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Reduced glucose metabolism in temporo-parietal cortices of women with borderline personality disorder

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Abstract

Individuals with borderline personality disorder (BPD) and posttraumatic stress disorder (PTSD) often experience dissociative symptoms. Evidence is increasing that stress-related hyperglutamatergic states may contribute to dissociative symptoms and neurodegeneration in temporo-parietal cortical areas. Seventeen young women with BPD who had been exposed to severe childhood physical/sexual abuse and presented with pronounced dissociative symptoms underwent ¹⁸fluoro-2-deoxyglucose positron emission tomography (FDG-PET). Nine healthy, matched volunteers served as comparison subjects. Borderline subjects displayed reduced FDG uptake (as analyzed by SPM) in the right temporal pole/anterior fusiform gyrus and in the left precuneus and posterior cingulate cortex. Impaired memory performance among borderline subjects was significantly correlated with metabolic activity in ventromedial and lateral temporal cortices. Our results demonstrate regional hypometabolism in temporal and medial parietal cortical regions known to be involved in episodic memory consolidation and retrieval. Currently, the precuneus/posterior cingulate cortex is modeled as part of a network of tonically active brain regions that continuously gather information about the world around and within us [Gusnard, D.A., Raichle, M.E., 2001. Searching for a baseline: functional imaging and the resting human brain. *Nature Reviews Neuroscience* 2, 685-694.]. Decreased resting metabolic rate of these regions may reflect dissociative symptoms and possibly also identity disturbances and interpersonal difficulties of individuals with BPD.

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1. Introduction

Borderline personality disorder (BPD) is defined as an intermediate level of personality organization that is considered to occupy a borderline area between

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neurosis and psychosis (Kernberg, 1967). Stress-related dissociative symptoms and psychotic features occur in about 75% of individuals with BPD (Skodol et al., 2002) and in about 40% of individuals with posttraumatic stress disorder (PTSD) (Bremner et al., 1992; David et al., 1999). However, dissociative symptoms in BPD and PTSD and their possible relationship to impaired brain mechanisms have received only limited systematic investigation.

Research so far has focused on size reductions of the amygdala and hippocampus in individuals with BPD who had been exposed to childhood physical or sexual abuse (Driessen et al., 2000; Schmahl et al., 2003a; Tebartz van Elst et al., 2003; Rüscher et al., 2003; Brambilla et al., 2004; Irle et al., 2005). Functional imaging studies showed that persons with BPD display pronounced prefrontal dysfunction (De la Fuente et al., 1997; Soloff et al., 2000, 2003; Juen-gling et al., 2003; New et al., 2004) and enhanced prefrontal and amygdala activation in response to emotional or traumatic stimuli (Herpetz et al., 2001, Donegan et al., 2003; Schmahl et al., 2003b; Driessen et al., 2004). Dysfunction in prefrontal regions (Brodmann areas 9–12) is suggested to be implicated in the deficits of persons with BPD to regulate emotional behavior (Soloff et al., 2003; New et al., 2004).

Studies investigating the structural and functional neural correlates of dissociative symptoms in BPD are lacking. However, research on individuals with epilepsy of the temporal or parietal lobes has consistently demonstrated that abnormal EEG activity, seizures, or brain stimulation of the temporal or parietal cortices are associated with dissociative states (Halgren et al., 1978; Mesulam, 1981; Gloor et al., 1982; Salanova et al., 1995; Blanke et al., 2002). Stimulation of the parietal cortex typically leads to somatosensory aura or disturbed perceptions of the body (Salanova et al., 1995; Blanke et al., 2002). Lesion studies provide evidence that the parietal cortex is engaged in the generation and maintenance of an internal (sensorimotor) representation of the body (Sirigu et al., 1996; Berlucchi and Aglioti, 1997; Wolpert et al., 1998).

Increasing evidence suggests that glutamatergic dysfunction represents an important part in the pathophysiology of dissociative states. The subanesthetic application of the *N*-methyl-D-aspartate (NMDA) antagonist ketamine is known to produce dissociative

symptoms in humans (Krystal et al., 1994). The proposition has been put forward that NMDA receptor hypofunction might cause excitotoxic limbic (i.e. hippocampal) and temporo-parietal cortical neurodegeneration (Olney and Farber, 1995). Evidence is increasing that stress-related hyperglutamatergic states may also contribute to dissociative symptoms and neural toxicity (i.e., hippocampal degeneration) in individuals who have been exposed to traumatic stress (Chambers et al., 1999). A recent study found that burn victims with enduring ketamine application in the posttraumatic state showed significantly stronger PTSD symptoms than burn victims without such treatment, and more severe PTSD symptoms of subjects with ketamine treatment were related to smaller hippocampal size (Winter and Irle, 2004).

In a previous investigation (Irle et al., 2005), we found reduced size of the hippocampus and parietal cortex in a sample of women with BPD who had been exposed to severe childhood sexual and physical abuse. All subjects presented with pronounced dissociative symptoms. In the present investigation, the brain glucose metabolism (by use of ¹⁸fluoro-2-deoxyglucose, FDG) of 17 women with BPD (who were also included in the report of Irle et al., 2005) was compared with that of a healthy matched control group (*n*=9). The goals of our study were 1) to investigate whether brain glucose metabolism is selectively reduced in temporo-parietal cortices of BPD subjects presenting with pronounced dissociative symptoms and 2) to investigate whether temporo-parietal metabolic changes are related to clinical symptoms and to memory deficits of BPD subjects.

2. Methods

2.1. Subjects

2.1.1. Subjects with borderline personality disorder

The sample comprised 17 young female in-patients with the diagnosis of borderline personality disorder (BPD) according to the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* (American Psychiatric Association, 1994) consecutively admitted to the Psychiatric State Hospital of Lower Saxony, Göttingen, Germany (Table 1). The hospital has a

Table 1
Demographic and clinical characteristics of borderline and control subjects

Variable	Borderline subjects ($n=17$)	Control subjects ($n=9$)	Statistic	P
Age, years	32 ± 4	33 ± 6	$t(24)=-0.53$	0.601
Education, years	11 ± 1	11 ± 1	$t(24)=-0.96$	0.345
Height, cm	167 ± 4	167 ± 7	$t(24)=0.01$	0.991
WAIS-R, Full Scale IQ	102 ± 15	119 ± 13	$t(24)=-2.88$	0.008
Wechsler Memory Scale-Revised (WMS-R)				
General memory	105 ± 16	121 ± 8	$t(24)=-2.81$	0.010
Verbal memory	106 ± 14	115 ± 11	$t(24)=-1.57$	0.131
Visual memory	99 ± 17	122 ± 18	$t(24)=-3.20$	0.004
Delayed recall	109 ± 17	123 ± 9	$t(24)=-2.35$	0.027
Attention/concentration	92 ± 14	105 ± 13	$t(24)=-2.17$	0.040
Traumatic Antecedent Questionnaire (TAQ) ^a				
Neglect	5.4 ± 1.3	3.1 ± 0.7	$t(24)=4.89$	0.000
Physical abuse	4.8 ± 1.8	2.8 ± 1.8	$t(22)=2.69$	0.014
Sexual abuse	4.0 ± 2.1	2.1 ± 0.1	$t(23)=2.87$	0.009
Dissociative Experiences Scale (DES)				
Absorption	38 ± 15	7 ± 5	$t(24)=5.70$	0.000
Dissociative amnesia	16 ± 16	2 ± 1	$t(24)=2.62$	0.015
Depersonalization/derealization	31 ± 17	2 ± 2	$t(24)=5.16$	0.000
Impact of Event Scale-Revised (IES-R)				
Intrusions	3.4 ± 1.1			
Avoidance	3.5 ± 0.5			
Hyperarousal	3.4 ± 1.1			
Beck Depression Inventory (BDI)	28 ± 9			

Table values are given as mean ± SD.

WAIS-R: Wechsler Adult Intelligence Scale-Revised, IQ estimates were derived from information, similarities, picture completion and block design scores.

^a Two borderline subjects felt unable to complete parts of the questionnaire.

specialized therapeutic unit for women who had experienced severe childhood sexual and physical abuse. All subjects were included in a previous report on parietal cortex size in BPD (Irlle et al., 2005).

All subjects underwent a routine physical and neurological examination, magnetic resonance imaging and laboratory testing. Subjects with a history of neurological disease were excluded. Subjects with psychotic disorders (*DSM-IV* axis I) were also excluded. Five subjects were on antidepressant medication. Some subjects were occasionally treated with benzodiazepines ($n=4$) or mild neuroleptics ($n=3$). None of these subjects had a reduced global brain glucose metabolism when compared with age-matched controls.

All borderline subjects were investigated with the *Structured Clinical Interview for DSM-IV (SCID-I and SCID-II)* (First et al., 1995, 1997; Wittchen et al., 1997) and the *Structured Clinical Interview for DSM-IV Dissociative Disorders (SCID-D)* (Steinberg, 1994; Gast et al., 2000). The interviews were conducted by a Master's level psychologist. Seven subjects received

a second *SCID-I* interview conducted by another clinician. Agreement between interviewers (expressed as kappa, which corrects for chance agreement) was 1.0 ($P=0.008$) for the current or lifetime diagnosis of major depression and PTSD, respectively.

All BPD subjects met *DSM-IV* criteria. They presented with pronounced dissociative symptoms and self-mutilating behavior. Accordingly, all subjects fulfilled *DSM-IV* criteria 5 (self-mutilating or suicidal behavior) and 9 (stress-related dissociative or psychotic symptoms) for BPD. Criteria tapping deficits in emotional regulation (criteria 4, 6, 8), interpersonal difficulties (criteria 1 and 2) or identity disturbance (criterion 3) were fulfilled by 41–65% of our borderline subjects.

Six borderline subjects (35%) met criteria for lifetime or current PTSD. Two (12%) subjects met criteria for lifetime panic disorder with agoraphobia, five (29%) for current panic disorder with agoraphobia, one (6%) for lifetime agoraphobia without panic disorder and two (12%) for current agoraphobia without

panic disorder. Two (12%) subjects met criteria for lifetime social phobia, two (12%) for current social phobia and four (24%) for current obsessive–compulsive disorder. Four (24%) subjects met criteria for lifetime major depression and 12 (71%) for current major depression. Two (12%) subjects met criteria for current somatization disorder. Four (24%) subjects met criteria for lifetime anorexia, three (18%) for lifetime bulimia, and three (18%) for current bulimia. Two (12%) subjects met criteria for lifetime alcohol abuse, three (18%) for lifetime alcohol dependence, and two (12%) for lifetime sedative abuse. Two (12%) subjects met criteria for lifetime depersonalization disorder and 14 (82%) for current depersonalization disorder. Four (24%) subjects met criteria for current dissociative amnesia and one (6%) for current dissociative identity disorder.

2.1.2. Control subjects

Borderline subjects were compared with nine healthy female control subjects matched for age, height and years of education. Control subjects were recruited for the study by an advertisement in a local newspaper and leaflets distributed in the Hospital of the University of Göttingen and in town. All subjects were physically healthy and did not use any medication or psychotropic drugs. Only subjects without a history of neurological or psychiatric (as assessed by the *SCID*) disorder were studied. Subjects with a history of childhood abuse or other traumatic events, or who reported signs of past or present depression, were also excluded.

The ethical committees of the medical faculty of the University of Göttingen and the medical faculty of the University of Köln approved the study design and PET procedures. After complete description of the study to the subjects, written informed consent was obtained.

2.2. Clinical and neuropsychological assessment

The *Traumatic Antecedent Questionnaire (TAQ)* (Herman et al., 1989) was used to assess neglect as well as physical and sexual abuse experiences during childhood and adolescence (7–18 years). The *Impact of Events Scale-Revised (IES-R)* (Weiss and Marmar, 1996; Maercker and Schützwohl, 1998) was used to assess PTSD symptoms. The *Dissociative Experiences Scale (DES)* (Bernstein and Putnam, 1986; Freyberger et al., 1999) (*absorption, dissociative am-*

nesia, depersonalization/derealization subscales) was applied as a measure of the severity of dissociative symptoms. Depressive symptoms were assessed with the *Beck Depression Inventory (BDI)* (Beck et al., 1960; Hautzinger et al., 1995). Intellectual and mnemonic functions were assessed using the *Wechsler Adult Intelligence Scale-Revised (WAIS-R)* (Wechsler, 1981; Tewes, 1991) and the *Wechsler Memory Scale-Revised (WMS-R)* (Wechsler, 1987).

2.3. PET acquisition and analysis

Images were acquired on an ECAT EXACT HR scanner (Siemens-CTI, Knoxville, TN) (Wienhard et al., 1994) in 3D mode at the Max Planck Institute for Neurological Research, Köln, Germany. In all subjects, 92.5 MBq (2.5 mCi) ^{18}F -FDG were administered. Scans with between 20 and 60 min of data acquisition and multiple arterialized venous blood samples were used to calculate the metabolic rate of glucose (MRglc) based on the Sokoloff-model with adaption of *K1* to measured activity (Wienhard et al., 1985) with a lumped constant of 0.52 for normal brain.

Statistical parametric maps of significant MRglc differences between borderline and control subjects were obtained using SPM 99 (Friston et al., 1996) implemented in MATLAB (Mathworks Inc., Sherborn, MA). All PET data were normalized to a standard stereotactic space (Talairach and Tournoux, 1988) by proportional scaling and smoothed with an 8-mm full-width half-maximum (FWHM) isotropic kernel (Friston, 1997). A group analysis was performed to map hypometabolic areas in the group of borderline subjects in contrast to their corresponding controls and vice versa. The resulting map of *t*-statistics was transformed to the unit normal distribution SPM $\{Z\}$ and thresholded at $P < 0.005$ ($Z = 2.79$). The significance of resulting foci was accepted if peak height or cluster size reached the threshold of $P < 0.05$, corrected for multiple comparisons.

3. Results

3.1. General

The groups did not differ with respect to demographic variables. Compared with control subjects,

Table 2
Regions of decreased MRglc in borderline subjects

Brain region	Brodmann area (BA)	<i>x</i>	<i>y</i>	<i>z</i>	<i>Z</i> score	Cluster size	<i>P</i> (corrected)
Left precuneus	31	−12	−52	32	2.84	917	0.05
Left posterior cingulate cortex	30	−14	50	12	4.22		
Right temporal pole	38	32	8	−34	3.86	3834	<0.001
Right fusiform gyrus	20	54	−36	−18	3.65		

Brain clusters with above-threshold significant decrease in MRglc of borderline subjects when compared with controls. Cluster size is given in pixels. For each cluster, the anatomical regions, *Z* score, and the Talairach coordinates (*x*, *y*, *z*) of the pixels with the highest *Z* score are given. The positive direction of *x* is to the right of midline, of *y* is anterior to the anterior commissure, and of *z* is superior to the bicommissural plane.

the BPD patients showed significantly lower intelligence (*WAIS-R*), memory and attentional (*WMS-R*) scores. The patients reported frequent neglect and abuse experiences (*TAQ*) during childhood and adolescence. They had strong dissociative symptoms (*DES*), and moderate to strong depressive symptoms (*BDI*) and PTSD symptoms (*IES-R*). For detailed results, see Table 1.

After the PET investigation, all subjects were interviewed about their experiences during the investigation. None of the BPD patients reported having recollected traumatic memories or having experienced anxiety or dissociation during the PET investigation.

3.2. Regional glucose metabolism

Global brain glucose metabolism did not differ significantly between BPD patients and controls (31.2 ± 4.1 vs. 30.7 ± 2.9 $\mu\text{mol}/100$ g/min). Thus, global scaling was used in all regional analyses.

Regions of impaired MRglc for each contrast are shown in Table 2. Fig. 1 presents the resulting SPM “glass brain” templates with the hypometabolic regions. As can be seen from Table 2, FDG uptake was decreased in borderline subjects in two areas: 1) an area in the right hemisphere extending from the temporal pole (BA 38) into the fusiform gyrus (BA 20) and 2) an area covering the posterior cingulate

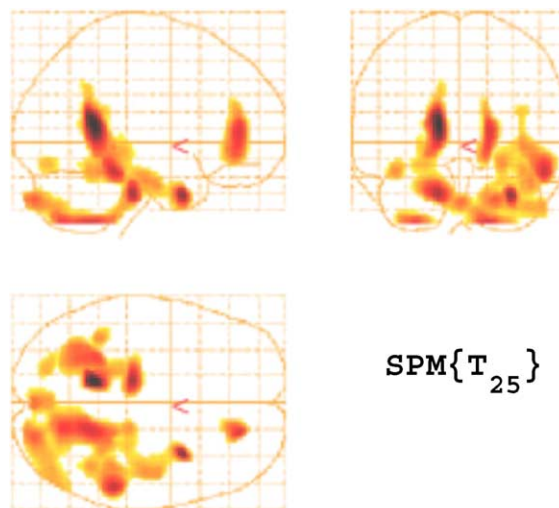


Fig. 1. Clusters with significant decreases of MRglc in borderline subjects projected onto a standardized stereotactic space. There were no regions with significant MRglc increases in borderline subjects compared with controls. Upper left: sagittal plane, upper right: coronal plane, bottom: transaxial plane.

gyrus (BA 30) and the precuneus (BA 31) of the left hemisphere.

Table 3 demonstrates the regions with significant correlations, across the 17 BPD patients, between regional MRglc decreases and memory performance (*WMS-R*). The *General Memory* index and the *Verbal Memory* index were related to clusters covering the left and right uncus, respectively, as well as to clusters covering parts of the temporal neocortex of both hemispheres. The *Attention/Concentration* index was related to clusters covering ventral temporal areas within the right hemisphere.

Correlations between MRglc decreases and dissociative symptom severity (*DES*), PTSD symptom severity (*IES-R*) and depressive symptom severity (*BDI*) were not significant.

3.3. Influence of comorbid disorders on brain glucose metabolism

All but one BPD patient met criteria for current or lifetime major depressive disorder. A median split was performed for the current depression score (*BDI*), resulting in two subgroups with eight (*BDI* score: 19 ± 4) and nine (*BDI* score: 35 ± 4) subjects. However, regional FDG uptake did not differ between these two subgroups. BPD patients fulfilling criteria for the additional diagnosis of PTSD ($n=6$) did not differ in regional FDG uptake from those not fulfilling PTSD criteria ($n=11$).

Four subjects had recovered (>1 year) from anorexia, and three subjects had recovered (>1 year) from alcohol dependence. These subjects presented with normal weight, normal laboratory testing and normal global brain glucose metabolism when compared with age-matched controls.

4. Discussion

In the present investigation we assessed regional glucose metabolism (FDG-PET) in a sample of 17 women with BPD who had been exposed to severe childhood physical and sexual abuse and nine matched healthy controls. The BPD patients presented with strong dissociative symptoms. Compared with control subjects, the patients had significantly reduced glucose metabolism in right-sided ventromedial temporal and left-sided medial parietal/posterior cingulate cortices (Table 2 and Fig. 1). Memory performance (*WMS-R*) among the BPD patient was significantly correlated with metabolic activity in ventromedial and lateral temporal cortices (Table 3).

4.1. Temporo-parietal glucose metabolism and memory performance in BPD

The BPD patients in the present study displayed marked deficits in the domain of memory (Table 1).

Table 3
Correlations between MRglc decreases and memory performance in borderline subjects

Brain region	Brodman area (BA)	<i>x</i>	<i>y</i>	<i>z</i>	Z score	Cluster size	<i>P</i> (corrected)
General memory							
Left inferior temporal gyrus	20	-50	12	-28	2.87	1139	0.011
Left uncus	38	-16	6	-34	2.84	53	0.012
Right uncus	38	20	8	-34	2.86	42	0.007
Verbal memory							
Left inferior temporal gyrus	20	-50	12	-28	3.40	1619	0.003
Left uncus	38	-16	8	-34	3.39	159	0.003
Left superior temporal gyrus	38	-20	2	-44	3.34	159	0.003
Right uncus	38	20	8	-34	3.42	92	0.002
Right middle temporal gyrus	37	60	-48	-10	3.32	229	0.002
Attention/concentration							
Right inferior temporal gyrus	20	50	-18	-34	2.38	245	0.025
Right middle temporal gyrus	21	46	6	-34	2.38	128	0.025
Right fusiform gyrus	37	48	-36	-10	2.37	13	0.025

Brain clusters with above-threshold significant correlations between MRglc decreases and participants' scores on the Wechsler Memory Scale-Revised (*WMS-R*). For further explanation, see legend to Table 2.

Similar neuropsychological findings have been obtained earlier in individuals with BPD (O'Leary et al., 1991), as well as in individuals exposed to traumatic stress (Bremner et al., 1995a,b, 1997; Gurvits et al., 1996, 2000; Winter and Irle, 2004; Irle et al., 2005). From our results it might be concluded that the reduced glucose metabolism in the temporal and parietal cortices of our BPD patients reflects an episodic memory deficit. Memory performance among the patients (as measured during a neuropsychological investigation several days prior to the PET investigation) was significantly correlated with resting metabolic activity in ventromedial and lateral temporal cortices (cf. Table 3). Previous PET studies with healthy volunteers have yielded correlations between episodic memory retrieval and blood flow in medial temporal cortices (Nyberg et al., 1996; Tulving et al., 1999).

Studies investigating individuals who had been exposed to traumatic stress demonstrated relationships between reduced hippocampal size and impaired mnemonic functioning in persons with PTSD or BPD (Bremner et al., 1995a, 1997; Gurvits et al., 1996), demonstrating a strong influence of reduced hippocampal size on mnemonic functioning. A relationship between reduced hippocampal size and the amount of memory deficit was also found in the subjects of the present study (Irle et al., 2005). However, the hippocampal size reduction of our BPD patients may not explain the correlations found between resting metabolic activity in ventromedial and lateral temporal cortices and memory performance. An exploratory analysis of our data did not reveal significant correlations between hippocampal size and focal MRglc decreases within the temporal lobes of our BPD patients.

Recent PET studies have also repeatedly found that episodic memory retrieval is associated with activation of the precuneus (Shallice et al., 1994; Fletcher et al., 1995a,b) and posterior cingulate cortex (Maddock, 1999). Fletcher et al. (1995b) provided evidence that the precuneus activation arises from the use of visual imagery to aid memory retrieval. The authors (Fletcher et al., 1995b) suggested that imagery requires conscious manipulation or “top-down”-processing, with the precuneus functioning as the “mind's eye” in conjunction with extrastriate visual areas.

4.2. Role of the precuneus for the representation of the mental self

Evidence from meta-analyses suggests that the precuneus in conjunction with the posterior cingulate cortex is associated with the highest resting perfusion rate in the human cerebral cortex (Gusnard and Raichle, 2001). The authors (Gusnard and Raichle, 2001) proposed that this area might be tonically active and continuously gathering information about the world around and within us, thus enabling a continuous, stable and unified perspective of the organism relative to its environment (i.e., a “self”). Accordingly, the precuneus was shown to be activated during imagination of one's own actions or movements (Stephan et al., 1995; Ruby and Decety, 2001) and during reflection on one's own personality traits (Kjaer et al., 2002). Conversely, induction of hypnosis was shown to be associated with decreased activity of the left-sided precuneus and posterior cingulate cortex (Maquet et al., 1999; Rainville et al., 1999).

The results of the present study demonstrated a significantly decreased resting metabolic rate of the left-sided precuneus/posterior cingulate cortex in BPD. A recent FDG-PET report on individuals with depersonalization disorder (Simeon et al., 2000) demonstrated increased metabolic activity of the precuneus, and the relative glucose metabolic rate of the precuneus among these subjects was related to dissociative symptom severity. However, the subjects were performing an episodic memory task using visual imagery during the PET scan, rendering it likely that the precuneus activation was an effect of episodic memory retrieval. In another functional magnetic imaging study, Lanius et al. (2002) demonstrated that traumatic memory-induced dissociative states of PTSD subjects with a history of severe childhood sexual and physical abuse were related to increased activity of the precuneus as well. In this study, activation of the right precuneus emerged during dissociative states, in contrast to our study, in which reduced activity of the left precuneus was observed in a resting state in which subjects did not experience dissociative symptoms.

Apart from differences in the study designs, sample characteristics could also contribute to the differing results of our study and the studies of Simeon et al. (2000) and Lanius et al. (2002). The psychopatholog-

ical spectrum (i.e., *DSM-IV* axis I comorbidity) of persons with depersonalization disorder (Simeon et al., 2003) is very similar to that of persons with BPD (Zanarini et al., 1998), and childhood interpersonal trauma is likely to play a role in the pathogenesis of depersonalization disorder (Simeon et al., 2001) as well as BPD and complex PTSD (MacLean and Gallop, 2003). However, none of the subjects of the study of Lanius et al. (2002) and Simeon et al. (2000) were reported to have BPD. It is possible that decreased resting metabolic rate of the precuneus is also a feature of BPD. It may be linked to dissociative symptoms, but additionally to identity disturbances or interpersonal difficulties of persons with BPD. This conclusion is supported by the fact that studies performing emotion-related experiments have found predominantly right precuneus/posterior cingulate activation (Maddock, 1999; Lanius et al., 2002), whereas studies investigating non-emotional memory, personal self-reflection or states of consciousness found bilateral or even left-sided precuneus activation (Fletcher et al., 1995b; Stephan et al., 1995; Maquet et al., 1999; Rainville et al., 1999; Ruby and Decety, 2001; Kjaer et al., 2002).

4.3. Neural correlates of distinct dimensions of BPD

Our BPD sample comprised inpatients drawn from a therapeutic unit for women who had been exposed to severe and chronic childhood abuse, presenting with severe dissociative and self-mutilating behavior. Accordingly, all subjects fulfilled *DSM-IV* criterion 5 (self-mutilating or suicidal behavior) and criterion 9 (stress-related dissociative or psychotic symptoms) for BPD. Criteria tapping deficits in emotional regulation (criteria 4, 6, and 8), interpersonal difficulties (criteria 1 and 2) or identity disturbance (criterion 3) were fulfilled by only 41–65% of our patients (Section 2.1.1.). It has been proposed that dimensions of BPD may be differentially expressed in subgroups of patients and that each dimension might have a distinct biological profile (Schmahl et al., 2002). Whereas prefrontal dysfunction is suggested to be implicated in the deficits of persons with BPD to regulate emotional behavior, dissociative and self-mutilating behavior of persons with BPD may rather depend on dysfunction of temporo-parietal limbic/paralimbic and sensory association cortices.

Previous FDG-PET studies on individuals with BPD reported pronounced prefrontal dysfunction in their subjects (De la Fuente et al., 1997; Soloff et al., 2000, 2003; Juengling et al., 2003; New et al., 2004). One of these studies (Soloff et al., 2003) found a significant relationship between measures of impulsivity and prefrontal hypometabolism of their BPD subjects. Impulsive/aggressive patients were shown to have a diminished prefrontal response to serotonergic stimulation (Siever et al., 1999; Soloff et al., 2000; New et al., 2002), and treatment with selective serotonin reuptake inhibitors was shown to normalize prefrontal metabolism and impulsive/aggressive behaviors (New et al., 2004). In contrast to our study, BPD subjects of the above-mentioned studies were recruited from BPD treatment or research programs, and very few of these subjects had been exposed to traumatic stress.

To our knowledge, this is the first report of impaired resting glucose metabolism of the posterior cortex in a sample of patients with BPD. All of our patient had a history of severe and enduring physical and/or sexual childhood abuse. They frequently reported that dissociative symptoms occurred in association with triggered traumatic memories, and that self-mutilating behavior stopped the dissociative episodes. We propose that BPD patient with a history of interpersonal trauma may develop stress-related neural degeneration in paralimbic/limbic temporo-parietal areas, which in turn may produce chronic PTSD and BPD symptoms (including dissociative and psychotic symptoms) and memory deficits (Bremner et al., 1995a, 1997, 2003; Gurvits et al., 1996; Gilbertson et al., 2002; Villarreal et al., 2002; Winter and Irle, 2004; Irle et al., 2005). A right-sided focus of impaired temporal resting glucose metabolism, as found in the present study, is paralleled by symptom-provocation studies in PTSD and BPD, which revealed predominantly right-sided paralimbic/limbic responses to traumatic stimuli (Rauch et al., 1996; Driessen et al., 2004).

4.4. Methodological considerations

Our BPD sample presented with a high degree of *DSM-IV* axis I comorbidity. Therefore, the findings of the present study must be considered with caution. Concurrent axis I disorders are found in the

vast majority of individuals with BPD (Zanarini et al., 1998), leading to the conclusion that any BPD sample being limited to subjects with the sole diagnosis of BPD cannot be considered representative (Skodol et al., 2002). Nevertheless, the use of outpatient or even non-patient BPD samples may allow for a more accurate characterization of neural correlates of the chronic symptoms of the personality disorder. However, the patients in the present study had a history of severe and chronic childhood abuse, producing trauma-related clinical symptoms long before admission to the hospital (14 ± 7 years before admission; Irle et al., 2005). Many of the comorbid axis I diagnoses, as well as medication usage, were also present since this time, leading to the assumption that investigating severely abused outpatient or non-patient BPD samples would not preclude comorbidity and medication usage in these subjects.

Our results do not give strong evidence for an influence of comorbid disorders on the temporo-parietal metabolic changes in our BPD group. Subjects with recovered anorexia or alcohol disorder presented with a normal global brain glucose metabolism as was reported previously (Volkow et al., 1994; Herholz, 1996). Subjects with high current depression scores did not differ in regional brain glucose metabolism from subjects with low current depression scores. Correlating MRglc decreases and depressive symptom severity (*BDI*) did not reveal significant results. However, we cannot completely rule out that comorbid depression had an influence on our findings. Fourteen of our BPD subjects met criteria for lifetime and/or current major depression, thus preventing a more rigorous test of subgroups (i.e., subjects with and without major depression).

Some of our subjects were occasionally treated with sedative drugs. Sedation with diazepam administered prior to the injection of FDG may depress overall glucose metabolism (Foster et al., 1987). However, none of our subjects received benzodiazepines prior to the PET investigation, and global brain glucose metabolism was not decreased in the patients compared with the age-matched controls. Furthermore, regional patterns of glucose uptake are the same in both the presence and absence of sedation (Foster et al., 1987), thus allowing the assumption that the temporo-parietal hypometabolism of our border-

line subjects cannot be attributed to the effects of sedative drugs.

The subjects of the present study presented with memory deficits, as was observed in other individuals who had been exposed to traumatic stress (Bremner et al., 1995a,b, 1997; Gurvits et al., 1996, 2000; Winter and Irle, 2004; Irle et al., 2005). Subjects of our study were inpatients. Memory testing in hospitalized patients may not yield an accurate measure of baseline functioning. However, many trauma subjects in earlier studies were outpatients or even non-patients, and an inspection of these studies suggests that the degree of memory impairment of outpatients or non-patients seems to be similar to that of inpatients, suggesting that the severity of memory deficits as revealed in individuals with exposure to traumatic stress does not vary with different recruitment strategies.

In a previous study (Irle et al., 2005), we found reduced size of the left and right hippocampus and the right-sided parietal cortex in a BPD sample, which also included the subjects in the present report. The temporal lobes of BPD subjects were of normal size when compared with controls (unpublished data), and hippocampal size was not related to MRglc decreases within the temporal lobes. A close inspection of the T_1 -weighted and FLAIR sequences of borderline subjects did not reveal any visually detectable structural lesions or atrophy. However, in the presence of hippocampal neuronal loss, a significant underestimation of temporal gray-matter radioactivity concentration due to the resulting partial volume averaging could occur. We did not include partial volume correction in our study since hippocampal gray–white-matter segmentation requires exceptionally high MRI quality that was not readily available in all subjects. Therefore, we cannot exclude that the presence of some minor local atrophy may have contributed to apparent focal reduction of temporal glucose metabolism.

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