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. 2002a,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. 2004a; 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. 2004).
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. 2002a,b) 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 \(\geq 4\) weeks \((n=10)\). Sixteen female control subjects (age range 20–34 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 \(\geq 12\) 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.

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

<table>
<thead>
<tr>
<th></th>
<th>CTL ((n=16))</th>
<th>BPD ((n=16))</th>
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<tbody>
<tr>
<td><strong>Demographics</strong></td>
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<tr>
<td>Age, years</td>
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<td>16</td>
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<td>Education, years</td>
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<td>11.6 (1.3)</td>
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<tr>
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<td><strong>Neuropsychological data</strong></td>
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<td>VLMT Trial 1–5</td>
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<td>52.49 (3.44)</td>
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<tr>
<td>Rey–Osterrieth CFT Copy</td>
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<td>34.36 (3.92)</td>
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<tr>
<td>Rey–Osterrieth CFT Delay</td>
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<td>23.16 (3.21)</td>
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<tr>
<td>TMT-A</td>
<td>25.33 (4.92)</td>
<td>25.91 (4.68)</td>
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<td><strong>Diagnostic data</strong></td>
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<td>HAMD-21</td>
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<td>FAF total</td>
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<td>BIS-11 total</td>
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<td>BDHI total</td>
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<tr>
<td>Previous suicide attempt</td>
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</table>

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

### 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 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 posP) and 12 negative (E negP) oddballs. E posP and E negP 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. LIp). 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 ± 1) corresponding to a time window of ±5 s. The design and timeline of the episodic memory test are illustrated in Fig. 1a, 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 ± 1, LI x) for the emotional (positive, negative) conditions, which were analysed in relation to the corresponding recall scores (P, P ± 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±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 (±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
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 SIp 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) × position (oddball, oddball ±1) 3 × 3 ANOVA restricted to the CTL group yielded effects of valence [$F(2,30)=13.408$, $p<0.0001$],
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 \( \times \) 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

\( \text{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 \( (E_{\text{neg}}) \) in combination with decreased arousal and valence scores for positive oddballs \( (E_{\text{pos}}) \) 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 \( \pm 1 \), standard items preceding or following the oddball; \( E_{\text{pos}} \), positive oddball; \( P \), neutral oddball; \( E_{\text{neg}} \), negative oddball. Error bars indicate 1 s.e.

\( R. \) Hurlemann et al.}
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) × condition × position 2 × 3 × 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 × group [F(2, 60) = 6.433, p = 0.003], position × group [F(2, 60) = 6.405, p = 0.003], condition × position [F(4, 120) = 31.617, p < 0.0001], and three-way condition × position × group [F(4, 120) = 4.090, p = 0.004] interaction effects. Post hoc two-sample t tests demonstrated that E −1 [t(30) = 4.945, p < 0.0001], E +1 [t(30) = −3.196, p = 0.003] and E pos−1 [t(30) = 3.250, p = 0.003] recall was different between BPD and CTL groups. A condition × 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 × position interaction [F(4, 60) = 21.769, p < 0.0001] effects. Post hoc one-sample t tests revealed enhanced retrograde E −1 (−41.15%) [t(15) = −8.399; p < 0.0001] and anterograde E +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 −1 −1, −21.35 (−38.02); E +1 +1, −12.50 (−28.65) (Fig. 2a, b).

Analysis of emotion ratings

The paper-and-pencil oddball arousal and valence ratings (mean ± s.d.) obtained after memory testing resulted in the following scores: CTL group: E posP oddballs (5.35 ± 0.76, 7.81 ± 0.75); E negP oddballs (5.56 ± 0.73, 2.06 ± 0.77); P oddballs (3.15 ± 0.69, 5.13 ± 0.72). BPD patients: (4.31 ± 0.79, 7.21 ± 0.80); E negP oddballs (7.15 ± 0.75, 1.94 ± 0.77); P oddballs (2.94 ± 0.77, 4.96 ± 0.65) (Fig. 2c). Separate group (CTL, BPD) × 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 negP oddballs [(30) = −6.112, p < 0.0001] as well as decreased arousal [(30) = 3.771, p = 0.001] and valence [(30) = 2.209, p = 0.035] scores for E posP 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 hypermnesia as a potential cognitive index of a hyperarousal-dyscontrol syndrome in BPD. Our findings indicate enhanced E −1 retrograde and E +1 anterograde amnesia, relative to controls, in response to items that elicit negative emotion. This profile contrasts with a lack of predicted E pos−1 retrograde hypermnesic and E 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 pos+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; Hurlemann 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 neuroimaging 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 raphé 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; Hurlemann 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 (Angelescu et al. 2005). Deficient PFC capacity to down-regulate negative emotion in BPD is also susceptible to psychotherapeutical 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 hyper-activation 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.

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