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Functional brain imaging in 14 patients with dissociative amnesia reveals right inferolateral prefrontal hypometabolism

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ABSTRACT

Dissociative amnesia is a condition usually characterized by severely impaired retrograde memory functioning in the absence of structural brain damage. Recent case studies nevertheless found functional brain changes in patients suffering from autobiographical–episodic memory loss in the cause of dissociative amnesia. Functional changes were demonstrated in both resting state and memory retrieval conditions. In addition, some but not all cases also showed other neuropsychological impairments beyond retrograde memory deficits. However, there is no group study available that examined potential functional brain abnormalities and accompanying neuropsychological deteriorations in larger samples of patients with dissociative retrograde amnesia. We report functional imaging and neuropsychological data acquired in 14 patients with dissociative amnesia following stressful or traumatic events. All patients suffered from autobiographical memory loss. In addition, approximately half of the patients had deficits in anterograde memory and executive functioning. Accompanying functional brain changes were measured by [^{18}F] fluorodeoxyglucose positron emission tomography (FDG-PET). Regional glucose utilization of the patients was compared with that of 19 healthy subjects, matched for age and gender. We found significantly decreased glucose utilization in the right inferolateral prefrontal cortex in the patients. Hypometabolism in this brain region, known to be involved in retrieval of autobiographical memories and self-referential processing, may be a functional brain correlate of dissociative amnesia.

1. Introduction

Dissociative amnesia is a condition usually characterized by severely impaired retrograde memory functioning in the absence of overt brain damage or a known neurological etiology. The amnesic state, also known as "functional" or "psychogenic" amnesia, mainly comprises deficits in retrieving autobiographical–episodic memories (Markowitsch, 2003) (personal context-based events) and – in the majority of cases to a lesser degree – autobiographical–semantic (personal non-context-based facts) and general semantic knowledge (facts) (Brandt and van Gorp, 2006). In addition, anterograde memory impairments accompanying retrograde amnesia are described in some (Markowitsch et al., 1998; Kritchevsky et al., 2004) but not in the majority of the cases (De Renzi et al., 1997; Glisky et al., 2004). Although very rare, anterograde amnesia with preserved retrograde memory can also be a consequence of psychological stress or trauma (Markowitsch et al., 1999a; Kumar et al., 2007).

Beyond the neuropsychological variability in patients with dissociative amnesia, it is still unclear whether or not functional brain abnormalities typically occur in these patients (see the review by Reinhold et al., 2006). In some patients task-specific (e.g., during retrieval attempt) functional brain changes, mainly within limbic and prefrontal regions, have been demonstrated (Markowitsch et al., 1997; Yasuno et al., 2000; Fujiwara et al., 2004).

Patients suffering from autobiographical–episodic memory loss may also exhibit more general or non-task-specific functional abnormalities within the prefrontal cortex, especially in the right hemisphere. The right prefrontal cortex is critically involved in synchronizing emotional and factual components of personal events so that they can be successfully retrieved with a sense of self-awareness (Tulving, 2002; Keenan et al., 2003; Wheeler and Stuss, 2003). Support for this hypothesis comes from previous patient data (Piolino et al., 2005) and neuroimaging investigations of autobiographical- episodic memory retrieval in healthy individuals (Tulving et al., 1994; Cabeza and Nyberg, 2000; Markowitsch et al.,

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Table 1
Summary of the patients' characteristics.

	AA	BB	CC	DD	EE	FF	GG	HH	II	JJ	KK	LL	MM	NN
Age	23	24	25	29	30	34	33	35	35	39	46	50	54	54
Gender	m	m	f	f	m	m	m	m	f	m	m	m	m	m
Education (years)	9	10	12	13	12	10	10	9	10	13	13	13	13	9
Family background	Partner, one child (from his girlfriend)	Partner	Single	Partner	Married, one child	Partner, two children	Married, no children	Married, two children	Partner	Married, one child (from his wife)	Married, no children	Divorced, new partnership (for 10 years), two children	Single	Married, two children, NN was adopted at very young age
Psychiatry history/somatic complaints	Headache, migraine (for two years)	No	No	No	Closed head injury with headache, ataxia, right arm hemi-paresis (eight years before), diagnosis of conversion hysteria (seven years before) with recovery from symptoms. Diffuse abdominal and chest pain without organic causation	No	No	Arrested because of two rapes (20 years ago), motor symptoms indicating potential mild apoplexy without structural verification (10 years ago and quick recovery)	No	No	No	Hypothyroidism	Episode of diss. amnesia two years ago (full recovery)	No
Stressful events/ circumstances	Unknown	Conflicts with mother	Stress at work	No	Stress at work	A lot of work	No	Accusation because of sexual duress	Stress with her partner, conflicts with her parents	Bullying at work, wife had problems with alcohol	No	Stress at work (bullying)	Unknown	Bullying at work
Critical incident	Car accident	Fire in his house	Sudden unconsciousness in the shower	Sudden unconsciousness while in the shower with her partner	Car accident during a foreign assignment	Fall from roof	Went unconscious for unknown reasons during a morning shower	Notification of accusation	Fall from staircase	Wife announced divorce, thereafter on the way to work by car he had hallucination about his wife lying in a puddle of blood	Fall from staircase	Fall from staircase	Unknown	Request of pay raise had been rejected
Amnesia type	Diss. amnesia	Diss. amnesia	Diss. amnesia	Diss. amnesia	Diss. amnesia	Diss. amnesia	Diss. amnesia	Diss. amnesia	Diss. amnesia	Diss. amnesia	Diss. amnesia	Diss. amnesia	Diss. fugue (two days)	Diss. amnesia
Amnesic time period	Whole life-span	Last six years	Last six months	Last two days	Whole life-span	Whole life-span	Last 12 years	Whole life-span	Last 15 years	Last 19 years	Whole life-span	Whole life-span	Last 34 years	Last two weeks

Abbreviation: diss. amnesia = dissociative amnesia. diss. fugue = dissociative fugue.

2003; Piefke et al., 2003). In accordance with the aforementioned hypothesis, in the case of a patient with dissociative retrograde amnesia (Piolino et al., 2005), the right ventrolateral/inferolateral prefrontal cortex was hypometabolic as shown in a resting state positron emission tomography (PET) investigation. Furthermore, autobiographical memory retrieval requires considerable self-referential processing (Tulving, 2002). Given that the prefrontal cortex is strongly involved in processing information related to one's own self (Johnson et al., 2002; Northoff et al., 2006), both the medial and the lateral prefrontal cortex play sections play crucial roles in autobiographical memory retrieval in healthy individuals.

On the basis of these findings, we hypothesized functional alterations in the prefrontal cortex of patients with dissociative amnesia. To the best of our knowledge, there is no group study available that examined potential functional brain abnormalities in larger samples of patients with dissociative amnesia. In addition, it is also unclear whether or not patients with this condition also suffer from anterograde memory deficits and other neuropsychological impairments. Therefore, we present a multi-case study of dissociative amnesia patients comprising both, functional neuroimaging and neuropsychological data. We examined a sample of 14 amnesic patients without structural brain damage with various neuropsychological tasks and resting state [^{18}F]fluorodeoxyglucose PET (FDG-PET) and compared their neuroimaging results with those of 19 healthy individuals without memory problems.

2. Methods

2.1. Participants

Participants comprised 14 patients (11 males) with the diagnosis of dissociative amnesia (DSM-IV, American Psychiatric Association, 1994). The patients' mean age was 36.57 years (S.D. = 10.66). The data were collected over the last 10 years. The patients were diagnosed by neurologists and psychiatrists after extensive neurological and psychological–psychiatric investigation. Other main diagnoses (axis 1) were excluded (posttraumatic stress disorder, major depression, schizophrenia, substance abuse or addiction). Previous or current neurological diseases (tumor, neurodegenerative diseases) were also exclusion criteria. However, co-morbid personality changes or previous dissociative symptoms (conversion-like symptoms or previous signs of dissociative amnesia), as well as somatic symptoms (migraine, headache, chest pain), did not lead to exclusion from the study. In addition, all subjects were extensively interviewed (in accordance with the German version of the Structured Clinical Interview for DSM-IV; First et al., 2002) and examined with several retrograde memory tasks (see Section 2.3) by the authors of this study (MB, NR, EF or HJM) in order to confirm the diagnosis of retrograde amnesia and to exclude potential other axis 1 diagnoses. Signs of dissociative identity disorder have also been assessed. No patient fulfilled the diagnostic criteria for dissociative identity disorder. In all patients, standard structural brain imaging (computed tomography or magnetic resonance imaging) did not reveal any signs of abnormalities. Standard neurological examinations and all laboratory tests were normal in all patients included in the study. The FDG-PET examination was conducted between 2 weeks and 6 months after the amnesia onset. Note that within this time window, none of the patients had recovered from amnesia. Information about the patients' sociodemographic and psychiatric background, including information about previously experienced stress and the type of critical incident before onset of amnesia, are shown in Table 1.

The control group for the PET analyses consisted of 19 healthy individuals (13 males) without previous or current neurological or psychiatric conditions. The control subjects were examined medically in order to exclude any participant with current or history of neurological or psychiatric disease. All participants gave written informed consent prior to the investigation. The control subjects' mean age was 45.32 years (S.D. = 13.2). The patients did not differ from the control subjects regarding age ($t = -2.03$, $df = 31$, $P > 0.05$) and gender ($Chi^2 = 0.419$, $df = 1$, $P > 0.05$). Note that the control subjects' mean age was slightly but not significantly higher than the patients' mean age. Potential age-related metabolic reductions would thus be in favor of the slightly younger patient group. Individual metabolic rates in each patient were also compared with a larger age-matched and standardized norm group (see description of the TSI method in Section 2.2).

Three patients enrolled in the current study have been published in previous articles. Case BB has been described as AMN in Markowitsch et al. (1998). Patients EE and GG are reported in Fujiwara et al. (2008) as cases CD and EF. All other patients have not been described in previous publications.

2.2. Positron emission tomography investigation

We measured regional cerebral metabolic rate for glucose using [^{18}F]fluorodeoxyglucose (FDG) PET and a high-resolution PET scanner. The scans were performed after overnight fasting on three different types of scanners: three patients on a ECAT EXACT-scanner with 47 transaxial image planes with a voxel size of 3.75 mm (Siemens CTI,

Table 2
Summary of the patients' performance in the neuropsychological tasks.

	AA	BB	CC	DD	EE	FF	GG	HH	II	JJ	KK	LL	MM	NN
Retrograde memory[a]														
Autobiographical														
Episodic	– –	– –	–	– –	– –	–	–	–	–	–	–	– –	–	– –
Semantic	–	–	0	0	–	–	0	–	–	0	0	–	–	0
General semantic	–	–	0	0	–	–	0	–	–	0	+	–	–	0
Anterograde memory														
Verbal	–	–	– –	– –	0	0	+	– –	– –	0	–	0	0	+
Figural	–	–	–	– –	–	0	+	– –	–	0	0	+	0	+
Intelligence	0	0	+	+	0	0	0	–	–	0	+	0	0	+
Working memory														
Verbal	–	–	0	+	0	0	0	–	–	0	–	0	–	+
Visuo-spatial	–	–	0	+	–	0	0	–	–	0	–	0	–	0
Attention and concentration	–	–	0	+	0	0	–	–	–	0	0	0	0	+
Executive functions														
Flexibility	–	– –	0	+	–	0	0	– –	– –	0	–	0	–	+
Problem solving	0	–	0	+	–	0	0	– –	–	0	–	0	0	+

+ = above average (above 1 S.D. from normal performance); 0 = average (within 1 S.D. of the norm group's mean); – = lower than average (outside 1 S.D. from normal performance); – – = impaired (outside 2 S.D. from normal performance).

[a] Retrograde memory performance refers to retrieval of information formerly acquired within the amnesic time period.

Knoxville, TN, USA), four patients on an ECAT EXACT HR-scanner with 47 transaxial image planes with a voxel size of 3.125 mm (Siemens CTI, Knoxville, TN, USA) and seven patients on a high-resolution scanner with 207 transaxial image planes with a voxel size of 1.219 mm (ECAT HRRT, Siemens CTI, Knoxville, TN, USA). The scans of the healthy control group were originally acquired at eight centers, with PET scanners that differed slightly with respect to field of view and spatial resolution. Thus, original images were not comparable. Due to pre-smoothing and normalization before statistical analyses, images had the best possible contrastable image quality. Cerebral metabolism was assessed after intravenous injection of 185–370 MBq. The investigations were conducted in a resting state with eyes closed and ears unplugged in a room with dimmed light and low background noise. Subjects were instructed to be relaxed and to not think about specific issues. Data were acquired in a 3-D mode, subsequently reconstructed, including a correction for random coincidences, attenuation, and scatter. All images from both the patients and the healthy control subjects were processed on a voxel-by-voxel basis using Statistical Parametric Mapping (SPM99, The Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB 6.1 (Mathworks, Sherborn, MA, USA). All scans were smoothed by a Gaussian filter of 8 mm FWHM. The images were subsequently spatially normalized to a standard stereotactic space by affine 12-parameter transformation using the SPM-99 standard brain template. For a general overview of patients and control subjects, each single image was achieved using the TSI tool (according to the method established by Herholz et al., 2002), which reveals statistically significant hypometabolic regions compared with age-matched normal controls. Significant regions are indicated on an MRI template with Talairach brain coordinates; cluster size and significance are shown separately. The TSI method is a diagnostic indicator to reveal FDG-PET scan abnormality, based on age-adjusted *t*-statistics and an automated voxel-based procedure that compares the individual FDG-PET results with those of a large data set comprising 110 normal controls. The TSI method was preferred to an individual SPM-statistic for reasons of a larger, standardized norm group.

2.3. Neuropsychological test battery and psychological–psychiatric inventories

In addition to the functional imaging investigation, an extensive neuropsychological test battery was conducted with each patient assessing intelligence, verbal and figural anterograde memory, attention, and executive functions. However, as this was a multi-center study, we unfortunately did not administer the same tests to all patients. Table 2 summarizes performance levels of the patients. Main functions were assessed by standard neuropsychological tasks, such as the Wechsler Memory Scale, the Rey-Osterrieth Complex Figure, the Modified Card Sorting Test, the Trail-Making Test, and verbal fluency (tests are described elsewhere, e.g., Lezak et al., 2004; Strauss et al., 2006). Personality and psychiatric symptoms were measured with standardized questionnaires: Freiburg Personality Inventory (Fahrenberg et al., 2001), the Beck Depression Inventory (BDI) (Hautzinger et al., 1995) and the Symptom Check List (SCL-90-R) (Franke, 2002).

Retrograde memory was assessed with tests measuring autobiographical–episodic, autobiographical–semantic and general semantic remote memory. Episodic remote memory was assessed by the Bielefeld Autobiographical Memory Inventory developed on the basis of the Autobiographical Memory Interview (Kopelman, 1990). This inventory consists of a semi-structured interview assessing memory for facts and incidents from the subjects' life regarding specific time periods (see also Fujiwara et al., 2008). Time periods of 0–5 years of age, 6–10 years, 11–17/18 years, 19–30 years and 31 years to onset of amnesia were tested (note that in patients younger than 31 years, the last part was not applied). In the five patients who were older than 36 years at the time of the examination, two additional time periods were tested (last 5 and last 10 years). Subjects were required to provide five autobiographical facts, two autobiographical episodes and additional details on one out of the two episodes per time period tested. Here, patients were asked to rate how imaginable and vivid the memory was, and they were asked to recall the specific context surrounding the episode (e.g., the weather, the temperature, the events before and after the specific episode and so on). To cue specific episodes, a list of generic events (e.g., "first kiss", "vacation", and "first day at school") was shown as a retrieval aid. Results were corrected for facts or events that were re-learned after onset of amnesia and these re-learning instances were validated by the patients' relatives.

Semantic remote memory was tested by a Famous Events Test adapted from Leplow and Dierks (1997) and ad hoc designed tasks (Famous Names and Current Words Tests) which have previously been used in another study on retrograde memory by Fujiwara et al. (2008). In the Famous Events Test, patients were given verbal descriptions of 24 public events (e.g., "In which city did Lady Diana die?") that had happened between 1980 and 2001. Subjects were asked to freely recall

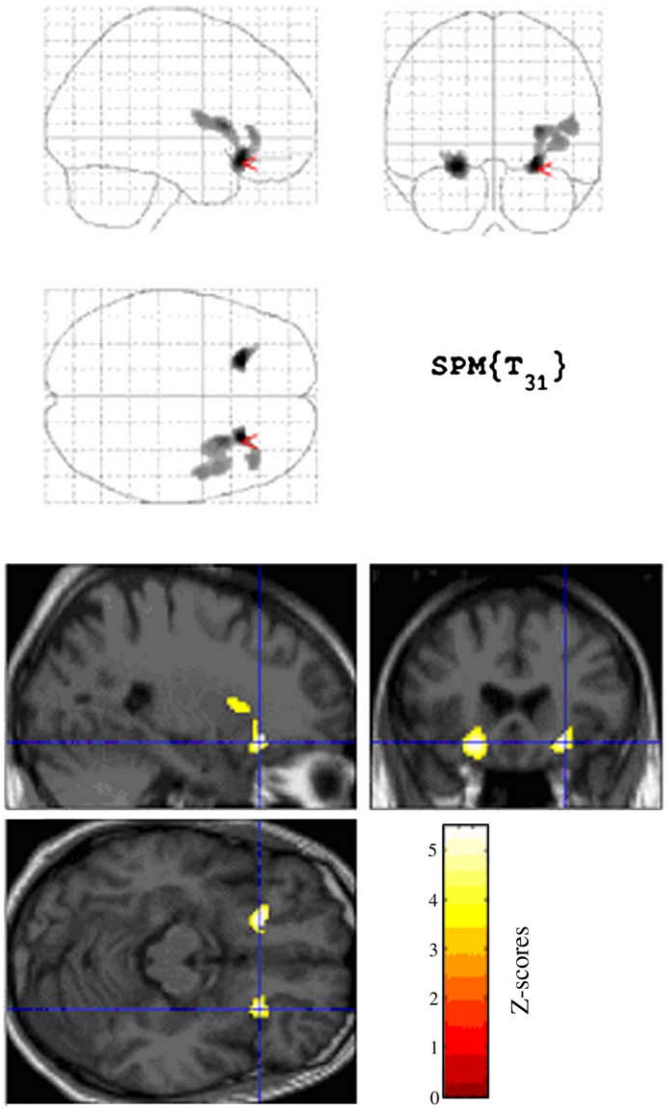

Fig. 1. Relative decreases in regional cerebral glucose metabolism in 24 patients with dissociative amnesia relative to 19 control subjects (sagittal, frontal and horizontal views as "glass brains" and superimposed on magnetic resonance imaging sections, MRI template). The cross indicates the locus of the only significantly deactivated spot in the right inferolateral prefrontal cortex ($P_{corrected}<0.001$, $x=26$ mm, $y=24$ mm, $z=-14$ mm). The homologous hypometabolic region within the left inferolateral prefrontal cortex failed to reach significance ($P_{corrected}=0.083$, $x=-22$ mm, $y=24$ mm, $z=-14$ mm).

the facts. In case they could not answer the specific questions, they were shown five potential answers and were asked to choose the correct one (multiple choice paradigm). The Famous Names Test consists of a total of 20 blocks of names each having five names. One of the five names per block is a famous person (from different categories such as sports, politics, or show business); the other four names per block are fictitious. The patients were asked to choose the famous name. They were also asked to provide any additional information about the famous person (e.g., profession). In the Current Words Test, 25 words that became common during roughly the last three decades (e.g., "Taliban", "www") were successively presented to the patients and they were asked to explain the meaning of the words.

In all tests, results were corrected for self-reported re-learned items after onset of amnesia. These re-learning instances were also validated by the patients' relatives. Further details on the tasks can be found in Fujiwara et al. (2008).

2.4. Statistical analyses

The patients' and the control subjects' age was compared by a two-sample *t*-test. Gender distribution in the two groups was analyzed using Chi^2-test. Both behavioral analyses were conducted with SPSS 12.0 for Windows (Chicago, SPSS Inc.). Patients' performance in the neuropsychological tasks was compared with norm group data and was rated as lower than average if a patient's score was outside the range of 1 standard deviation and rated as impaired if a patient's score was outside of 2 standard deviations from the normal population's scores (see Table 2). We used the two-sample *t*-test option in SPM99 for the analysis of regionally specific glucose utilization in the patients compared with the control subjects. The brain data of all patients were compared with the healthy subjects at each voxel for either hypometabolic or hypermetabolic regions. Potential regional hypermetabolism was also analyzed because previous studies showed that some circumstances (e.g., HPA axis hyperactivity) may result in hypermetabolism in prefrontal and limbic regions (Aihara et al., 2007). Therefore, we aimed to test functional brain changes in both directions: hypo- and hypermetabolism. The threshold *P*-level was 0.001 (corrected). A correction for multiple comparisons as implemented in SPM99 was done.

3. Results

Comparing regional glucose utilization as measured by FDG-PET revealed only one significant group difference between patients and control subjects ($P_{corrected}<0.001$, cluster level; cluster size: 441, $z=5.43$), namely a metabolic reduction in the right inferolateral prefrontal cortex in the patient group (at Talairach coordinates $x=26$ mm, $y=24$ mm, $z=-14$ mm, Fig. 1). This metabolic decrease in the right inferolateral prefrontal cortex was significant individually in 10 of the 14 patients as revealed by a case-by-case analysis (on the basis of the TSI normalization; see Section 2.2). Further individual reductions of metabolic rates were within the left supramarginal gyrus (four patients), bilateral orbitofrontal cortex (two patients), left insula (two patients), left hippocampus and left cingulate gyrus (two patients), left superior temporal gyrus (two patients), and cerebellum, left posterior cingulate gyrus, left medial frontal gyrus and right superior temporal gyrus in one patient, respectively. Compared with the control group and the healthy subjects (TSI method), respectively, hypermetabolic regions in the patients were found neither in the group analysis nor in the case-by-case analysis.

The results of the neuropsychological test battery are shown in Table 2. In summary, all patients had severe autobiographical–episodic memory deficits covering either the whole life-span (in six patients) or ranging from the last 2 days to the last 34 years prior to the critical incident. Autobiographical–semantic memory was reduced in eight patients. However, in all of these subjects, the autobiographical–episodic memory deficits were more prominent than the autobiographical–semantic impairments. In general semantic memory, eight patients had moderate difficulties in at least one of the administered tasks. In additional neuropsychological tasks, six patients showed deficits or lower performance than average in both verbal as well as figural anterograde memory. Two further patients had either verbal or figural anterograde memory impairments or lower performance than average, respectively. Executive functioning was reduced in seven patients (four patients had scores lower than average, three patients performed outside of 2 standard deviations). In the personality and psychiatric screenings, 10 patients showed abnormalities in at least two assessed domains, most frequently lower scores on the "openness" scale (nine patients). Eight patients reported depressive symptoms in the depression questionnaire (without having the diagnosis of major depression according to DSM-IV) and six patients showed signs of additional psychiatric symptoms as indicated by a high general index score in the administered psychiatric screening inventory.

4. Discussion

4.1. General considerations

This is the first study that revealed functional brain changes in a relatively large sample of patients with dissociative amnesia. The main result is that in the absence of structural alterations in all 14 patients, functional brain changes in the right inferolateral prefrontal cortex accompanied this amnesic syndrome dominated by severe autobiographical–episodic memory deficits.

The localization of the hypometabolism in the right inferolateral prefrontal cortex across cases is an interesting finding. It emphasizes and expands previous reports on the right prefrontal cortex as an essential structure for triggering information related to the self and that its malfunction may disrupt access to self-related memories. It is known that the (right) prefrontal cortex is associated with the evaluation of one's own self (Schmitz et al., 2004; Schmitz and Johnson, 2006), self-regulatory processes (Declerck et al., 2006; Marsh et al., 2006), emotion regulation (Phillips et al., 2003), and the discrimination between lies and truth (Langleben et al., 2005). Furthermore, the inferolateral region is linked to retrieval of emotional autobiographical content with a predominance for negative or sad events (Markowitsch et al., 2003). Its role in emotional memory is supported by the strong interconnections between the inferolateral prefrontal section and the amygdala, a structure critically involved in processing emotionally loaded memories (McGaugh, 2005, 2006). The inferolateral prefrontal region is also engaged in higher order control mechanisms and active memory retrieval (Kostopoulos and Petrides, 2003). In accordance with the aforementioned findings, we suggest that in patients with dissociative amnesia, a consistent malfunction in this brain region indicates that stress- or trauma-related experiences may deactivate the right prefrontal cortex and thereby inactivate trigger signals that are necessary for synchronizing limbic and neocortical structures for reinstating engrams of personal relevance.

Beyond this, the (primarily right-sided) inferolateral prefrontal cortex supports functioning of the dorsolateral section, which is linked to executive components (Brand et al., 2004; Lie et al., 2006; Vanderhasselt et al., 2006), working memory (Hillary et al., 2006), and memory organization (Ptak and Schnider, 2004). All the aforementioned functions constitute important aspects of consciously remembering one's own biography (Conway and Pleydell-Pearce, 2000; Kopelman, 2000; Kopelman and Kapur, 2001; Tulving, 2002). This means that in patients with dissociative amnesia, hypometabolism within the inferolateral prefrontal cortex may indirectly compromise executive functioning that can also be linked to retrieval deficits, as proposed by Kopelman (2000).

In addition to these prefrontal cortex functions, the locus of hypometabolism found in our patients is comparable to the results in

the single case reported by Piolino et al. (2005). The result that this frontal section is hypometabolic even in a resting state condition in the absence of a memory retrieval task supports the view of fundamental brain dysfunction in patients with dissociative amnesia. Furthermore, it is also comparable with the region of damage or dysfunctions in patients suffering from retrograde amnesia of organic origin (Costello et al., 1998; Levine et al., 1998). These convergent findings emphasize the crucial role of the right inferolateral prefrontal cortex in retrieving remote autobiographical information. They also point to possible similarities between organic and dissociative amnesias (Markowitsch, 1996a,b; Markowitsch et al., 1999b) meaning that even in patients without structural brain damage functional brain alterations accompany the amnesic syndrome. The functional changes may be comparable to functional imaging findings in patients with retrograde amnesia of organic causation, such as caused by hypoxia (Markowitsch et al., 1998).

As proposed by Piolino et al. (2005) and Costello et al. (1998), the right inferolateral prefrontal cortex may be a crucial node in triggering autobiographical memory retrieval in patients with dissociative amnesia. One might argue that these patients suppress unwanted memories rather than that they suffer from a retrieval deficit. However, as shown by Anderson et al. (2004), motivated forgetting of memories seems to be associated with activation of the dorsolateral prefrontal cortex and decreased activity in the right hippocampal formation. Interestingly, we failed to find right-sided hippocampal hypometabolism in our sample of patients in either the group comparison or the individual analyses. Note that we only found a decreased metabolic rate in the left hippocampus in two patients. Therefore, we suggest that retrieval deficits in patients with dissociative amnesia are related to stress-associated dysfunctions in the inferolateral prefrontal section rather than to active and motivated forgetting of memories.

One has to mention that functional abnormalities of inferolateral prefrontal regions are also found in psychiatric diseases besides dissociative amnesia. For instance, functional abnormalities in prefrontal sections have been reported in patients with depression (Brooks et al., 2009) and schizophrenia (Horacek et al., 2006). Thus, inferolateral prefrontal hypometabolism is not necessarily a specific neural correlate of dissociative amnesia. Interestingly, however, patients with depression and schizophrenia also frequently suffer from autobiographical memory abnormalities (Corcoran and Frith, 2003; Danion et al., 2007; Warren and Haslam, 2007). Thus, functional abnormalities of the inferolateral prefrontal cortex may be a main correlate of autobiographical memory dysfunctions, which are most pronounced in the condition of dissociative amnesia and dissociative fugue.

Future studies may also compare neural correlates of dissociative amnesia with those of other types of dissociation, because there are current studies on the neural bases of dissociation, such as out-of-body experience (e.g., Blanke et al., 2004; Bünning and Blanke, 2005), depersonalization (e.g., Lemche et al., 2007), and dissociative identity disorder (e.g., Reinders et al., 2003; Reinders, 2008). Comparing potential functional brain abnormalities across different forms of dissociation may contribute to a better understanding of the nature and origin of dissociative symptoms.

We would also like to comment briefly on the additional hypometabolic regions found in the individual case analyses (TSI method). For instance, in two patients we found hypometabolic rates in the orbitofrontal cortex bilaterally. The orbitofrontal cortex is known to be critically involved in memory retrieval whenever the information recalled is emotionally colored (Brand and Markowitsch, 2006), which is particularly the case in autobiographical memory retrieval (Markowitsch et al., 2003). Furthermore, left insula, left hippocampal formation and left cingulate gyrus were hypometabolic in two patients. These structures are also part of limbic circuits that are engaged in episodic memory encoding and retrieval (Markowitsch, 2000; Cabeza and St Jacques, 2007; Daselaar et al., 2008). These additional findings give further support for our suggestion that functional brain changes in dissociative amnesia correspond to the episodic memory pathology.

The result of deficient anterograde memory in some but not in all cases is in accordance with the multi-case study of Kritchevsky et al. (2004) in which five out of nine patients with retrograde amnesia were impaired or performed lower than average in verbal anterograde memory, while four patients performed normally. Other cases and multi-case studies also give evidence for both deteriorated as well as normal anterograde memory (De Renzi et al., 1997; Glisky et al., 2004; Fujiwara et al., 2008). The finding that cognitive flexibility and problem solving were impaired or lower than average in half of the patients studied emphasizes the important role of executive functions in the recall of autobiographical–episodic memories, and – consequently – the relationship between executive problems and dissociative amnesia as proposed by Kopelman (2000) and also shown by Glisky et al. (2004). Note that in our sample the majority of patients with executive functioning lower than average in at least one executive domain (patients AA, EE, KK, and MM) and those with executive dysfunctions (outside of 2 standard deviations, patients BB, HH, and II) had more pronounced retrograde memory deficits than those with normal executive functioning. As the inferolateral prefrontal cortex strongly supports dorsolateral functioning, at least in higher order executive functions necessary for retrieving autobiographical memories, executive dysfunctions and retrieval deficits in patients with dissociative amnesia can co-vary and potentially share a similar neural basis.

4.2. Limitations and conclusions

We would like to mention the following limitations of the current study. First, we did not have the chance to administer the same neuropsychological tasks to all patients. As described in the Sections 1 and 2, the phenomenon of dissociative amnesia is a very rare condition. We collected the data over several years and in collaboration with different clinics. Most of the patients' cognitive functions were assessed at intake and with varying neuropsychological test batteries at the respective hospitals. Therefore, patients were not examined with exactly the same tasks in all cases. Consequently, with the current setup we cannot quantify the exact extent to which the neuropsychological status of the patients co-varied with the imaging findings. A group study with dissociative amnesia patients in which all patients are assessed identically and within a short period of time would certainly be desirable, although this may prove difficult due to the rarity of the syndrome. Secondly, the PET results may have been affected by the time of investigation (2 weeks to 6 months after onset of amnesia). Although we did not find a systematic co-variation between time after onset and PET findings in the case-by-case analyses, we cannot rule out that the findings would have been stronger if the time of the PET investigations had been more consistent across patients. Thirdly, given the fact that half of the patients reported depressive symptoms – but again, without fulfilling the diagnostic criteria for a major depression (cf. Section 2) – we also cannot exclude that the PET findings were also affected by the concomitant depressive mood of some of the patients. On a descriptive level, however, the single case analyses (see Section 3) did not indicate a co-variation between self-reported depressive symptoms and metabolic rate within the inferolateral prefrontal cortex. Nevertheless, the inclusion of a psychiatric comparison group (e.g., patients with depression) in future neuroimaging studies on dissociative amnesia could delineate the brain mechanisms that co-vary specifically with the memory symptoms of dissociative amnesia in contrast to those accompanying mood changes. In addition, it seems worth investigating potential commonalities on both neuropsychological and brain levels between dissociative amnesia and dissociative identity disorder. That comparison would be interesting because previous studies (see the intriguing review by Reinders, 2008) have reported specific structural and functional brain changes in dissociative identity disorder which should be contrasted against those found

in patients with dissociative amnesia (see comments above on other types of dissociative conditions).

Structural damage was excluded by visual inspection of CT or MRI scans of all patients. This measure may further benefit from group-level voxel-wise analyses to discount potential microscopic structural brain damage. Since some of the patients could not be examined with MRI (due to metal implants), unfortunately, such finer-grained structural brain analysis was impossible in the current study. This should be done in future studies whenever possible.

We used two different methods for the comparison of the FDG-PET data but did not correct for partial volume effects in the analyses. The TSI method was published earlier by Herholz et al. (2002) and they did not report any methodological problems with the TSI method in their patient sample due to partial volume effects. The SPM evaluation done in our current study was also not corrected for partial volume effects. However, in the relatively young patient sample, higher atrophy seems to be unlikely. In addition, the localization of the hypometabolism found is not typical for significant partial volume effects. Thus we do not expect a high influence of partial volume effects in our patient group. Finally, we did not assess direct neural correlates of the amnesic symptoms or retrieval attempt, but functional brain abnormalities in a resting state. As pointed out in previous work (e.g., Markowitsch, 2003; Brandt and van Gorp, 2006; Reinhold et al., 2006), one has to consider that the syndrome is inter-individually heterogeneous. Therefore, applying one "standard" activation design for studying neural correlates of retrograde memory functioning in these patients is extremely difficult. For instance, patients in whom the PET investigation was carried out 6 months after onset of amnesia would have re-learned most of their autobiographical "milestones". In these cases, presenting, e.g., sentences describing important autobiographical events – as done in other patients by Fujiwara et al. (2004) – could trigger remembering re-learned events (i.e., confounding possible effects of activation to truly remembered, forgotten and re-learned events). Taken together, it is difficult to develop an activation design applicable to all patients with dissociative amnesia, although in principle this would be ideal. Nevertheless, we think that even though we investigated resting state activity in our patients using PET only, the findings support the main hypotheses on functional brain abnormalities centering on the prefrontal cortex in dissociative amnesia patients.

Considering these important limitations, we nevertheless conclude that malfunction of the inferolateral prefrontal cortex may contribute to the retrieval deficits in patients suffering from retrograde amnesia in the absence of structural brain changes as this region is crucially involved in triggering autobiographical memory retrieval by synchronizing emotional and factual components of the personal past linked to the self.

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References

Aihara, M., Ida, I., Yuuki, N., Oshima, A., Kumano, H., Takahashi, K., Fukuda, M., Oriuchi, N., Endo, K., Matsuda, H., Mikuni, M., 2007. HPA axis dysfunction in unmedicated major depressive disorder and its normalization by pharmacotherapy correlates with alteration of neural activity in prefrontal cortex and limbic/paralimbic regions. Psychiatry Research: Neuroimaging 155, 245–256.

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Author, Washington, DC.

Anderson, M.C., Ochsner, K.N., Kuhl, B., Cooper, J., Robertson, E., Gabrieli, S.W., Glover, G.H., Gabrieli, J.D., 2004. Neural systems underlying the suppression of unwanted memories. Science 303, 232–235.

Blanke, O., Landis, T., Spinelli, L., Seeck, M., 2004. Out-of-body experience and autoscopy of neurological origin. Brain 127, 243–258.

Brand, M., Markowitsch, H.J., 2006. Memory processes and the orbitofrontal cortex. In: Zald, D., Rauch, S. (Eds.), The Orbitofrontal Cortex. Oxford University Press, Oxford, pp. 285–306.

Brand, M., Kalbe, E., Kracht, L.W., Riebel, U., Münch, J., Kessler, J., Markowitsch, H.J., 2004. Organic and psychogenic factors leading to executive dysfunctions in a patient suffering from surgery of a colloid cyst of the Foramen of Monro. Neurocase 10, 420–425.

Brandt, J., van Gorp, W.G., 2006. Functional ("psychogenic") amnesia. Seminars in Neurology 26, 331–340.

Brooks 3rd, J.O., Wang, P.W., Bonner, J.C., Rosen, A.C., Hoblyn, J.C., Hill, S.J., Ketter, T.A., 2009. Decreased prefrontal, anterior cingulate, insula, and ventral striatal metabolism in medication-free depressed outpatients with bipolar disorder. Journal of Psychiatric Research 43, 181–188.

Bünning, S., Blanke, O., 2005. The out-of body experience: precipitating factors and neural correlates. Progress in Brain Research 150, 331–350.

Cabeza, R., Nyberg, L., 2000. Imaging cognition II: an empirical review of 275 PET and fMRI studies. Journal of Cognitive Neuroscience 12, 1–47.

Cabeza, R., St Jacques, P., 2007. Functional neuroimaging of autobiographical memory. Trends in Cognitive Sciences 11, 219–227.

Conway, M.A., Pleydell-Pearce, C.W., 2000. The construction of autobiographical memories in the self-memory system. Psychological Review 107, 261–288.

Corcoran, R., Frith, C.D., 2003. Autobiographical memory and theory of mind: evidence of a relationship in schizophrenia. Psychological Medicine 33, 897–905.

Costello, A., Fletcher, P.C., Dolan, R.J., Frith, C.D., Shallice, T., 1998. The origins of forgetting in a case of isolated retrograde amnesia following a haemorrhage: evidence from functional imaging. Neurocase 4, 437–446.

Danion, J.M., Huron, C., Vidailhet, P., Berna, F., 2007. Functional mechanisms of episodic memory impairment in schizophrenia. Canadian Journal of Psychiatry 52, 693–701.

Daselaar, S.M., Rice, H.J., Greenberg, D.L., Cabeza, R., Labar, K.S., Rubin, D.C., 2008. The spatiotemporal dynamics of autobiographical memory: neural correlates of recall, emotional intensity, and reliving. Cerebral Cortex 18, 217–229.

Declerck, C.H., Boone, C., De Brabander, B., 2006. On feeling in control: a biological theory for individual differences in control perception. Brain and Cognition 62, 143–176.

De Renzi, E., Lucchelli, F., Muggia, S., Spinnler, H., 1997. Is memory without anatomical damage tantamount to a psychogenic deficit? The case of pure retrograde amnesia. Neuropsychologia 35, 781–794.

Fahrenberg, J., Hampel, R., Selg, H., 2001. Das Freiburger Persönlichkeitsinventar (FPI-R). Hogrefe, Göttingen.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 2002. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. (SCID-I/P). Biometrics Research. New York State Psychiatric Institute, New York.

Franke, G.H., 2002. SCL-90-R — Die Symptom-Checkliste von L.R. Derogatis. Beltz Test, Göttingen.

Fujiwara, E., Piefke, M., Lux, S., Fink, G.R., Kessler, J., Kracht, L., Diebel, A., Netz, J., Markowitsch, H., 2004. Brain correlates of functional retrograde amnesia in three patients. Brain and Cognition 54, 135–136.

Fujiwara, E., Brand, M., Kracht, L., Kessler, J., Diebel, A., Netz, J., Markowitsch, H.J., 2008. Functional retrograde amnesia: a multiple case study. Cortex 44, 29–45.

Glisky, E.L., Ryan, L., Reminger, S., Hardt, O., Hayes, S.M., Hupbach, A., 2004. A case of psychogenic fugue: I understand, aber ich verstehe nichts. Neuropsychologia 42, 1132–1147.

Hautzinger, M., Bailer, M., Worall, H., Keller, F., 1995. Beck-Depressions-Inventar (BDI). Hogrefe, Göttingen.

Herholz, K., Salmon, E., Perani, D., Baron, J.C., Holthoff, V., Frolich, L., Schonknecht, P., Ito, K., Mielke, R., Kalbe, E., Zundorf, G., Delbeuck, X., Pelati, O., Anchisi, D., Fazio, F., Kerrouche, N., Desgranges, B., Eustache, F., Beuthien-Baumann, B., Menzel, C., Schroder, J., Kato, T., Arahata, Y., Henze, M., Heiss, W.D., 2002. Discrimination between Alzheimer dementia and controls by automated analysis of multicenter FDG PET. Neuroimage 17, 302–316.

Hillary, F.G., Genova, H.M., Chiaravalloti, N.D., Rypma, B., DeLuca, J., 2006. Prefrontal modulation of working memory performance in brain injury and disease. Human Brain Mapping 27, 837–847.

Horacek, J., Dockery, C., Kopecek, M., Spaniel, F., Novak, T., Tislerova, B., Klirova, M., Palenicek, T., Höschl, C., 2006. Regional brain metabolism as the predictor of performance on the Trail Making Test in schizophrenia. A 18FDG PET covariation study. Neuroendocrinology Letters 27, 587–594.

Johnson, S.C., Baxter, L.C., Wilder, L.S., Pipe, J.G., Heiserman, J.E., Prigatano, G.P., 2002. Neural correlates of self-reflection. Brain 125, 1808–1814.

Keenan, J., Wheeler, M.A., Ewers, M., 2003. The neural correlates of self-awareness and self-recognition. In: Kircher, T., David, A. (Eds.), The Self in Neuroscience and Psychiatry. Cambridge University Press, Cambridge, pp. 166–179.

Kopelman, M.D., 1990. The Autobiographical Memory Interview. Thames Valley Test Company, Bury St. Edmunds.

Kopelman, M.D., 2000. Focal retrograde amnesia and the attribution of causality: an exceptionally critical review. Cognitive Neuropsychology 17, 585–621.

Kopelman, M.D., Kapur, N., 2001. The loss of episodic memories in retrograde amnesia: single case and group studies. Philosophical Transactions of the Royal Society of London — Series B: Biological Sciences 356, 1409–1421.

Kostopoulos, P., Petrides, M., 2003. The mid-ventrolateral prefrontal cortex: insights into its role in memory retrieval. European Journal of Neuroscience 17, 1489–1497.

Kritchevsky, M., Chang, J., Squire, L.R., 2004. Functional amnesia: clinical description and neuropsychological profile of 10 cases. Learning and Memory 11, 213–226.

Kumar, S., Rao, S.L., Sunny, B., Gangadhar, B.N., 2007. Widespread cognitive impairment in psychogenic anterograde amnesia. Psychiatry and Clinical Neurosciences 61, 583–586.

Langleben, D.D., Loughead, J.W., Bilker, W.B., Ruparel, K., Childress, A.R., Busch, S.I., Gur, R.C., 2005. Telling truth from lie in individual subjects with fast event-related fMRI. Human Brain Mapping 26, 262–272.

Lemche, E., Surguladze, S.A., Giampietro, V.P., Anilkumar, A., Brammer, M.J., Sierra, M., Chitnis, X., Williams, S.C., Gasston, D., Joraschky, P., David, A.S., Phillips, M.L., 2007. Limbic and prefrontal responses to facial emotion expressions in depersonalization. Neuroreport 18, 473–477.

Leplow, B., Dierks, C., 1997. Diagnostik des Altgedächtnisses mit der endgültigen Lang- und Kurzform des "Kieler Altgedächtnistests". Diagnostica 43, 192–210.

Levine, B., Black, S.E., Cabeza, R., Sinden, M., Mcintosh, A.R., Toth, J.P., Tulving, E., Stuss, D.T., 1998. Episodic memory and the self in a case of isolated retrograde amnesia. Brain 121, 1951–1973.

Lezak, M.D., Howieson, D.B., Loring, D.W., 2004. Neuropsychological Assessment, 4th ed. Oxford University Press, New York.

Lie, C.H., Specht, K., Marshall, J.C., Fink, G.R., 2006. Using fMRI to decompose the neural processes underlying the Wisconsin Card Sorting Test. Neuroimage 30, 1038–1049.

Markowitsch, H.J., 1996a. Organic and psychogenic retrograde amnesia: two sides of the same coin? Neurocase 2, 357–371.

Markowitsch, H.J., 1996b. Retrograde amnesia: similarities between organic and psychogenic forms. Neurology, Psychiatry and Brain Research 4, 1–8.

Markowitsch, H.J., 2000. The anatomical bases of memory. In: Gazzaniga, M.S. (Ed.), The New Cognitive Neurosciences. The MIT Press, Cambridge, pp. 781–795.

Markowitsch, H.J., 2003. Psychogenic amnesia. Neuroimage 20, S132–S138.

Markowitsch, H.J., Thiel, A., Kessler, J., von Stockhausen, H.-M., Heiss, W.-D., 1997. Ecphorizing semi-conscious episodic information via the right temporopolar cortex — a PET study. Neurocase 3, 445–449.

Markowitsch, H.J., Kessler, J., Van der Ven, C., Weber-Luxenburger, G., Heiss, W.-D., 1998. Psychic trauma causing grossly reduced brain metabolism and cognitive deterioration. Neuropsychologia 36, 77–82.

Markowitsch, H.J., Kessler, J., Kalbe, E., Herholz, K., 1999a. Functional amnesia and memory consolidation. A case of persistent anterograde amnesia with rapid forgetting following whiplash injury. Neurocase 5, 189–200.

Markowitsch, H.J., Kessler, J., Russ, M.O., Frölich, L., Schneider, B., Maurer, K., 1999b. Mnestic block syndrome. Cortex 35, 219–230.

Markowitsch, H.J., Vandekerckhove, M.M., Lanfermann, H., Russ, M.O., 2003. Engagement of lateral and medial prefrontal areas in the ecphory of sad and happy autobiographical memories. Cortex 39, 643–665.

Marsh, R., Zhu, H., Schultz, R.T., Quackenbush, G., Royal, J., Skudlarski, P., Peterson, B.S., 2006. A developmental fMRI study of self-regulatory control. Human Brain Mapping 27, 848–863.

McGaugh, J.L., 2005. Emotional arousal and enhanced amygdala activity: new evidence for the old perseveration–consolidation hypothesis. Learning & Memory 12, 77–79.

McGaugh, J.L., 2006. Make mild moments memorable: add a little arousal. Trends in Cognitive Sciences 10, 345–347.

Northoff, G., Heinzel, A., de Greck, M., Bermpohl, F., Dobrowolny, H., Panksepp, J., 2006. Self-referential processing in our brain—a meta-analysis of imaging studies on the self. Neuroimage 31, 440–457.

Phillips, M.L., Drevets, W.C., Rauch, S.L., Lane, R., 2003. Neurobiology of emotion perception I: the neural basis of normal emotion perception. Biological Psychiatry 54, 504–514.

Piefke, M., Weiss, P.H., Zilles, K., Markowitsch, H.J., Fink, G.R., 2003. Differential remoteness and emotional tone modulate the neural correlates of autobiographical memory. Brain 126, 650–668.

Piolino, P., Hannequin, D., Desgranges, B., Girard, C., Beaunieux, H., Giffard, B., Lebreton, K., Eustache, F., 2005. Right ventral frontal hypometabolism and abnormal sense of self in a case of disproportionate retrograde amnesia. Cognitive Neuropsychology 22, 1005–1034.

Ptak, R., Schnider, A., 2004. Disorganised memory after right dorsolateral prefrontal damage. Neurocase 10, 52–59.

Reinders, A.A.T.S., 2008. Cross-examining dissociative identity disorder: neuroimaging and etiology on trial. Neurocase 14, 44–53.

Reinders, A.A.T.S., Nijenhuis, E.R.S., Paans, A.M.J., Korf, J., Willemsen, A.T.M., den Boer, J.A., 2003. One brain, two selves. Neuroimage 20, 2119–2125.

Reinhold, N., Kühnel, S., Brand, M., Markowitsch, H.J., 2006. Functional brain imaging in memory and memory disorders. Current Medical Imaging Reviews 2, 35–57.

Schmitz, T.W., Johnson, S.C., 2006. Self-appraisal decisions evoke dissociated dorsal–ventral aMPFC networks. Neuroimage 30, 1050–1058.

Schmitz, T.W., Kawahara-Baccus, T.N., Johnson, S.C., 2004. Metacognitive evaluation, self-relevance, and the right prefrontal cortex. Neuroimage 22, 941–947.

Strauss, E., Sherman, E.M.S., Spreen, O., 2006. A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary. Oxford University Press, New York.

Tulving, E., 2002. Episodic memory: from mind to brain. Annual Review of Psychology 53, 1–25.

Tulving, E., Kapur, S., Craik, F.I.M., Moscovitch, M., Houle, S., 1994. Hemispheric encoding/retrieval asymmetry in episodic memory: positron emission tomography findings. Proceedings of the National Academy of Sciences of the United States of America 91, 2016–2020.

Vanderhasselt, M.A., De Raedt, R., Baeken, C., Leyman, L., D'haenen, H., 2006. The influence of rTMS over the right dorsolateral prefrontal cortex on intentional set switching. Experimental Brain Research 172, 561–565.

Warren, Z., Haslam, C., 2007. Overgeneral memory for public and autobiographical events in depression and schizophrenia. Cognitive Neuropsychiatry 12, 301–321.

Wheeler, M.A., Stuss, D.T., 2003. Remembering and knowing in patients with frontal lobe injuries. Cortex 39, 827–846.

Yasuno, F., Nishikawa, T., Nakagawa, Y., Ikejiri, Y., Tokunaga, H., Mizuta, I., Shinozaki, K., Hashikawa, K., Sugita, Y., Nishimura, T., Takeda, M., 2000. Functional anatomical study of psychogenic amnesia. Psychiatry Research: Neuroimaging 99, 43–57.