgroup factor were obtained \( (P > 0.2) \). In the light of this result, the waveforms were collapsed across the four control subgroups.

To examine whether object-based and spatial-based old/new effects differed in scalp topography, an ANOVA with the factors condition (two levels) and electrode (nine levels) was performed on the differences between old and new responses in the 300–600 ms (object condition) and the 300–500 ms (spatial condition) time interval. This analysis revealed a significant condition \( \times \) electrode interaction \( F(8,184) = 3.45, P < 0.03 \). This interaction was also significant \( F(8,184) = 2.89, P < 0.04 \) when the mean amplitude measures were normalized such that amplitude differences between the two conditions were removed (cf. McCarthy and Wood, 1985) indicating that different neuronal structures contribute to the old/new effects in both recognition conditions (Johnson, 1993).

Contrasting the old/new effects of the controls \( (n = 24) \) and the patients with above-chance recognition performance revealed highly significant interactions between response type and group for the object condition \( F(1,29) = 6.36, P < 0.02 \) and the spatial condition \( F(1,28) = 13.53, P < 0.001 \), indicating that old/new effects were present for the controls but not for the patients.

**Discussion**

This study examined visual recognition memory in a group of eight hypoxic brain-injured patients and 24 age-matched controls using ERPs and performance measures. All subjects performed a visual oddball task and two versions of a memory
task, in which recognition judgements were required either for line drawings of familiar objects or their respective spatial locations within a two-dimensional spatial matrix. The main results can be summarized as follows. First, for all patients under investigation reliable P300 oddball effects were observed. However, the P300 was prolonged and displayed a different scalp topography in the patients compared with the controls. Secondly, in both recognition conditions the reaction times and accuracy were substantially degraded in the patients compared with the controls. Secondly, in both recognition conditions the reaction times and accuracy were substantially degraded in the patients compared with the controls. Thirdly, the controls displayed reliable ERP old/new effects for both types of recognition judgement, these effects being parietally focused for spatial-based judgements and more broadly distributed for object-based judgements (see also Mecklinger and Meinshausen, 1998). This difference in scalp topography can be taken as evidence that different brain regions mediate the old/new effects in the two conditions. Interestingly, the old/new effects were virtually absent in both conditions for all patients. These results will now be discussed with respect to the functional characteristics of memory impairments after ischaemic hypoxic encephalopathy.

For the P300 component in the oddball task, differences and similarities were found for patients and controls. Both groups showed significant oddball effects, i.e. larger P300s for targets than for standards, these effects being statistically indistinguishable between the two groups. It has been argued that P300 amplitude is related to stimulus categorization processes and reflects the degree to which a current model of the environment is modified or updated once sensory information has been analysed (Donchin and Coles, 1988; Mecklinger and Ullsperger, 1993). In oddball tasks, P300

Fig. 6 Patients: object condition. Grand average ERPs for old and new objects for the seven patients who showed above-chance recognition performance in the object condition. For details see legend of Fig. 4.
latency is assumed to reflect the speed of these stimulus-related processes (Polich, 1991). In the light of these models the present results suggest that the cognitive processes associated with memory updating during visual classification are not affected by transient global ischaemia. However, despite these similar oddball effects, P300 components were delayed for ~50 ms in the patient group. Between-group differences in P300 latency of similar magnitude have been reported in studies examining P300 across the lifespan (Picton et al., 1984; Pfefferbaum et al., 1984). For example, Picton et al. (1984) found a delay of 70 ms in the auditory P300 of subjects aged 70 years compared those aged 20 years. Delayed P300 components in oddball tasks have also been found in a variety of ERP studies of demented patients (Goodin et al., 1978; Johnson et al., 1991; Polich, 1991; Johnson, 1992). On the basis of these studies, it can be assumed that stimulus categorization processes, though functionally comparable with normal controls, are significantly delayed by ischaemic–hypoxic encephalopathy.

In addition to differing in latency, the P300 also differed in scalp topography between patients and controls. Consistent with other studies, the target P300 in the control group was largest at the parietal recording sites but acquired a more frontal scalp distribution in subjects of increasing age (Picton et al., 1984; Friedman and Simpson, 1994; Friedman et al., 1997). In showing a central or frontocentral maximum, the patients’ P300 was topographically clearly dissociable from the P300 of the control group. This topographical dissociation was also obtained when the effects of age were taken into account. Recent evidence from intracranial ERP recordings (Halgren et al., 1995a, b), from combined functional MRI and ERP recordings (Menon et al., 1997) and from ERPs recorded from patients with circumscribed brain lesions (Knight et al., 1989; Verleger et al., 1994; Knight, 1997)

**Fig. 7** Patients: spatial condition. Grand average ERPs for old and new spatial locations for the six patients who showed above-chance recognition performance in the spatial condition. For details see legend of Fig. 4.
suggests that multiple brain regions contribute to the generation of the parietal maximal P300, some of these regions being in the primary and secondary cortices. Thus, it is conceivable that the parietal attenuation of the patients’ visual P300 arose from neuronal cortical alterations along the cortical arterial boundary zones in the posterior cortex, typical of those found in cerebral hypoxia (Cervós-Navarro and Diemer, 1991; Auer and Benveniste, 1997).

Even more pronounced differences between patients and controls were found in the memory task. The patients showed degraded recognition performance that was significantly different from chance in all but one patient. Their proportion of correct responses was 23% lower compared with the controls in both conditions, and the patients’ decrease in the number of hits was equivalent to their increase in false alarms. Moreover, the patients, especially those who were diagnosed as demented according to DSM IV (i.e. patients 22, 32 and 92) responded substantially more slowly and with lower accuracy than the age-matched controls (Table 2). In showing substantially degraded recognition performance in all patients the results are contrary to those reporting intact recognition memory in amnesic patients. For instance, Volpe et al. (1986) found intact recognition performance for words in hypoxic brain-injured patients after a comparable short delay of 3 s. Similarly, Hirst et al. (1986) report intact recognition performance in amnesic patients, even with retention intervals of 5 min. An explanation for this discrepancy could be derived from procedural differences of the recognition tasks. Whereas in the studies of Volpe et al. (1986) and Hirst et al. (1986) trial-unique stimuli were employed, in the present experiment we used recurrent stimuli, i.e. the study stimuli were drawn from a fixed set. Consequently the latter procedure imposed more demands on working memory because previously studied stimuli are more likely to generate interference on stimuli that are task-relevant in an actual trial. Given these procedural differences, i.e. the higher working memory demands imposed by the necessity to inhibit task-irrelevant stimuli, it is conceivable that the patients’ low recognition performance in the present study resulted from a higher degree of susceptibility to proactive interference compared with the controls. It could also be argued that elevated false alarm rates could be evidence for increased susceptibility to interference in the patients. However, given that the subjects were provided with feedback after each recognition judgement, it is conceivable that, besides the target status, the non-target status of the items was also memorized. For this reason it is more likely that susceptibility to interference resulted from increases in the numbers of both misses and false alarms.) We tentatively suggest that susceptibility to interference accounts for the discrepancy of the patients’ recognition memory performance in the present experiment and the two studies mentioned above.

The patients’ low recognition memory performance was paralleled by reduced or virtually absent ERP old/new effects for both kinds of recognition judgement. Prior to discussing these effects in the light of memory disorders in ischaemic-hypoxic patients, alternative interpretations will be considered. First, it could be argued that the patients show a general deficit in cognitive ERP components. Given the observation that all patients under investigation showed reliable P300 oddball effects, the interpretation of a general deficit in cognitive ERP components appears to be unlikely. Secondly, it is conceivable that the deficit in recognition accuracy and the reduced ERP old/new effect reflect increased rehearsal demands. It has been found as that old/new effects get smaller, the more information has to be retained in memory or with decreases in recognition performance (Mecklinger et al., 1992). However, digit spans and visual spans were within the normal limits except for one patient (patient 160) (Table 1C). Thus, short-term memory capacity can be assumed to be sufficient to perform the recognition task. Moreover, there was no relationship between the patients’ old/new effects and memory performance. For example, in patients 2 and 160, who showed the lowest impairment in spatial memory performance, the corresponding old/new effects were negligible (patient 2) or even inverted in polarity (patient 160). Thus, neither a general deficit in cognitive ERP components nor limitations in working (short-term) memory appear to be adequate to account for the absence of old/new effects in the patients’ ERPs.

A memory-based interpretation of the degraded recognition performance and the absence of ERP old/new effects can be derived from so-called dual process models of recognition memory. According to these models an item can be recognized as ‘old’ following the retrieval of an earlier study episode, i.e. an explicit memory phenomenon, or on the basis of its familiarity or increased perceptual fluency, an implicit memory phenomenon (Mandler, 1980;Jacobi and Dallas, 1981). Based on the view that ERP old/new effects reflect brain activity mediating the retrieval of an earlier study episode, i.e. one of the two modes by which recognition
judgements can be made (cf. Paller and Kutas, 1992; Rugg, 1995), it can be assumed that the functional locus of recognition memory impairments in ischaemic–hypoxic patients is in the retrieval of information from earlier study episodes. An objection to this interpretation might be that the present task contains a contribution from working (short-term) memory processes, because the task permits the use of rehearsal between the study and the test phase such that the ERP results cannot unequivocally be related to long-term episodic memory retrieval. Although at present there is no objective time standard that separates short-term memory from long-term memory, two aspects provide arguments against this objection. First, the mean delay between two repetitions was 20 s. Previous studies have shown that amnesic patients with lesions of the medial temporal lobes who perform well in a memory task with very short retention intervals, i.e. when information can be held in a short-term store, show degraded memory performance when retention intervals exceed 15 s (Sidman et al., 1968; Cave and Squire, 1992; see also Ringo, 1993). Given this, it was proposed that in memory tasks with retention intervals >15 s mainly long-term memory processes mediated by medial temporal lobe structures have to be assumed. Thus, it is reasonable to assume that, in the present task, working memory processes (i.e. rehearsal) were probably restricted to the interval between the study and test phases, and because of these rehearsal processes information entered episodic long-term memory and was retrieved from there in the test phase. Secondly, the old/new effects in the control group as well as in previous studies employing this paradigm (cf. Mecklinger, 1998; Mecklinger and Meinshausen, 1998) were closely similar in their temporal and topographical characteristics to those reported in previous ERP recognition memory experiments. This suggests that the present old/new effects, as in previous studies, can be considered as an electrophysiological correlate of episodic memory retrieval.

The observation that old/new effects were equally degraded in both recognition conditions provides evidence against a selective recognition deficit for either object forms or object locations, and rather indicates that the brain regions mediating the retrieval of object forms and spatial locations are equally damaged by an ischaemic–hypoxic encephalopathy. The assumption that the conscious recollection of study episodes is impaired in ischaemic–hypoxic patients together with the patients’ above-chance recognition performance also suggests that relying on the products of the retrieval processes is not always necessary for correct recognition performance. Rather than solely supporting recognition judgements, consciously recollected information of an earlier study episode presumably serves as input for other evaluation or strategic control systems that operate on the products of the retrieval process (cf. Moscovitch, 1992).

Conversely, the patients’ above-chance recognition performance also implies that some memory processes not required for conscious remembering are intact after transient global ischaemia. The memory processes usually spared in amnesic patients are considered implicit (non-declarative) memories. ‘Implicit memory’ refers to a heterogeneous collection of abilities (cf. Squire, 1994). They enable skill acquisition and priming and are expressed implicitly by facilitation in performance without the conscious recollection of previous events (cf. Musen and Squire, 1991; Squire, 1994). To examine the extent to which facilitation in performance, indicative of spared implicit memories actually occurred, we contrasted memory performance for the first and last five test blocks for patients and controls. If some form of implicit memory remains intact after transient global ischaemia, we would expect both patients and controls to show better performance in the last than in the first test blocks. In this post hoc analysis only the performance data for those patients and conditions in which recognition performance was significantly above chance were considered. For the patients, recognition performance increased from 72 to 78% in the object condition and from 82 to 85% in the spatial condition. As revealed by t tests for dependent samples, this improvement in performance was significant in the object condition \( t(6) = 2.79, P < 0.03 \) and marginally significant in the spatial condition \( t(5) = 1.91, P < 0.10 \). The corresponding values for the control group were 91 and 95% (object condition) and 93 and 95% (spatial condition), the differences being significant in both the object task \( t(23) = 4.5, P < 0.001 \) and the spatial task \( t(23) = 2.15, P < 0.001 \). This pattern of results suggests that repeated task performance led to an improvement in object recognition and possibly in spatial recognition in the patients, and that these facilitatory effects were very similar for patients and controls.

To obtain an estimate of the potential contribution of short-term memory capacity to these practice-related changes in recognition performance, we examined the correlations between the visual span scores from the WMS-R (Table 1C) and the performance differences between the first and last test blocks. Only those patients and those conditions in which recognition performance was significantly above chance were considered in this analysis. No reliable correlations were obtained (object condition, \( r = 0.14 \); spatial condition, \( r = 0.16, P > 0.47 \)). Nor were there any reliable correlations between the proportion of correct responses in both conditions and the visual span scores (object condition, \( r = -0.18 \); spatial condition, \( r = 0.29, P > 0.52 \)). These results suggest that the patients’ differential short-term memory capacities, as revealed by visual span scores, can account neither for practice-related improvements in recognition performance nor for recognition memory performance in general.

Within the dual-process framework of recognition memory, facilitatory effects of similar kinds in amnesic patients have been interpreted as evidence for a spared familiarity or perceptual fluency component of recognition memory. However, preserved familiarity or perceptual fluency is unlikely to be the source of the present behavioural facilitation effects, mainly because items from a fixed set were interchangeably used as targets and non-targets in different
blocks, such that familiarity with target stimuli could not build up across the experiment. The latter view is supported by the observation that some forms of implicit memory in amnesic patients, such as the acquisition of reading skills or priming of novel verbal stimuli, are item-specific with little or no transfer to other items or task situations (Musen et al., 1990; Musen and Squire, 1991).

Given this, the behavioural facilitation effects seen in the patients in the present study are more likely to reflect intact general learning skills. Consistent with this view, a variety of learning skills are known to be preserved in amnesic patients. For example, amnesics show learning curves when reading mirror-reflections of words that are closely similar to those of controls even for unique, non-repeated words (Cohen and Squire, 1980). Thus, it is conceivable that in the present experiment patients acquired skills for accessing and retrieving memory information that can be applied to multiple object forms or object locations and that led to behavioural facilitation during recognition memory judgements. This latter process is apparently intact in ischaemic hypoxic patients, whereas the retrieval of previous study episodes, which requires conscious access to a specific memory trace and which is indexed by ERP old/new effects, is degraded in these patients.

The notion that transient global ischaemia causes a selective deficit in explicit memory functions like the retrieval of an item’s study context is also consistent with the cases of R.B. (Zola-Morgan et al., 1986) and G.D. (Rempel-Clower et al., 1991) most of the hippocampus, including the head and the anterior portion of the body, were removed, confirming the view that the integrity of the hippocampus proper seems to be crucial for intact explicit memory functions (see also Zola-Morgan and Squire, 1986).

In conclusion, the absence of ERP old/new effects during visual recognition memory in ischaemic–hypoxic patients suggests that one functional locus of memory impairments in these patients is on the level of consciously accessing memory-stored information from earlier study episodes. Practice-related changes in recognition memory performance, indicative of implicit memory processes that occur without awareness, are similar to those observed in controls and thus appear to be spared after ischaemic–hypoxic encephalopathy. In the light of their similarity to selective memory disorders after focal damage to the mediobasal temporal lobes (Squire and Cohen, 1984) or the hippocampus proper (Zola-Morgan et al., 1986), the present results support the view that ERP old/new effects can be considered as an index of the explicit memory processes mediated by mediobasal temporal structures.

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