

Enhanced emotion-induced amnesia in borderline personality disorder

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ABSTRACT

Background. Current biological concepts of borderline personality disorder (BPD) emphasize the interference of emotional hyperarousal and cognitive functions. A prototypical example is episodic memory. Pre-clinical investigations of emotion–episodic memory interactions have shown specific retrograde and anterograde episodic memory changes in response to emotional stimuli. These changes are amygdala dependent and vary as a function of emotional arousal and valence.

Method. To determine whether there is amygdala hyper-responsiveness to emotional stimuli as the underlying pathological substrate of cognitive dysfunction in BPD, 16 unmedicated female patients with BPD were tested on the behavioural indices of emotion-induced amnesia and hypermnesia established in 16 healthy controls.

Results. BPD patients displayed enhanced retrograde and anterograde amnesia in response to presentation of negative stimuli, while positive stimuli elicited no episodic memory-modulating effects.

Conclusion. These findings suggest that an amygdala hyper-responsiveness to negative stimuli may serve as a crucial aetiological contributor to emotion-induced cognitive dysfunction in BPD.

INTRODUCTION

More than any other species, humans are beneficiaries and victims of emotion. A lack of emotional equilibrium is a common denominator across psychiatric conditions, with particular significance in borderline personality disorder (BPD) (Skodol *et al.* 2002*a,b*). The BPD clinical phenotype is characterized by an emotionally unstable and impulsive cognitive and behavioural style (Domes *et al.* 2006), which has led to suggestions that the core pathology of BPD is a hyperarousal-dyscontrol syndrome (Lieb *et al.* 2004).

To date, no specific cognitive dysfunction in BPD has been identified (Kunert *et al.* 2003;

Ruocco, 2005). However, current theories of BPD emphasize the disruptive potential of negative emotion on cognition (Fertuck *et al.* 2006). One cognitive domain where the interference with emotion can be characterized is episodic (autobiographical) memory (Dolan, 2002; McGaugh, 2004; LaBar & Cabeza, 2006; Phelps, 2006). Functional imaging studies of the associated neural circuitry have revealed amygdala–hippocampal interactions during emotional episodic memory encoding, with hippocampal circuits being modulated by amygdala input (Kilpatrick & Cahill, 2003; Dolcos *et al.* 2004*a*; Kensinger & Corkin, 2004; Richardson *et al.* 2004). One classic experimental design to study amygdala–hippocampal connectivity is the subsequent memory paradigm, which demonstrates variations in recall of emotional items as a function of amygdala activation at encoding of these items (Cahill *et al.*

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1996; Hamann *et al.* 1999; Canli *et al.* 2000; Kilpatrick & Cahill, 2003; Dolcos *et al.* 2004a; Kensinger & Corkin 2004). A key neurochemical mediator of this effect is norepinephrine (NE), which has its major source in the locus coeruleus (LC) (Berridge & Waterhouse, 2003; Aston-Jones & Cohen, 2005). Notably, the amplification of emotional memory encoding by endogenous LC–NE release can be further augmented by NE agonists such as reboxetine (Harmer *et al.* 2003, 2004) and blocked by NE antagonists such as propranolol (Strange *et al.* 2003; Strange & Dolan, 2004; van Stegeren *et al.* 2005).

Amygdala lesion eliminates the episodic memory advantage of emotional stimuli as does amygdala suppression with propranolol, indicating a key intra-amygdalar role for LC–NE in enhancing emotional memory encoding (Strange *et al.* 2003; Strange & Dolan, 2004; van Stegeren *et al.* 2005). The psychological ‘costs and benefits’ of such enhancement have been modelled with free recall tests of episodic memory, in which facilitated encoding of a heterogeneous item (oddball) presented within a train of homogeneous standard items (the von Restorff effect) (von Restorff, 1933; Wallace, 1965) interferes with the encoding of preceding and following standard items, particularly if the oddball is emotional (Tulving, 1969; Angelini *et al.* 1994; Hurlemann *et al.* 2005). In keeping with a taxonomy of emotion along orthogonal dimensions of valence and arousal (Russell, 1980; Lang, 1995), retrograde interference is valence dependent in that emotionally negative items elicit amnesia and emotionally positive items elicit hypermnesia. By contrast, anterograde interference is arousal dependent, with emotionally negative and positive items eliciting amnesia. As for the emotional oddball effect *per se*, both the retrograde and anterograde episodic memory changes driven by this effect are under amygdala and LC–NE control (Hurlemann *et al.* 2005, 2006).

In BPD patients, episodic memory formation is biased towards enhanced encoding of emotionally negative items, possibly resulting from LC–NE (Skodol *et al.* 2002b) and amygdala hyper-responsiveness to negative emotion (Herpertz *et al.* 2001; Donegan *et al.* 2003). Moreover, emotional instability and impulsivity increase under treatment with the NE agonist

reboxetine (Anghelescu *et al.* 2005) and decrease under treatment with the NE antagonist clonidine (Philipsen *et al.* 2004). Furthermore, challenge studies with the NE agonist yohimbine in controls have linked elevated noradrenergic tone to increased impulsivity (Swann *et al.* 2005). These observations provide the basis for our experimental hypothesis that BPD patients would display greater retrograde and anterograde amnesia in response to negative emotion as compared to controls. Such a finding would indicate LC–NE hyperactivation of the amygdala as an aetiological contributor to emotion-induced cognitive dysfunction in BPD. Thus, we tested 16 unmedicated female patients with BPD on a robust laboratory index of emotion-induced amnesia and hypermnesia established in healthy controls.

METHOD

Subjects

Informed written consent was obtained from all patients and controls after a complete and extensive description of the study, which was approved by the Ethics Committee of the University of Bonn in accordance with the principles of the Declaration of Helsinki (Rickham, 1964). The study included 16 self-harming female out-patients (age range 19.5–34.5 years; mean age 25.2 ± 4.6 years) treated at the Department of Psychiatry, University of Bonn. In clinical populations, BPD occurs predominantly in females (Lieb *et al.* 2004). Patients fulfilled both DSM-IV diagnostic criteria for BPD and BPD criteria from the Revised Diagnostic Interview for BPD (DIP-R; Gunderson & Zanarini, 1983). Structured Clinical Interviews for DSM-IV Diagnoses (SCID I and II; Wittchen *et al.* 1997) were performed to exclude lifetime diagnosis of Axis I and II co-occurring disorders as a potential confounding factor in the assessment of emotion–episodic memory interactions. The Global Assessment of Functioning (GAF) Scale as part of the DSM-IV Axis V assessment served to evaluate patients’ overall level of psychological, social and occupational functioning (APA, 1994).

Cutting, as the most common form of self-harm, provided an objective index of impulsive behaviour (Herpertz *et al.* 1997) and allowed us

to recruit a homogeneous patient sample (Berlin *et al.* 2005; Domes *et al.* 2006). BPD patients were drug-naïve ($n=6$) or free of psychotropic medication for ≥ 4 weeks ($n=10$). Sixteen female control subjects (age range 20.3–34.2 years; mean age 25.6 ± 4.3 years), matched for age and educational status and determined to be free of personal as well as first-degree family history of DSM-IV Axis I and II disorders, were enrolled in the study. Neither patients nor controls were included if they had current substance or alcohol abuse or a history of neurological or severe somatic disorder. Controls had not been on psychotropic medication for ≥ 12 weeks.

To ensure that potential abnormalities in our test of emotion-episodic memory interactions could not be attributed to deficits in visual, verbal and cognitive functions, both patients and controls underwent brief neuropsychological screening. This included the Verbaler Lern- und Merkfähigkeitstest (VLMT), a German version of the Rey Auditory Verbal Learning Test, to assess immediate verbal learning span, new learning, susceptibility to interference, and recognition memory (Helmstaedter *et al.* 2001). The Rey-Osterrieth Complex Figure Test (CFT) was used to test incidental visual memory and the visuospatial constructional ability (Rey, 1941; Osterrieth, 1944). Motor speed and visual attention were examined with the Trail Making Test, Part A (TMT-A; Raitan, 1958). The Wortschatztest (WST), a vocabulary test implemented in the Hamburg-Wechsler Intelligenztest für Erwachsene (HAWIE-R), a German adaptation of the Wechsler Adult Intelligence scale, provided an estimate for intelligence (IQ) (Tewes, 1991). The demographic and neuropsychological data for the patient and control groups are reported in Table 1.

Diagnostic instruments and questionnaires

BPD patients were characterized using a battery of clinician- and self-rating tools. State euthymia was confirmed by a score < 10 on the Hamilton Depression Scale (HAMD-21; Hamilton, 1960). The Questionnaire for Measuring Factors of Aggression, Fragebogen zur Erfassung von Aggressivitätsfaktoren (FAF; Hampel & Selg, 1975), the Barrat Impulsiveness Scale (BIS-11; Patton *et al.* 1995) and the Buss-Durkee Hostility Inventory (BDHI; Buss & Durkee, 1957) were administered to assess

Table 1. Demographics, neuropsychological and diagnostic data for the sample^a

	CTL ($n=16$)	BPD ($n=16$)
Demographics		
Age, years	25.6 (4.6)	25.2 (4.3)
Female sex	16	16
Height, cm	168.4 (6.7)	167.1 (5.4)
Weight, kg	64.4 (7.1)	68.1 (14.5)
Education, years	11.9 (1.5)	11.6 (1.3)
IQ (WST)	105.6 (9.3)	106.8 (10.5)
With partner	10	8
Employed	15	14
Neuropsychological data		
VLMT Trial 1–5	51.94 (3.26)	52.49 (3.44)
Rey-Osterrieth CFT Copy	33.95 (3.54)	34.36 (3.92)
Rey-Osterrieth CFT Delay	22.81 (2.97)	23.16 (3.21)
TMT-A	25.33 (4.92)	25.91 (4.68)
Diagnostic data		
GAF	—	76.63 (5.72)
DIB-R scaled	—	7.80 (0.80)
HAMD-21	—	6.10 (3.10)
FAF total	—	23.19 (7.77)
BIS-11 total	—	85.63 (11.48)
BDHI total	—	43.40 (10.50)
FDS	—	20.66 (15.86)
CTQ	—	82.32 (17.97)
Medication-free/-naïve	0/16	10/6
Psychiatric hospitalization	0	7
Self-injury	0	16
Previous suicide attempt	0	7

^a Data are given as mean (standard deviation) unless otherwise specified.

CTL, Controls; BPD, borderline personality disorder; IQ (WST), Wortschatztest, a vocabulary test implemented in the HAWIE-R (German adaptation of the Wechsler Adult Intelligence Scale); VLMT, Verbaler Lern- und Merkfähigkeitstest (German version of the Rey Auditory Verbal Learning Test); CFT, Rey-Osterrieth Complex Figure Test; TMT-A, Trail Making Test (part A); GAF, Global Assessment of Functioning; DIB-R, Revised Diagnostic Interview for Borderline personality disorder; HAMD-21, Hamilton Depression Scale; FAF, Questionnaire for Measuring Factors of Aggression; BIS-11, Barrat Impulsiveness Scale; BDHI, Buss-Durkee Hostility Inventory; CTQ, Childhood Trauma Questionnaire; FDS, Fragebogen für Dissoziative Symptome (German version of the American Dissociative Experiences Scale).

aggressive and impulsive behaviour. The Fragebogen für Dissoziative Symptome (FDS), a German adaptation of the American Dissociative Experiences Scale, served to determine the frequency of dissociative symptoms (Freyberger *et al.* 1998). The Childhood Trauma Questionnaire (CTQ) was used to investigate prevalence of childhood trauma and relations between childhood trauma and dissociation in adult life (Bernstein *et al.* 1994). The diagnostic data for the patient group are reported in Table 1.

Episodic memory test

The experimental design and stimulus set-up have been detailed elsewhere (Hurlemann *et al.* 2005) and are described in abbreviated form here. Subjects were exposed to 36 study-distraction-test sequences. During each 40-s study phase, a von Restorff list composed of one oddball and seven standard stimuli in the form of picture items paired with their verbal descriptors was presented. Standard stimuli included black-and-white line drawings of living and non-living entities (Snodgrass & Vanderwart, 1980; Cycowitz *et al.* 1997), while oddballs included images primarily selected and edited from the International Affective Picture System (IAPS; Lang *et al.* 2005). Of 36 oddballs implemented in the paradigm, 12 were perceptual-neutral (P), and 24 were perceptual-emotional (E_xP), including 12 positive ($E_{pos}P$) and 12 negative ($E_{neg}P$) oddballs. $E_{pos}P$ and $E_{neg}P$ oddballs differed from each other in terms of valence, but were matched for arousal. E_xP oddballs differed from P oddballs in terms of valence and arousal. Each von Restorff list was followed by a 30-s arithmetic distraction task, before episodic memory was tested by free recall.

Recall profiles were pooled according to the three oddball types, thus yielding a neutral, positive and negative condition. As outcome parameter, memory performance was determined condition-wise by calculating the percentage of correct recall (i.e. the output/input ratio) for the following three list positions: oddball -1 , oddball, and oddball $+1$. Additionally, a list index (LI) based on the seven non-oddball list positions was calculated for each condition (e.g. LI_p). Contrasting the emotional conditions (E_xP) with the neutral condition (P) (according to $E_xP - P = E_x$) allowed us to isolate retrograde and anterograde effects generated by positive (E_{pos}) and negative (E_{neg}) emotion on the adjacent standard item ($E_x \pm 1$) corresponding to a time window of ± 5 s. The design and timeline of the episodic memory test are illustrated in Fig. 1*a, b*.

While our previous paradigm was devised to investigate $E_{neg}-1$ retrograde effects as a function of emotional oddball effects (Strange *et al.* 2003), the present paradigm was optimized to dissociate the contributions of emotional

valence and arousal to E_x-1 retrograde and E_x+1 anterograde effects by using a subtractive design (Hurlemann *et al.* 2005). As BPD might be associated with potential changes in the cognitive appraisal of emotion, patients and controls both performed paper-and-pencil valence and arousal ratings to E_xP and P oddballs on a nine-point scale after the episodic memory test.

Statistics

Demographic and neuropsychological data obtained from the patient and control groups were compared on the basis of two-sample *t* tests. The episodic memory test resulted in different recall scores (E_x , $E_x \pm 1$, LI_x) for the emotional (positive, negative) conditions, which were analysed in relation to the corresponding recall scores (P, $P \pm 1$, LI_p) for the neutral condition. Two-factor within-subject and three-factor mixed analyses of variance (ANOVAs) were followed by two-tailed one-sample and two-sample *t* tests to determine the source of significance. The Greenhouse–Geisser correction for inhomogeneity of variance was applied whenever a sphericity assumption was violated. To account for an inflation of the type I error attributable to multiple *post hoc* testing, the threshold for significance was Bonferroni adjusted.

RESULTS

As summarized in Table 1, patients (BPD, $n=16$) were euthymic, medication-naive ($n=6$) or medication-free for ≥ 4 weeks ($n=10$), and demonstrated a high level of psychological, social and occupational functioning, when tested on the behavioural measures of $E_x \pm 1$ modulatory effects established in controls (CTL, $n=16$). The lack of between-group differences with respect to demographic or neuropsychological variables (two-sample *t* tests, $p > 0.05$) confirmed careful matching of patients and controls.

Analysis of the episodic memory test

The percentages of mean recall (\pm S.D.) for oddballs and standard items (collapsed across the positive, negative and neutral conditions) were as follows: CTL, 96.88 (4.15) and 56.47 (7.21); BPD, 96.70 (2.42) and 51.27 (7.87). One-sample *t* tests confirmed the presence of

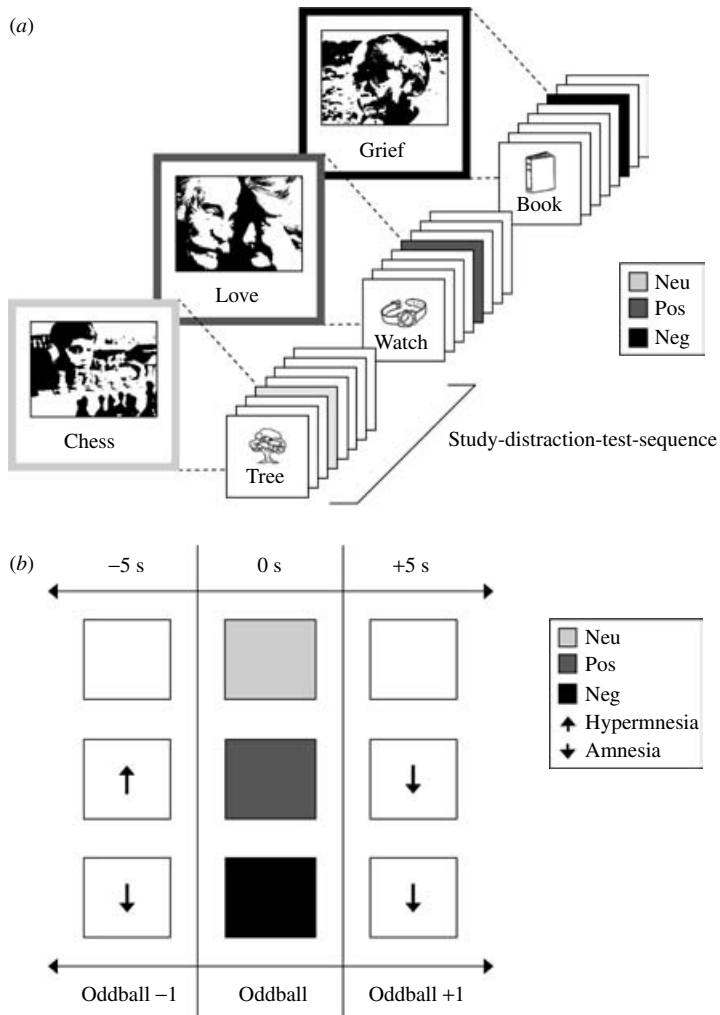


FIG. 1. Episodic memory test. (a) Timeline. Participants were exposed to 36 study-distraction-test sequences. During each 40-s study phase, they were presented with a list of eight items, including seven standard items and one oddball inserted on list position 3, 4, 5 or 6. After a 30-s arithmetic distraction task, encoding strength for the eight list items was tested by free recall. (b) Analysis. In each list, one oddball, either emotional (E_x : positive, $E_{pos}P$; negative, $E_{neg}P$) or neutral (P), was temporally flanked by a preceding (oddball-1) and following (oddball+1) standard item. Results from the list recall were pooled according to the three oddball types, yielding a positive, negative and neutral condition. Contrasting the positive and negative conditions with the neutral condition (according to $E_xP - P = E_x$) allowed us to quantify retrograde and anterograde episodic memory-modulating effects of positive and negative emotion within a time window of $E_x \pm 1$ items or ± 5 s. Positive oddballs ($E_{pos}P$) interfere with $E_x \pm 1$ encoding in the form of retrograde memory increments (hypermnesia) and anterograde memory decrements (amnesia), while negative oddballs ($E_{neg}P$) provoke both retrograde and anterograde memory decrements (amnesia). Neg, negative; neu, neutral; pos, positive.

near-ceiling von Restorff effects within each group: CTL, $t(15) = 24.372$, $p < 0.0001$; BPD, $t(15) = 19.455$, $p < 0.0001$. A one-way ANOVA with group (CTL, BPD) as the between-subjects factor showed no difference in SI_P scores between groups [$F(1, 31) = 0.819$, $p > 0.05$], that

is BPD did not compromise an ability to recall standard items in the neutral condition.

An exploratory condition (positive, negative, neutral) \times position (oddball, oddball ± 1) 3×3 ANOVA restricted to the CTL group yielded effects of valence [$F(2, 30) = 13.408$, $p < 0.0001$],

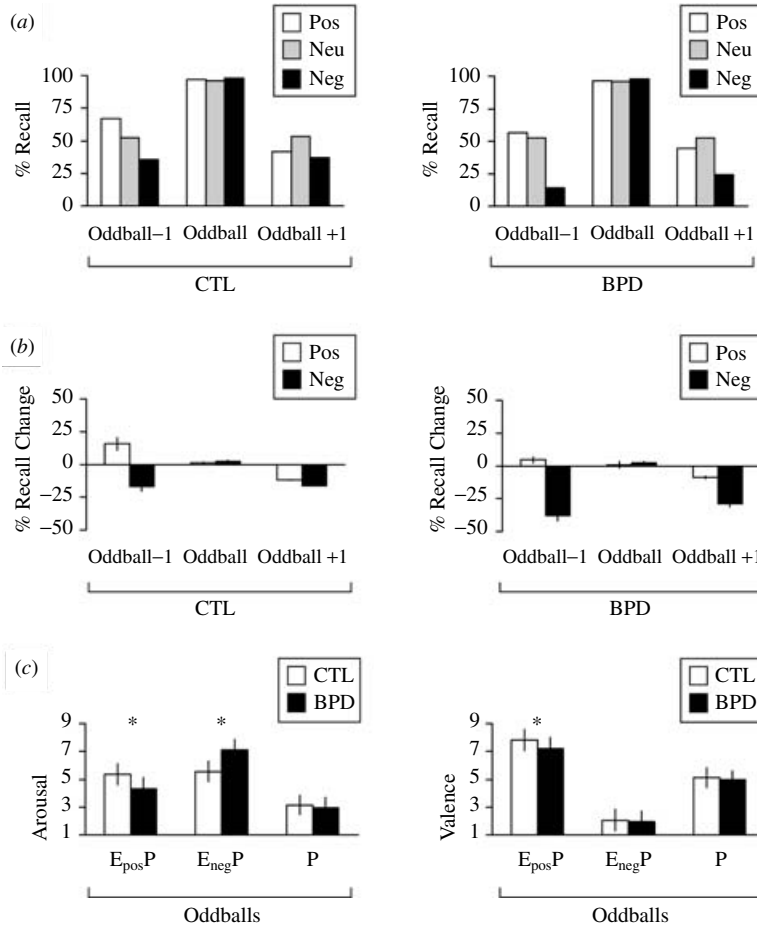


FIG. 2. Results of the episodic memory test and oddball ratings. (a) Percentage correct recall as determined in controls (CTL) and patients (BPD). Equal (near-ceiling) von Restorff effects were obtained in both the emotional and the neutral conditions. (b) Percentage of recall change in the emotional conditions relative to the neutral condition. Controls (CTL) displayed a characteristic pattern of emotion-induced memory increments and decrements: negative emotion elicited retrograde (-16.67%) and anterograde (-16.15%) amnesia, whereas positive emotion elicited retrograde ($+15.62\%$) hypermnesia and anterograde (-11.97%) amnesia. In patients (BPD), no episodic memory-modulating effects of positive emotion were present, whereas enlarged retrograde (-41.15%) and anterograde (-27.08%) amnesic effects of negative emotion were measured. (c) Oddball arousal and valence ratings. Increased arousal scores for negative oddballs (E_{negP}) in combination with decreased arousal and valence scores for positive oddballs (E_{posP}) in patients (BPD) relative to controls (CTL) are consistent with a substantial negativity bias in the cognitive appraisal of emotion in BPD. Asterisks indicate significant rating differences between controls (CTL) and patients (BPD). neg, negative; neu, neutral; pos, positive; oddball ± 1 , standard items preceding or following the oddball; E_{posP} , positive oddball; P, neutral oddball; E_{negP} , negative oddball. Error bars indicate 1 s.e.

position [$F(2, 30) = 369.463, p < 0.0001$] and condition \times position interaction [$F(4, 60) = 14.235, p < 0.0001$] effects. As depicted in Fig. 2a, b, *post hoc* one-sample *t* tests confirmed the presence of retrograde $E_{\text{neg}-1}$ amnesic (-16.67%) [$t(15) = -3.130, p = 0.007$] and $E_{\text{pos}-1}$ hypermnesic ($+15.62\%$) [$t(15) = 3.101, p = 0.007$] as well as anterograde $E_{\text{neg}+1}$ (-16.15%) [$t(15) = -3.725,$

$p = 0.002$] and $E_{\text{pos}+1}$ (-11.97%) [$t(15) = -3.360, p = 0.004$] amnesic effects. Additional session (first, second, third) \times condition 3×3 within-subjects ANOVAs showed that recall performance for both oddballs [$F(2, 30) = 1.328, p > 0.05$] and standard items [$F(2, 30) = 1.542, p > 0.05$] remained stable throughout the experiment. The pattern of memory increments

and decrements measured in the CTL group paralleled those of previous investigations and served as baseline for subsequent comparisons.

Analysing the influence of BPD diagnosis, a group (CTL, BPD) \times condition \times position $2 \times 3 \times 3$ ANOVA yielded group [$F(1, 30) = 11.972, p = 0.002$], condition [$F(2, 60) = 60.160, p < 0.0001$], position [$F(2, 60) = 793.660, p < 0.0001$], two-way condition \times group [$F(2, 60) = 6.405, p = 0.003$], position \times group [$F(2, 60) = 6.433, p = 0.003$], condition \times position [$F(4, 120) = 31.617, p < 0.0001$], and three-way condition \times position \times group [$F(4, 120) = 4.090, p = 0.004$] interaction effects. *Post hoc* two-sample *t* tests demonstrated that $E_{\text{neg}} - 1$ [$t(30) = 4.945, p < 0.0001$], $E_{\text{neg}} + 1$ [$t(30) = -3.196, p = 0.003$] and $E_{\text{pos}} - 1$ [$t(30) = 3.250, p = 0.003$] recall was different between BPD and CTL groups. A condition \times position 3×3 ANOVA restricted to the BPD group yielded effects of valence [$F(2, 30) = 53.553, p < 0.0001$], position [$F(2, 30) = 545.084, p < 0.0001$] and condition \times position interaction [$F(4, 60) = 21.769, p < 0.0001$] effects. *Post hoc* one-sample *t* tests revealed enhanced retrograde $E_{\text{neg}} - 1$ (-41.15%) [$t(15) = -8.399; p < 0.0001$] and anterograde $E_{\text{neg}} + 1$ (-27.08%) [$t(15) = -6.343, p < 0.0001$] amnesic effects in the BPD group. By contrast, neither retrograde nor anterograde episodic memory changes in response to positive oddballs were present. The percentage recall differences relative to the CTL group negative condition (relative to the CTL group neutral condition) were as follows: $E_{\text{neg}} - 1, -21.35$ (-38.02); $E_{\text{neg}} + 1, -12.50$ (-28.65) (Fig. 2a, b).

Analysis of emotion ratings

The paper-and-pencil oddball arousal and valence ratings (mean \pm s.d.) obtained after memory testing resulted in the following scores: CTL group: $E_{\text{pos}}P$ oddballs ($5.35 \pm 0.76, 7.81 \pm 0.75$); $E_{\text{neg}}P$ oddballs ($5.56 \pm 0.73, 2.06 \pm 0.77$); P oddballs ($3.15 \pm 0.69, 5.13 \pm 0.72$). BPD patients: ($4.31 \pm 0.79, 7.21 \pm 0.80$); $E_{\text{neg}}P$ oddballs ($7.15 \pm 0.75, 1.94 \pm 0.77$); P oddballs ($2.94 \pm 0.77, 4.96 \pm 0.65$) (Fig. 2c). Separate group (CTL, BPD) \times oddball type (positive, negative, neutral) 2×3 ANOVAs were calculated, yielding significant between-group effects on arousal scores [$F(1, 1) = 14.222, p = 0.001$] and valence scores [$F(1, 1) = 4.879, p = 0.035$]. *Post hoc* two-sample *t* tests demonstrated

increased arousal scores for $E_{\text{neg}}P$ oddballs [$t(30) = -6.112, p < 0.0001$] as well as decreased arousal [$t(30) = 3.771, p = 0.001$] and valence [$t(30) = 2.209, p = 0.035$] scores for $E_{\text{pos}}P$ oddballs in patients with BPD. This constellation of changes provides evidence for a robust negativity bias in the cognitive appraisal of emotional oddballs.

DISCUSSION

In the absence of uniquely defined and identifiable biological markers in BPD (Herpertz *et al.* 1999; Posner *et al.* 2002; Berlin *et al.* 2005), the current experiment focused on emotion-induced amnesia and hypermnnesia as a potential cognitive index of a hyperarousal-dyscontrol syndrome in BPD. Our findings indicate enhanced $E_{\text{neg}} - 1$ retrograde and $E_{\text{neg}} + 1$ anterograde amnesia, relative to controls, in response to items that elicit negative emotion. This profile contrasts with a lack of predicted $E_{\text{pos}} - 1$ retrograde hypermnestic and $E_{\text{pos}} + 1$ anterograde amnesic effects in response to items that elicit positive emotion. This constellation of hyper-responsiveness to negative emotion and hypo-responsiveness to positive emotion provides biological evidence that BPD is indeed characterized by enhanced processing of emotionally negative stimuli and relative lack of processing of emotionally positive stimuli. As the effects we observed were unrelated to task demands *per se*, they suggest that this aberrant processing is an obligatory feature in BPD.

In previous studies, $E_x + 1$ anterograde effects have been interpreted as reflecting the psychological 'cost' of devoting attentional resources to preferential encoding of E_x emotional items (Hurlemann *et al.* 2005, 2006). Specifically, it has been suggested that during serial attentive and mnemonic processing, as required in the present paradigm, an amygdala-dependent E_x emotional item-induced capture of attention evokes a transient refractory period, of at least 5-s duration, which disrupts attentional reorienting and causes an inertia in encoding a following $E_x + 1$ non-emotional item. Enhanced $E_{\text{neg}} + 1$ anterograde amnesia in BPD may reflect such a process and would be in keeping with a role for the amygdala in focusing attention on E_{neg} emotional items. Enhanced attention to emotionally negative events thus

may provide a basis for less processing capacity for encoding a competing non-emotional event. By contrast, BPD patients exhibit no $E_{\text{pos}+1}$ anterograde amnesic effect (as seen in controls), a finding that may reflect a bias away from processing emotionally positive events. We note that near-ceiling von Restorff effects are preserved across valences in BPD patients, indicating no global deficit in directing attention to the perceptual 'pop-out' features of oddballs. This is consistent with reports of intact attentional faculties in non-depressed BPD patients under emotionally neutral experimental conditions (Posner *et al.* 2002; Lenzenweger *et al.* 2004).

While E_x+1 anterograde effects are thought to reflect an amygdala-driven attentional modulation of episodic encoding, E_x-1 retrograde effects are most likely to result from a direct modulation of hippocampal circuits by amygdala and prefrontal cortex (PFC) inputs (Strange *et al.* 2003; Hurlmann *et al.* 2005, 2006). This is consistent with a prevailing concept that during emotional memory formation, the amygdala communicates E_x emotional item-evoked arousal to the hippocampus, thus rendering it susceptible to valence transfer from the PFC (Dolcos *et al.* 2004b; Kensinger, 2004; Kensinger & Corkin, 2004). According to this model, PFC input is crucial for a differential expression of $E_{\text{neg}-1}$ retrograde amnesic *versus* $E_{\text{pos}-1}$ retrograde hypermnesic effects, whereas the magnitude of these effects is amygdala dependent.

The enhancement of $E_{\text{neg}\pm 1}$ modulatory effects in the present study is compatible with abnormal low-threshold and high-amplitude amygdala responses to aversive facial expressions (Donegan *et al.* 2003) and IAPS items (Herpertz *et al.* 2001) in BPD. We suggest that this negative emotion response bias in BPD is compatible with diminished reactivity of the PFC circuits involved in producing positive emotion and/or regulating negative emotion. Evidence for this view comes from neuro-imaging studies in BPD patients indicating PFC alterations at baseline (Goyer *et al.* 1994; De La Fuente *et al.* 1997; Lyoo *et al.* 1998; Juengling *et al.* 2003) as well as in response to negative emotion (Herpertz *et al.* 2001; Donegan *et al.* 2003) and serotonergic (5-HT) challenges (Soloff *et al.* 2000; Leyton *et al.* 2001). Further evidence links BPD to functional and structural

abnormalities in PFC subareas such as the orbital prefrontal cortex (OFC) (Berlin *et al.* 2005), specifically hypometabolism (Goyer *et al.* 1994; De La Fuente *et al.* 1997; Soloff *et al.* 2003) and decreased volume (Lyoo *et al.* 1998; Tebartz van Elst *et al.* 2003). OFC dysfunction in BPD would be compatible with deficient computation of positive emotion in this subregion (Dolcos *et al.* 2004b). Together, these lines of evidence provide support for the hypothesis of dual amygdala and PFC pathology as the aetiological contributor to a hyperarousal-dyscontrol syndrome in BPD (Lieb *et al.* 2004).

The degree of inhibitory control over negative emotion is a potent modulator of its psychological impact. To date, research on controllability has largely focused on the monoamine brainstem nuclei such as the 5-HT dorsal raphe nucleus (DRN) and the LC (Amat *et al.* 2005). As LC-NE signalling is under PFC top-down inhibitory control (Arnsten & Goldman-Rakic, 1984; Weiss & Simson, 1986; Jodo *et al.* 1998; Berridge & Waterhouse, 2003; Aston-Jones & Cohen, 2005) and determines the magnitude of $E_x\pm 1$ effects (Strange *et al.* 2003; Hurlmann *et al.* 2005), enhanced $E_{\text{neg}-1}$ retrograde amnesic effects in the present study may reflect deficient regulation of LC-NE bottom-up input to the amygdala. We suggest that such phasic hyperactivation of the amygdala is crucial for emotion-induced cognitive dysfunction in BPD.

On the basis of our results we speculate that interventions aimed at normalizing negativity bias and increasing PFC top-down inhibitory control provide an effective treatment strategy to influence amygdala hyper-responsiveness to negative emotion in BPD. We note that NE antagonists such as clonidine (Philipsen *et al.* 2004) are reported as exerting beneficial effects on emotional instability and impulsivity in BPD, underscoring the link between these symptoms and increased noradrenergic tone (Arnsten *et al.* 1999; Swann *et al.* 2005). By contrast, further exogenous elevation of NE levels with NE agonists such as reboxetine may provoke an exacerbation of emotional instability and impulsivity in BPD (Angheliescu *et al.* 2005). Deficient PFC capacity to down-regulate negative emotion in BPD is also susceptible to psychotherapeutic strategies aimed at

controlling attention to, and changing the subjective interpretation of, aversive events (Lieb *et al.* 2004). Such improved cognitive control in BPD may significantly decrease LC–NE hyperactivation of the amygdala in response to negative emotion and neutralize its disruptive effects on cognition (Jackson *et al.* 2000; Ochsner & Gross, 2005).

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DECLARATION OF INTEREST

None.

REFERENCES

- Amat, J., Baratta, M. V., Paul, E., Bland, S. T., Watkins, L. R. & Maier, S. F. (2005). Medial prefrontal cortex determines how stressor controllability affects behavior and dorsal raphe nucleus. *Nature Neuroscience* **8**, 365–371.
- Angelini, R., Capozzoli, F., Lepore, P., Grossi, D. & Orsini, A. (1994). Experimental amnesia induced by emotional items. *Perceptual and Motor Skills* **78**, 19–28.
- Anghelescu, I., Janen, B., Schindler, F. & Lammers, C. H. (2005). Worsening of borderline symptoms under reboxetine treatment. *Journal of Neuropsychiatry and Clinical Neurosciences* **17**, 9–560.
- APA (1994). *Diagnostic and Statistical Manual of Mental Disorders* (4th edn). American Psychiatric Press: Washington, DC.
- Arnsten, A. F. & Goldman-Rakic, P. (1984). Selective prefrontal cortical projections to the region of the locus coeruleus and raphe nucleus in the rhesus monkey. *Brain* **306**, 9–18.
- Arnsten, A. F., Mathew, R., Ubriani, R., Taylor, J. R. & Li, B. M. (1999). Alpha-1 noradrenergic receptor stimulation impairs prefrontal cortical cognitive function. *Biological Psychiatry* **45**, 26–31.
- Aston-Jones, G. & Cohen, J. D. (2005). An integrative theory of locus coeruleus–norepinephrine function: adaptive gain and optimal performance. *Annual Review of Neuroscience* **28**, 403–450.
- Berlin, H. A., Rolls, E. T. & Iversen, S. D. (2005). Borderline personality disorder, impulsivity, and the orbitofrontal cortex. *American Journal of Psychiatry* **162**, 2360–2373.
- Bernstein, D. P., Fink, L., Handelsman, L., Foote, J., Lovejoy, M., Wenzel, K., Sapareto, E. & Ruggiero, J. (1994). Initial reliability and validity of a new retrospective measure of child abuse and neglect. *American Journal of Psychiatry* **151**, 1132–1136.
- Berridge, C. W. & Waterhouse, B. D. (2003). The locus coeruleus–noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. *Brain Research Reviews* **42**, 33–84.
- Buss, A. H. & Durkee, A. (1957). An inventory for assessing different kinds of hostility. *Journal of Consulting Psychology* **21**, 343–349.
- Cahill, L., Haier, R. J., Fallon, J., Alkire, M. T., Tang, C., Keator, D., Wu, J. & McGaugh, J. L. (1996). Amygdala activity at encoding correlated with long-term, free recall of emotional information. *Proceedings of the National Academy of Sciences USA* **93**, 8016–8021.
- Canli, T., Zhao, Z., Brewer, J., Gabrieli, J. D. & Cahill, L. (2000). Event-related activation in the human amygdala associates with later memory for individual emotional experience. *Journal of Neuroscience* **20**, RC99.
- Cycowicz, Y. M., Friedman, D., Rothstein, M. & Snodgrass, J. G. (1997). Picture naming by young children: norms for name agreement, familiarity, and visual complexity. *Journal of Experimental Child Psychology* **65**, 171–237.
- De La Fuente, J. M., Goldman, S., Stanus, E., Vizuete, C., Morlan, I., Bobes, J. & Mendlewicz, J. (1997). Brain glucose metabolism in borderline personality disorder. *Journal of Psychiatric Research* **31**, 531–541.
- Dolan, R. J. (2002). Emotion, cognition, and behavior. *Science* **298**, 1191–1194.
- Dolcos, F., LaBar, K. S. & Cabeza, R. (2004a). Interaction between the amygdala and the medial temporal lobe memory system predicts better memory for emotional events. *Neuron* **42**, 855–863.
- Dolcos, F., LaBar, K. S. & Cabeza, R. (2004b). Dissociable effects of arousal and valence on prefrontal activity indexing emotional evaluation and subsequent memory: an event-related fMRI study. *Neuroimage* **23**, 64–74.
- Domes, G., Winter, B., Schnell, K., Vohs, K., Fast, K. & Herpertz, S. C. (2006). The influence of emotions on inhibitory functioning in borderline personality disorder. *Psychological Medicine* **36**, 1163–1172.
- Donegan, N. H., Sanislow, C. A., Blumberg, H. P., Fulbright, R. K., Lacadie, C., Skudlarski, P., Gore, J. C., Olson, I. R., McGlashan, T. H. & Wexler, B. E. (2003). Amygdala hyperreactivity in borderline personality disorder: implications for emotional dysregulation. *Biological Psychiatry* **54**, 1284–1293.
- Fertuck, E. A., Lenzenweger, M. F., Clarkin, J. F., Hoermann, S. & Stanley, B. (2006). Executive neurocognition, memory systems, and borderline personality disorder. *Clinical Psychology Review* **26**, 346–375.
- Freyberger, H. J., Spitzer, C., Stieglitz, R. D., Kuhn, G., Magdeburg, N. & Bernstein-Carlson, E. (1998). Questionnaire on dissociative symptoms. German adaptation, reliability and validity of the American Dissociative Experience Scale (DES). *Psychotherapie, Psychosomatik, Medizinische Psychologie* **48**, 223–229.
- Goyer, P. F., Andreason, P. J., Semple, W. E., Clayton, A. H., King, A. C., Compton-Toth, B. A., Schulz, S. C. & Cohen, R. M. (1994). Positron-emission tomography and personality disorders. *Neuropsychopharmacology* **10**, 21–28.
- Gunderson, J. G. & Zanarini, M. C. (1983). *The Revised Diagnostic Interview for Borderlines (DIB-R)*. McLean Hospital: Belmont, MA.
- Hamann, S. B., Ely, T. D., Grafton, S. T. & Kilts, C. D. (1999). Amygdala activity related to enhanced memory for pleasant and aversive stimuli. *Nature Neuroscience* **2**, 289–293.
- Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry* **23**, 56–62.
- Hampel, R. & Selg, H. (1975). *FAF – The Questionnaire for Measuring Factors of Aggression* [in German]. Hogrefe: Göttingen.
- Harmer, C. J., Hill, S. A., Taylor, M. J., Cowen, P. J. & Goodwin, G. M. (2003). Toward a neuropsychological theory of antidepressant drug action: increase in positive emotional bias after potentiation of norepinephrine activity. *American Journal of Psychiatry* **160**, 990–992.
- Harmer, C. J., Shelley, N. C., Cowen, P. J. & Goodwin, G. M. (2004). Increased positive versus negative affective perception and memory in healthy volunteers following selective serotonin and norepinephrine reuptake inhibition. *American Journal of Psychiatry* **161**, 1256–1263.
- Helmstaedter, C., Lendt, M. & Lux, S. (2001). *Verbaler Lern- und Merkfähigkeitstest (VLMT)*. Hogrefe: Göttingen.
- Herpertz, S., Sass, H. & Favazza, A. (1997). Impulsivity in self-mutilative behavior: psychometric and biological findings. *Journal of Psychiatric Research* **31**, 451–465.
- Herpertz, S. C., Dietrich, T. M., Wenning, B., Krings, T., Erberich, S. G., Willmes, K., Thron, A. & Sass, H. (2001). Evidence of

- abnormal amygdala functioning in borderline personality disorder: a functional MRI study. *Biological Psychiatry* **50**, 292–298.
- Herpertz, S. C., Kunert, H. J., Schwenger, U. B. & Sass, H. (1999). Affective responsiveness in borderline personality disorder: a psychophysiological approach. *American Journal of Psychiatry* **156**, 1550–1556.
- Hurlmann, R., Hawellek, B., Matusch, A., Kolsch, H., Wollersen, H., Madea, B., Vogeley, K., Maier, W. & Dolan, R. J. (2005). Noradrenergic modulation of emotion-induced forgetting and remembering. *Journal of Neuroscience* **25**, 6343–6349.
- Hurlmann, R., Hawellek, B., Vogeley, K., Wagner, M., Pieperhoff, P., Amunts, K., Oros-Peusquens, A. M., Shah, N. J., Maier, W. & Dolan, R. J. (2006). Amygdala control of emotion-induced forgetting and remembering: evidence from Urbach-Wiethe syndrome. *Neuropsychologia* **45**, 877–884. Published online 5 October 2006. PMID: 17027866.
- Jackson, D. C., Malmstadt, J. R., Larson, C. L. & Davidson, R. J. (2000). Suppression and enhancement of emotional responses to unpleasant pictures. *Psychophysiology* **37**, 515–522.
- Jodo, E., Chiang, C. & Aston-Jones, G. (1998). Potent excitatory influence of prefrontal cortex activity on noradrenergic locus coeruleus neurons. *Neuroscience* **83**, 63–79.
- Juengling, F. D., Schmahl, C., Hesslinger, B., Ebert, D., Bremner, J. D., Gostomzyk, J., Bohus, M. & Lieb, K. (2003). Positron emission tomography in female patients with borderline personality disorder. *Journal of Psychiatric Research* **37**, 109–115.
- Kensinger, E. A. (2004). Remembering emotional experiences: the contribution of valence and arousal. *Reviews in the Neurosciences* **15**, 241–251.
- Kensinger, E. A. & Corkin, S. (2004). Two routes to emotional memory: distinct neural processes for valence and arousal. *Proceedings of the National Academy of Sciences USA* **101**, 3310–3315.
- Kilpatrick, L. & Cahill, L. (2003). Amygdala modulation of parahippocampal and frontal regions during emotionally influenced memory storage. *Neuroimage* **20**, 2091–2099.
- Kunert, H. J., Druce, H. W., Sass, H. & Herpertz, S. C. (2003). Frontal lobe dysfunctions in borderline personality disorder? Neuropsychological findings. *Journal of Personality Disorders* **17**, 497–509.
- LaBar, K. S. & Cabeza, R. (2006). Cognitive neuroscience of emotional memory. *Nature Reviews Neuroscience* **7**, 54–64.
- Lang, P. J. (1995). The emotion probe. Studies of motivation and attention. *The American Psychologist* **50**, 372–385.
- Lang, P. J., Bradley, M. M. & Cuthbert, B. N. (2005). *International Affective Picture System (IAPS): Affective Ratings of Pictures and Instruction Manual*. Technical Report A-6. University of Florida: Gainesville, FL.
- Lenzenweger, M. F., Clarkin, J. F., Fertuck, E. A. & Kernberg, O. F. (2004). Executive neurocognitive functioning and neurobehavioral systems indicators in borderline personality disorder: a preliminary study. *Journal of Personality Disorders* **18**, 421–438.
- Leyton, M., Okazawa, H., Diksic, M., Paris, J., Rosa, P., Mzengeza, S., Young, S. N., Blier, P. & Benkelfat, C. (2001). Brain regional alpha-¹⁴C-methyl-L-tryptophan trapping in impulsive subjects with borderline personality disorder. *American Journal of Psychiatry* **158**, 775–782.
- Lieb, K., Zanarini, M. C., Schmahl, C., Linehan, M. M. & Bohus, M. (2004). Borderline personality disorder. *Lancet* **364**, 453–461.
- Lyoo, I. K., Han, M. H. & Cho, D. Y. (1998). A brain MRI study in subjects with borderline personality disorder. *Journal of Affective Disorders* **50**, 235–243.
- McGaugh, J. L. (2004). The amygdala modulates the consolidation of memories of emotionally arousing experiences. *Annual Review of Neuroscience* **27**, 1–28.
- Ochsner, K. N. & Gross, J. J. (2005). The cognitive control of emotion. *Trends in Cognitive Sciences* **9**, 242–249.
- Osterrieth, P. A. (1944). Le test de copie d'une figure complexe. *Archives de Psychologie* **30**, 206–356.
- Patton, J. H., Stanford, M. S. & Barratt, E. S. (1995). Factor structure of the Barratt Impulsiveness Scale. *Journal of Clinical Psychology* **51**, 768–774.
- Phelps, E. A. (2006). Emotion and cognition: insights from studies of the human amygdala. *Annual Review of Psychology* **57**, 27–53.
- Philipsen, A., Richter, H., Schmahl, C., Peters, J., Rusch, N., Bohus, M. & Lieb, K. (2004). Clonidine in acute aversive inner tension and self-injurious behavior in female patients with borderline personality disorder. *Journal of Clinical Psychiatry* **65**, 1414–1419.
- Posner, M. I., Rothbart, M. K., Vizuetta, N., Levy, K. N., Evans, D. E., Thomas, K. M. & Clarkin, J. F. (2002). Attentional mechanisms of borderline personality disorder. *Proceedings of the National Academy of Sciences USA* **99**, 16366–16370.
- Raitan, R. M. (1958). Validity of the trail making test as an indication of organic brain damage. *Perceptual and Motor Skills* **8**, 271–276.
- Rey, A. (1941). L'examen psychologique dans les cas d'encéphalopathie traumatique. *Archives de Psychologie* **30**, 286–340.
- Richardson, M. P., Strange, B. A. & Dolan, R. J. (2004). Encoding of emotional memories depends on amygdala and hippocampus and their interactions. *Nature Neuroscience* **7**, 278–285.
- Rickham, P. P. (1964). Human experimentation. Code of ethics of the World Medical Association. Declaration of Helsinki. *British Medical Journal* **5402**, 177–178.
- Ruocco, A. C. (2005). The neuropsychology of borderline personality disorder: a meta-analysis and review. *Psychiatry Research* **137**, 191–202.
- Russell, J. A. (1980). A circumplex model of affect. *Journal of Personality and Social Psychology* **39**, 1161–1178.
- Skodol, A. E., Gunderson, J. G., Pfohl, B., Widiger, T. A., Livesley, W. J. & Siever, L. J. (2002a). The borderline diagnosis I: psychopathology, comorbidity, and personality structure. *Biological Psychiatry* **51**, 936–950.
- Skodol, A. E., Siever, L. J., Livesley, W. J., Gunderson, J. G., Pfohl, B. & Widiger, T. A. (2002b). The borderline diagnosis II: biology, genetics, and clinical course. *Biological Psychiatry* **51**, 951–963.
- Snodgrass, J. G. & Vanderwart, M. (1980). A standardized set of 260 pictures: norms for name agreement, image agreement, familiarity, and visual complexity. *Journal of Experimental Psychology: Human Learning* **6**, 174–215.
- Soloff, P. H., Meltzer, C. C., Becker, C., Greer, P. J., Kelly, T. M. & Constantine, D. (2003). Impulsivity and prefrontal hypometabolism in borderline personality disorder. *Psychiatry Research* **123**, 153–163.
- Soloff, P. H., Meltzer, C. C., Greer, P. J., Constantine, D. & Kelly, T. M. (2000). A fenfluramine-activated FDG-PET study of borderline personality disorder. *Biological Psychiatry* **47**, 540–547.
- Strange, B. A. & Dolan, R. J. (2004). Beta-adrenergic modulation of emotional memory-evoked human amygdala and hippocampal responses. *Proceedings of the National Academy of Sciences USA* **101**, 11454–11458.
- Strange, B. A., Hurlmann, R. & Dolan, R. J. (2003). An emotion-induced retrograde amnesia in humans is amygdala- and beta-adrenergic-dependent. *Proceedings of the National Academy of Sciences USA* **100**, 13626–13631.
- Swann, A. C., Birnbaum, D., Jagar, A. A., Dougherty, D. M. & Moeller, F. G. (2005). Acute yohimbine increases laboratory-measured impulsivity in normal subjects. *Biological Psychiatry* **57**, 1209–1211.
- Tebartz van Elst, L., Hesslinger, B., Thiel, T., Geiger, E., Haegle, K. & Lemieux, L. (2003). Frontolimbic brain abnormalities in patients with borderline personality disorder: a volumetric magnetic resonance imaging study. *Biological Psychiatry* **54**, 163–171.
- Tewes, U. (1991). *Hamburg-Wechsler-Intelligenztest für Erwachsene – Revision 1991*. Hogrefe: Göttingen.
- Tulving, E. (1969). Retrograde amnesia in free recall. *Science* **164**, 88–90.
- von Restorff, H. (1933). Ueber die Wirkungen von Bereichsbildung im Spurenfeld. *Psychologische Forschung* **18**, 299–342.
- van Stegeren, A. H., Goekoop, R., Everaerd, W., Scheltens, P., Barkhof, F., Kuijer, J. P. & Rombouts, S. A. (2005).

Noradrenaline mediates amygdala activation in men and women during encoding of emotional material. *Neuroimage* **24**, 898–909.

Wallace, W. P. (1965). Review of the historical empirical and theoretical status of the von Restorff phenomenon. *Psychological Bulletin* **63**, 410–424.

Weiss, J. M. & Simson, P. G. (1986). Depression in an animal model: focus on the locus ceruleus. *Ciba Foundation Symposium* **123**, 191–215.

Wittchen, H. U., Zaudig, M. & Fydrich, T. (1997). *Structured Clinical Interviews for DSM-IV Diagnoses (SCID I and II)* [in German]. Hogrefe: Göttingen.