Brain correlates of functional retrograde amnesia in three patients

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Functional retrograde amnesia was studied with fMRI in three patients without structural brain damage. A paradigm was applied contrasting true and fictitious episodes before and after the onset of their amnesias. In all patients, no differential activation was detected contrasting true and fictitious episodes within the amnesic period, while comparing true and fictitious episodes outside the amnesic period revealed distinct and different brain activations. Contrasting true episodes outside and within the amnesic time, patient 1 showed left lateralised temporal activation, while patient 3 demonstrated right inferior frontal activity. In patient 2, there was no differential activity. We assume functional amnesia to be accompanied by deviant brain activation during retrieval of remote episodes. These deviations may reflect neuropsychological and psychiatric background of the amnesic conditions in the studied patients.

Report

Introduction

Retrograde amnesia (RA) is characterised by complete or partial loss of episodic and/or semantic information acquired before a critical incident and is usually accompanied by anterograde amnesia. However, recent case reports demonstrate the eventuality of rather selective or isolated RA. Aetiology independent, RA seems to be particularly vulnerable to psychological or psychiatric processes. In this regard, there have been several cases in whom RA occurred following psychological stress without detectable brain damage. Since in recent times the unequivocal distinction between either organic or psychogenic RA has been discussed controversially (Kopelman, 2000), the term 'functional RA' may be applied to all patients in whom RA symptoms occur without corresponding structural brain damage. In brain imaging studies of functional RA, functional/metabolic disturbances have been detected in some cases while in others no dysfunctions have been observed. Only very few single case studies concentrated directly on functional brain correlates during the retrieval of the lost remote memories in patients with functional RA. The aim of the current study was to elucidate and compare functional brain correlates of episodic remote memory retrieval in three patients with functional RA using fMRI. Thus, in three functional RA-patients blood-oxygen-level-dependent (BOLD) contrasts were compared during the retrieval of true and fictitious episodes within and outside the amnesic time periods.

Subjects

All patients (patient 1: female, 17 years; patient 2: male, 30 years; patient 3: male, 33 years) experienced mild head trauma and a short period of unconsciousness after a fall to the head without sustaining structural brain damage. Since these instances, profound retrograde amnesia started. While the amnesia covered the whole life of patient 1 and patient 2, patient 3 was amnesic only for the 14 years preceding his accident. FDG-PET was administered to patient 2 and patient 3 and revealed no abnormalities in patient 2, while significant cerebellar hypometabolism was observed in patient 3. In search of psychological triggers of the amnesia, definite stressors were found in patient 1. In the preceding year there were four committed suicides in her circle of friends, and she suffered from major depression which recovered due to the amnesia. Medical history of patient 2 revealed two instances in which he previously had developed conversion-like symptoms following head trauma without brain damage. In patient 3, no comparable triggers or precursors were found.

All patients underwent extensive neuropsychological examination comprising intelligence, attention, anterograde memory, executive functions, emotional processing, psychiatric symptoms, and personality. Retrograde memory was assessed by neuropsychological tests for remote episodic and semantic memory. In summary, all patients had episodic RA, while patient 2 and patient 3 showed also semantic retrieval deficits. Additional to their RA, all patients showed mild attentional and working memory deficits. Furthermore, patient 2 had also mild executive and anterograde learning problems. Additional neuropsychological deficits were clearly disproportionate to the profound and extensive RA.

Methods

Stimuli were acquired by interviewing the patients' relatives, who were asked to describe episodes of the patients from the time preceding onset of the amnesia (last 5–10 years) and from the time after onset. By this procedure, 10 true old episodes and 10 true new episodes were collected for each patient. Furthermore, 10 fictitious old and 10 fictitious new highly realistic episodes were composed with the help of the patients' relatives. Six non-identical stimulus sentences were constructed for each true and fictitious episode, resulting in 60 individual sentences per condition. This material (240 sentences per patient) was visually presented during the fMRI scan. The sessions were conducted 12 months (patient 1, patient 2) or 6 months (patient 3) after the incident. Prior to participation written informed consent was obtained from all patients, and they were informed that fictitious episodes would be presented to them as well. Presentation and timing of stimuli was accomplished using Presentation (Neurobehavioral Systems, San Francisco, USA). Six individual trials of one of the four conditions were blocked together (SOT = 5.17s, ISI = 1.5s, 1 block = 40.02s) to evoke neural responses associated with retrieval attempt of true old (TO), true new (TN), fictitious old (FO), and fictitious new (FN) episodes. Conditions were separated from each other by low-level baselines (each lasting 16 s), during which identical retrieval instructions for the next block of trials were shown. Scanning was performed using a 1.5 T whole-body scanner (Siemens Vision, Erlangen) with echo-planar imaging (EPI) capability. Functional MR images were acquired in axial plane with gradient-echo EPI pulse sequence using BOLD contrast (TE = 66 ms, TR = 4 s, flip angle = 90°, slice thickness = 4 mm, inter-slice-gap = 0.4 mm, FOV = 200 mm, in plane resolution = 3.125 mm x 3.125 mm, matrix = 64 x 64, 30 transversal slices). Statistical analyses were performed with SPM99 (p < 0.05, corrected). Coordinates of pixels showing local maximum activation were determined within areas of significant relative changes in neural activity associated with the demands of the different conditions. These local maxima were anatomically localised with reference to the standard Talairach and Tournoux stereotactic atlas.

Results

Significant increases in neural activity (p < 0.05, corrected) related to all true memory conditions (TO and TN) relative to baselines were observed in all patients bilaterally in lateral temporal cortex.
dorsal-occipital cortex extending into fusiform gyrus, superior parietal cortex, cerebellum, and prefrontal cortex. In patient 1 and patient 2, there was additional activation bilaterally in temporal–frontal junction area. Furthermore, patient 1 showed additional activation of anterior cingulate and posterior cingulate/retrosplenial cortex. Patient 2 displayed additionalthalamic activation.

Comparing conditions revealed significant ($p < .05$) activation in contrasts TO>TN, TN>TO, TN>FN, and FN>TN. Contrasting true episodes within the amnesic period with those outside (TO>TN) revealed left lateralised activation of superior temporal/parietal brain regions (supramarginal gyrus, angular gyrus) in patient 1. In patient 2, no significant activation was detected. Patient 3 showed activation of mainly right hemispheric regions in inferior and medial prefrontal cortex. The reversed contrast (TN>TO) revealed fusiform activation in patient 3 only.

Contrasting true and fictitious episodes after the onset of the amnesia revealed activation in contrast TN>FN in all patients. Patient 1 showed significant left hemispheric activation in the middle temporal, inferior parietal, and parahippocampal region, as well as bilateral cerebellar and fusiform activation. Patient 2 showed right hemispheric activity in inferior cortex. Anterior cingulate activation was detected in patient 3, though not significant ($p = .106$ corrected). The reversed contrast (FN>TN) revealed left lateralised activation in patient 1 comprising lateral temporal regions as well inferior and medial prefrontal activation in patient 2. No significant activation was found in patient 3.

**Discussion**

The areas activated by all memory conditions compared to baseline correspond to networks supporting episodic memory retrieval (cf. Pieffe, Weiss, Zilles, Markowitsch, & Fink, in press). However, no medial temporal (e.g., hippocampal) activation was detected possibly reflecting partly disturbed retrieval processes in the patients. In patient 1, retrieval of true episodes within the amnesic period evoked a clearly left lateralised activation of supramarginal and angular gyrus which might reflect a language associated, semantic processing of these episodes, resembling a previously studied patient suffering from dissociative amnesia (Markowitsch, Fink, Thöne, Kessler, & Heiss, 1997). Processing true episodes of the non-amnesic time however, evoked additional parahippocampal and more bilateral activation in patient 1. It can be hypothesised that she treated old autobiographical episodes in a more language-oriented and emotional (“semantic”) way compared to episodes from the non-amnesic time.

In patient 2, differential activation between conditions was found only within the non-amnesic period. Here, retrieval of true compared to fictitious episodes was associated with right insular activation possibly reflecting emotional recall during demanding emotional retrieval tasks (Phan, Wager, Taylor, & Liberzon, 2002). In contrast, fictitious compared to true episodes evoked left hemispheric inferior and medial prefrontal activation reflecting evaluative and attentional processes or effortless retrieval attempt rather than actual retrieval success.

Comparable regions were activated in the right hemisphere in patient 3 during retrieval of true episodes within the amnesic period compared to the non-amnesic time. Also here, the attempt to retrieve autobiographical episodes may have contributed to the inferior and medial prefrontal activation whereas the lateralisation to the right hemisphere may be associated with episodic retrieval mode. Additional activity in fusiform region was detected in the reversed contrast which may be related to higher imagery of newly experienced and recallable events.

One of the main results concerns the absence of differential activation contrasting fictitious and true episodes for the amnesic time period in all patients. This may reflect a possible neuronal correlate of the functional retrieval deficit seen on the behavioural level. Besides possible differences in the clinical picture in patients with RA, we conclude that functional RA can be the cause or the effect of the observed functional/metabolic disturbances during episodic memory retrieval or even both.

**References**


