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To Professor Robin Murray Psychological Medicine Editorial Office Douglas House, 18E Trumpington Road Cambridge CB2 8AH, UK

Dear Professor Murray,

We are pleased to submit our manuscript

"The neural correlates of affective dysregulation in the attachment narratives of patients with borderline personality disorder: An fMRI study"

to the Journal Psychological Medicine as an Original Article.

Our work provides a unique approach to neuroimaging data on patients with a Borderline Personality Disorder (BPD) while they were overtly talking in the scanner. The paradigm included the instruction to tell narrative-based stories in response to a set of validated attachment pictures from the Adult Attachment Projective (George & West 2003). This established interview-assessment procedure evaluates the mental organization of attachment status by coding linguistic processes of attachment disorganization, a type of attachment frequently reported in attachment studies examining BPD patients.

Our paradigm was validated in a recently published pilot study with healthy controls (Buchheim et al. 2006). In the present study, we provide data that underly two components related to BPD, i. e. emotional hyersensitivity and emotional dysregulation. Borderline patients with unresolved (i.e., disorganized) attachment classifications do not only show increased amygdala activation during the attachment task, but also fail to recruit the cognitive control system that is comprised of the rostral cingulate zone and the right dorsolateral prefrontal cortex

We think that our paper is of substantial interest with respect to understanding the neural substrates of the relationship between borderline personality disorder and attachment. It might also be useful from a methodological point of view, as investigating neural correlates of overt speech is of great interest for a wider variety of psychiatric disorders.

We are looking forward to hearing from you.

Yours sincerely

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Neural correlates of attachment dysregulation in BPD

The neural correlates of affective dysregulation in the attachment narratives of

patients with borderline personality disorder: An fMRI study

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Abstract

Background: Individuals with borderline personality disorder (BPD) are characterized by emotional instability, impaired emotion regulation and disorganized (unresolved) attachment patterns associated with abusive childhood experiences. We explored the neural correlates of affective dysregulation during the activation of the attachment system in BPD patients compared to healthy controls using functional magnetic resonance imaging.

Methods: 11 female patients with BPD without posttraumatic stress disorder and 17 healthy female controls matched for age and education told stories in the scanner in response to the Adult Attachment Projective, a seven-picture set assessment of adult attachment. The picture set includes theoretically-derived attachment scenes, such as separation, death, threat and potential abuse. The picture presentation order is designed to gradually increase the activation of the attachment system. Each picture stimulus was presented for 2 minutes. Analyses examine group differences in attachment classifications and neural activation patterns over the course of the task.

Results: The disorganized (unresolved) attachment was associated with increasing amygdala activation over the course of the attachment task in patients as well as controls. Unresolved controls, but not patients, showed activation in the right dorsolateral prefrontal cortex and the rostral cingulate zone. We interpret this as a neural signature of BPD patients' inability to exert top-down control under conditions of attachment distress.

Conclusions: These findings point to possible neural mechanisms for underlying affective dysregulation in BPD in the context of attachment trauma and fear.

Key words: Borderline Personality Disorder, emotion, attachment system, amygdala, functional MRI

Introduction

Affect dysregulation is one of the core features of borderline personality disorder (BPD). It is thought to result from emotional vulnerability combined with the inability to modulate emotional responses (Linehan *et al.*, 1994; Skodol *et al.*, 2002; Lieb *et al.*, 2004; Putnam and Silk, 2005; Conklin *et al.*, 2006). Early experiences of maltreatment, such as sexual and physical abuse and emotional neglect, are implicated in the etiology of BPD (Gunderson *et al.*, 2006; Zanarini *et al.*, 2006). Adverse attachment experiences are considered to be risk factors for poor emotion-regulation, anxiety, and fear (Bowlby, 1973).

Attachment theory provides a powerful framework for understanding links between close relationships, mental representations of attachment, and psychopathology (Westen et al., 2006). Adult attachment research has typically used the Adult Attachment Interview (AAI) as the "gold standard" of narrative-based assessment of mental representations of attachment (George et al., 1984/1985/1996; Main and Goldwyn, 1995; George et al., 1999; George and West, 2001). Attachment classifications are derived from the linguistic analysis of attachment narratives. These classifications represent "states of mind" regarding childhood experience with attachment figures. Classifications fall into two main attachment patterns: organized/"resolved" and disorganized/"unresolved." Unresolved attachment is defined as a breakdown of organized forms of affective regulation that is conceived as the dysregulation of the attachment system. AAIbased research has demonstrated a consistent predominance of unresolved attachment in borderline patients. These patients' attachment narratives are characterized by mental and narrative lapses that evidence their inability to contain and organize memories of distressing loss, sexual abuse, or physical abuse (Fonagy et al., 1996; Fonagy et al., 2000; Agrawal et al., 2004; Levy et al., 2006). In short, narrative-based representation is disorganized and dysregulated by the distress they experience when asked to tell their personal attachment "story."

Emotional vulnerability may result from a marked sensitivity to emotional stimuli, an impairment of emotion regulation, or both. From a neurophysiological perspective, increased emotional sensitivity should be reflected in increased amygdala activation (Davis and Whalen, 2001) and emotion regulation should be mediated by prefrontal regions (Ochsner and Gross, 2005).

Studies using the startle reflex as a measure for emotional hyper-reactivity reported evidence that favored (Ebner-Priemer et al., 2005) and failed (Herpertz et al., 1999) to support this hypothesis. Two fMRI studies reported emotional hyper-reactivity as measured by increased amygdala activation in response to emotional pictures (Herpertz et al., 2001) or faces (Donegan et al., 2003). Furthermore, reductions in amygdala (and hippocampal) volume have been reported for BPD patients (Driessen et al., 2000; Schmahl et al., 2003; Tebartz van Elst et al., 2003; Irle et al., 2005). Positron emission tomography studies have found hypometabolism in prefrontal cortex (PFC) of BPD patients compared with normal controls (De La Fuente et al., 1997; Soloff et al., 2000) and above-normal activation of dorsolateral PFC when BPD patients were confronted with scripts designed to evoke personal memories of abandonment and abuse (Schmahl et al., 2003; Schmahl et al., 2004). In a magnetic resonance spectroscopy study (Tebartz van Elst et al., 2001), BPD patients showed decreased levels of N-acetyl aspartate (suggestive of impaired neural functioning) in the dorsolateral PFC. Two further recent studies investigated brain activation during processing of autobiographical memory in BPD. One study found less activation in emotion processing areas (Schnell et al., 2007) whereas an other study looking at unresolved life events compared to resolved life events found, among other regions, increasing activation of amygdala and anterior cingulate cortex (Beblo et al., 2006).

The functional neuroimaging studies summarized above measured brain activation patterns in response to visual stimuli (pictures, faces) or passively presented scripts. Several studies have investigated the neural correlates of "social" attachment (i.e., defined loosely as individuals in intimate relationships) in healthy populations. These studies were mostly presenting pictures of the beloved sexual partner or the own infant by contrasting familiar versus non-familiar stimuli (Bartels and Zeki, 2000; Bartels and Zeki, 2004; Leibenluft *et al.*, 2004; Nitschke *et al.*, 2004). One study challenged subjects to think or not to think about attachment related situations (Gillath *et al.*, 2005). A recent study investigated brain activity and skinconductance during a semantic conceptual priming attachment task (Lemche *et al.* 2006). Results showed that these unique intimate emotional states were linked to both cortical and subcortical responses, including the amygdala, cingulate cortex, insula, basal ganglia, and orbitofrontal cortex. No patient study has been reported which examined the neural activation by instructing subjects to talk about attachment relevant material while being scanned.

Recently, we developed an fMRI paradigm to investigate the neural correlates of attachment representation while subjects tell stories to attachment picture stimuli (Buchheim *et al.*, 2006a; Buchheim *et al.*, 2006b). This study of healthy subjects from a community sample examined neural activation in the scanner as subjects responded to a validated narrative-based assessment for attachment, the Adult Attachment Projective (George and West, 2003). We found unresolved attachment to be associated with increasing activation of the right amygdala, the left hippocampus and the right prefrontal cortex over the course of the attachment task (i.e. from the first to the last attachment pictures).

The present study investigated neural correlates of attachment narratives in borderline patients using the same paradigm. Based on research linking BPD to unresolved attachment, we expected that amygdala activation in our task would be stronger in the patient group than the

control group. We also expected that neural signs of emotion regulation in the cognitive control system (dorsolateral prefrontal cortex and/or anterior cingulate) would be decreased or absent in the patient group.

Methods and Materials

Subjects

Thirteen female BPD patients were recruited from an inpatient psychiatric hospital and compared to 21 healthy female volunteers. Subjects were matched for age and education. Clinical diagnoses were assessed by a trained psychiatrist using the Structured Clinical Interview for DSM-IV (SCID-I and SCID-II) and the International Personality Disorder Examination (IPDE). Exclusion criteria were left handedness, metal in body, language problems, and serious medical or neurological illness, including comorbid psychotic disorders and bipolar disorder. None of our patients met diagnostic criteria for posttraumatic stress disorder or dissociative disorder. Six subjects had to be excluded from our main analysis. Four controls were excluded for movement in the fMRI apparatus (> 2 mm, see below). The only two patients who were classified as resolved were excluded from analysis because two subjects were not enough to allow any substantial group inferences. The final sample consisted of 11 BPD patients and 17 controls. Exclusion of the six subjects did not affect group homogeneity with respect to age (BPD. 27.8) years \pm 6.7; controls, 28.4 years \pm 7.5) and education (BPD, 10.8 years \pm 1.4; controls, 10.9 years \pm 1.6). Comorbidity in the final group included depression (n=6), anxiety or panic disorder (n=2), and somatoform disorder (n=3). 45% (5/11) of the patients were treated with psychotropic medication, including low doses of neuroleptics (perazin, promethazine and chlorprothixene, n=3), serotonin-reuptake inhibitors (n=2) and lithium (n=1). After complete description of the study, participants provided written informed consent. The protocol was approved by the local

| institutional eth | ics committee. | Clinical c | haracteristics | s of the sam | ple are show | vn in Table 1 |
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Attachment Stimulus Presentation and Attachment Coding

Participants were administered with the fMRI-adapted version of the Adult Attachment Projective (AAP) (Buchheim *et al.*, 2006a), a validated measure that assesses mental representations of attachment. The measure is comprised of a set of eight drawings, one neutral scene and seven attachment scenes. The picture set includes events known to activate attachment, such as illness, separation, solitude, death, and threat. The picture presentation order is designed to gradually increase the activation of the attachment system (George *et al.*, 1999; George and West, 2003). Pictures are administered in the following sequence: Child at Window – a child looks out a window; Departure – an adult man and woman stand facing each other with suitcases positioned nearby; Bench – a youth sits alone on a bench; Bed – a child and woman sit opposite each other on the child's bed; Ambulance – a woman and a child watch someone being put on an ambulance stretcher; Cemetery – a man stands by a gravesite head stone; and Child in Corner – a child stands askance in a corner (example picture stimuli are provided in Figure 1).

| Insert Figure 1 here |
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| |

AAP-interviews are classified on the basis of verbatim narratives. The AAP coding system defines unresolved attachment as an individual's failure to contain frightening or threatening narrative material demonstrated, for example, by story elements representing attachment

dysregulation, i. e. death, attack, abuse or devastation (George *et al.*, 1999; George and West, 2003). AAP stories are classified as resolved when the story material is emotionally contained. This requires the story characters to demonstrate the capacity to think through solutions drawing on internalized attachment resources (the "internalized secure base"), the ability to seek out attachment figures, the capacity for positive action, or for other characters to provide comfort, explanation, or assistance to quell frightening distress (Table 2).

Insert Table 2 here

The psychometric properties of the AAP were established in an independent validity study with 144 non-patient subjects. This study found strong psychometric validity, including statistically significant inter-judge reliability, test-retest reliability (after three months), discriminant validity, and convergent construct validity with the Adult Attachment Interview (AAI) (George *et al.*, 1984/1985/1996; George and West, 2003).

In the present study, two blind, reliable AAP judges independently coded the AAP narratives of the stories that participants told in the scanner. Inter-judge agreement for resolved versus unresolved classification categories was kappa = .93. AAP validity for scanner-produced stories was established through convergent classifications with the AAI, administered one month after fMRI acquisition and classified by a blind trained AAI judge. As also reported in a review on AAP classifications in different clinical groups (Buchheim and George), the correspondence between the AAP and AAI resolved vs. unresolved categories in this sample was high (kappa = .70).

MRI Acquisition

Experimental procedure: Subjects were first trained in the AAP story telling task prior to entering the scanner using two non-AAP "neutral" (i.e., not attachment scenes) pictures. The training procedure was repeated two more times, if necessary. During scanning, subjects were presented the standard AAP instruction ("what led up to that scene, what are the characters thinking or feeling, and what might happen next?") for 10 sec and a fixation cross for 10 sec. This was followed by one of the seven AAP pictures (120 sec) in the order of picture presentation described in the method section. Subjects were instructed to talk about the picture for 2 minutes or as long as possible. A fixation cross was shown for 15 sec after picture presentation until beginning a new cycle of instruction and picture presentation. The total procedure included 9 pictures, the 2 neutral and 7 standard AAP attachment stimuli.

Data Acquisition: 1.5 Tesla Siemens Magnetom Symphony scanner (Siemens, Erlangen, Germany), image size: 64 × 64 voxels, FoV of 192 mm, slice thickness 4 mm with 1 mm gap, 25 slices, TE/TR 40 ms/2500 ms, total acquisition time 25 minutes (= 598 volumes, one session). Instructions and pictures were presented with fMRI compatible video-goggles (Resonance Technologies, Northridge, CA). Speech was digitally recorded beginning at the onset of each picture using an fMRI compatible microphone and saved digitally on a computer using Cool Edit Pro (Syntrillium Software Cop. Phoenix, Arizona). Head movement was minimized by using padded earphones fixating the head within the gradient insert coil.

Statistical Analysis and Image Analysis

Group differences of the behavioral attachment data were analyzed using the Kruskal-Wallis H-test and the exact Mann-Whitney U-test (SPSS version 14). Non-parametric tests were used because of the non-normal distribution of the dependent variables. Preprocessing and statistical analysis of fMRI data were carried out with SPM2 (http://www.fil.ion.ucl.ac.uk) and MATLAB 6.1 (MathWorks, Natick, Massachusetts). The first four images were discarded to

account for equilibration effects. Individual functional images were corrected for motion artifacts by realignment to the first volume of each session. As noted earlier, we excluded four control subjects because of excessive head movement (> 2 mm within a trial cycle) in order to minimize movement effects. Further preprocessing included spatial normalization (3x3x3 mm) and smoothing (FWHM 8 mm). The regression model for each subject was as follows: Each of the nine pictures had three or two individual regressors with variable duration depending on the time of speech: Regressor 1, modeling the time from onset of picture till onset of speech; regressor 2, modeling the picture during speaking; and regressor 3, modeling the time from offset of speech till end of picture presentation (if the subject did talk for less than 2 minutes). Three more regressors were built, each modeling all nine pictures: Regressor 4, (onset of every single word of all pictures as a stick function); regressor 5, (instructions); and regressor 6, (all fixation crosses = base line). Regressors of interest were convolved with a function that modeled a prototypical hemodynamic response before inclusion into the regression model. Finally, six more regressors modeled residual motion. For each trial the variance of each voxel was estimated according to the General Linear Model Individual regionally specific effects of interest were calculated for each participant using linear contrasts, resulting in a t-statistic for every voxel.

The effects of interests for this study were narrative story responses to the seven attachment pictures. We calculated the contrast picture presentation for each subject during speech (regressor 2) + picture presentation before the subjects starts to speak (regressor 1) versus baseline (fixation cross), thereby including potential mental processes before the actual speaking phase starts. For each subject, contrasts for single pictures were calculated, that is, seven contrasts for the attachment pictures ordered 1-7.

A within subject ANOVA with three groups (resolved healthy controls, unresolved healthy controls and unresolved BPD patients) was calculated as a second level analysis in order

to test for effects of group and attachment classification. The AAP is designed to activate the attachment system increasingly from picture 1 to 7. The contrast of interest within each group was labeled "AAP effect" (-3-2-10123), in accordance with the results of our pilot study (Buchheim *et al.*, 2006a). *t*-statistics for each voxel were set at a threshold of p < 0.001 uncorrected for multiple comparisons and a cluster threshold of p < 0.05. We allowed a small volume correction for regions of interest with family wise error correction of p < 0.05 for those regions for which we had a priori hypotheses (amygdala, dorsolateral prefrontal cortex, dorsal anterior cingulate). Talairach and Tournoux (Talairach and Tournoux, 1988) and Duvernoy (Duvernoy, 1999) atlases were used to identify all brain areas.

Results

Behavioral data

Borderline patients differed significantly from controls in all clinical scales (Table 1). As expected, the majority of the BPD patients were judged unresolved (11/13, 85%) in the AAP. Ten of 17 (59%) controls were judged resolved and seven (41%) were judged as unresolved. The overall distribution of attachment status differed significantly between borderline patients and controls (Fisher's exact test, p = .026).

Neuroimaging data:

The goal of the neuroimaging analysis was to examine the AAP effect (increasing attachment activation during the task) in control and borderline subjects. The first analysis examined the AAP effect for the control group. Three regions showed increasing activation during the task: right amygdala, right dorsolateral prefrontal cortex and medial prefrontal cortex in the rostral cingulate zone (Tab. 3). The second analysis compared all controls with all patients.

We found significantly more activation of the rostral cingulate zone in the healthy controls and significantly more activation of the right amygdala in the patient group. The third analysis examined these three regions in order to understand the contribution of attachment status and diagnosis to these activations. This analysis was performed by contrasting the three subgroups of our sample with each other (Fig. 2).

The results of these analyses are shown in Table 3. An AAP effect was found in the amygdala in both unresolved groups (unresolved controls and unresolved BPD patients). An AAP effect in the rostral cingulate zone was found only in the controls (resolved and unresolved). An AAP effect in the right DLPFC was found only in the unresolved controls.

Insert Figure 2 and Table 3 here

Discussion

In the present study, we investigated the neural correlates of attachment dysregulation in BPD patients compared to controls. This study used an a new paradigm that evaluated neural response patterns while subjects told attachment stories in response to AAP stimuli in the fMRI scanner. The fMRI analysis model followed the logic of the design of the attachment measure. According to this logic, the picture presentation sequence increasingly activates the attachment system by introducing more and more stressful attachment stimuli. This increasing activation over the task we labeled as "AAP effect". Due to the fact that almost all BDP patients were classified as unresolved we investigated only three classification groups: resolved controls, unresolved controls and unresolved BDP patients. There were three main imaging finding. First, all unresolved subjects (borderline and controls), but not the resolved controls, showed the AAP

effect in relation to increasing amygdala activation. Second, all controls (resolved and unresolved), but not the unresolved patients, showed the AAP effect in relation to increasing activation of the rostral cingulate zone. Third, only the unresolved controls showed an AAP effect of increasing activation of the right DLPFC. This effect was not found in the resolved controls or the unresolved patients. We now discuss these results in the context of the attachment research.

As expected based on prior studies (Fonagy *et al.*, 2000; Agrawal *et al.*, 2004), the majority of the BPD patients in our sample were classified as unresolved. This was found using two independent attachment measures as we did in our pilot sample (Buchheim *et al.*, 2006b). How do these attachment findings can be related to the neural patterns found in the three groups?

As shown in Figure 2, the AAP effect (increasing activation during the task) was present in the right amygdala in both unresolved groups. This finding is consistent with the results of our pilot study (Buchheim *et al.*, 2006b). Amygdala activation has been found in other studies as associated with a range of negative and positive emotional stimuli (Davis and Whalen, 2001). The stimuli used in the present study were not general emotional stimuli. The AAP picture stimuli were selected specifically because of their established ability to activate attachment. Therefore, we interpret this amygdala activation as a neural correlate of negative emotional arousal that is associated with dysregulated attachment fear that is evident in the verbatim narratives. In contrast, resolved controls do not show the AAP effect in the amygdala. Resolved attachment is defined by the ability to re-organize attachment related fearful and threatening themes emerging in their stories. This re-organization appears to have blocked the AAP effect in the amygdala. The attachment system of resolved controls, therefore, is not dysregulated by the negative emotions associated with attachment distress.

Increased amygdala activation in BPD patients has been found in a variety of passive

stimulation paradigms and interpreted as heightened emotional sensitivity to aversive stimuli (Davis and Whalen, 2001; Herpertz *et al.*, 2001; Donegan *et al.*, 2003). Our results are consistent with these findings. Moreover, they provide an empirical link to the frequently reported unresolved attachment found in BPD samples (Agrawal *et al.*, 2004). The fact that the amygdala activation AAP effect was found in both our BPD and unresolved controls, the effect is likely to be related to adverse abuse and loss experiences that is not necessarily specific to BPD diagnosis. In order to disentangle the contribution of attachment and diagnosis, it would be desirable to include a resolved BPD group. This was not possible in the current study because of the small number of resolved BDP patients precluded such an analysis. However resolved BPD patients are unlikely to find.

The rostral cingulate zone showed the AAP effect in both control groups, resolved or unresolved. A recent review in primate and human studies shows that the rostral cingulate zone (RCZ, the posterior MFC border zone between the medial areas BA8, BA6 and BA32′with some extension into BA24′) is involved in monitoring for unfavorable outcomes, response errors, response conflict, and decision uncertainty (Ridderinkhof *et al.*, 2004). The attachment stories of our controls, especially resolved controls, demonstrated the use of internalized mental strategies (i.e., internalized secure base) to re-organize threatening contents. We interpret the AAP effect in the RCZ as the ability of controls subjects to detect conflict or possible unfavorable outcomes within their narratives. Resolved controls actually do contain emerging threatening themes and, accordingly, do not show an AAP effect in the amygdala. In contrast, unresolved controls do not contain these themes. This suggests that the AAP effect also observed in the amygdala is a neural signature of increasing negative affect.

The AAP effect in the DLPFC was found only in the unresolved control group; it was not observed in the resolved controls or the unresolved patients. The right DLPFC has been described

as being involved in cognitive control (Duncan and Owen, 2000) emotion regulation (Ochsner and Gross, 2005) and more generally in executive functions, which help to cope with extraordinary affordances. Several neuroimaging studies describe a dysfunction of the right DLPFC in BPD patients (De La Fuente et al., 1997; Soloff et al., 2000; Schmahl et al., 2003). Resolved subjects in the present study show a low incidence of threatening situations in their narratives, suggesting that the cognitive control system is not increasingly engaged over the course of the task. Unresolved controls, however, have increasing affective involvement. We, therefore, interpret the accompanying right DLPFC activation as an effort in this group to cope with this increasing affective involvement. BPD patients showing the highest proportion of unresolved attachment patterns in this sample, are neither able to recruit the DLPFC (cognitive control) nor the RCZ (conflict monitoring) while being emotionally overwhelmed reflected in the enhanced amygdala activation. Although our interpretation of the different activation patterns as depicted in Fig. 2 cannot be directly proven, we think that we have provided a novel and interesting approach to understanding emotional instability in BPD patients with respect to attachment. The subjects in our task were actively talking about their subjective perception of attachment scenes reflecting their mental organization of these crucial topics. This approach contrasts with other published neuroimaging studies of affective dysregulation in BPD, which used passive stimulation.

There are several limitations to our study that need to be taken into account when interpreting our findings. First, two resolved BPD patients were such a small subsample in this group that it had to be dropped. The attachment literature suggests that unresolved is the predominant classification group, therefore a substantially larger sample would need to be collected to include also resolved BPD subjects. Even then, there would be no guarantees that the sample could be generated. Although this limits the interpretation of our data to a certain extent,

we were able to meaningfully evaluate the results of the other three groups. Second, we did not include a clinical control group. This leads to questions as to whether our results may also be present also in patients with other psychiatric disorders and not specific to BPD. Third, 62% of the BPD subjects were under low dose medication. This could be a confounding factor in comparing patients and controls. Finally, overt speech in the scanner always is accompanied with head movements. The head movement in this study was less than 2 mm, and we took steps to eliminate residual influences. These included dropping subjects, including movement parameters as a covariate of no interest, and modeling the onset of every spoken word.

Our results provide evidence for possible mechanisms related to affective dysregulation, a core clinical feature of BPD symptomatology. We found that both increased emotional sensitivity, as well as impaired emotion regulation, contribute to affective dysregulation in unresolved BPD patients. Increased emotional sensitivity as evidenced by an AAP effect in the right amygdala can be explained in large part by attachment type. Impairment of the cognitive control system (rostral cingulate zone and right DLPFC) is found when unresolved attachment and diagnosis of BDP are present simultaneously. Modulation of BPD patients' responses in attachment situations during treatment and psychotherapy to patterns similar to those described in the control group might be an important indication of their increasing capacity to regulate attachment distress and to show sufficient cognitive control.

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Declaration of Interest:

The authors report no biomedical financial interests or potential conflicts of interest.

References

- **Agrawal, H. R., Gunderson, J., Holmes, B. M. and Lyons-Ruth, K.** (2004). Attachment studies with borderline patients: a review. *Harv Rev Psychiatry*. **12**(2), 94-104.
- **Bartels, A. and Zeki, S.** (2000). The neural basis of romantic love. *Neuroreport.* **11**(17), 3829-3834.
- **Bartels, A. and Zeki, S.** (2004). The neural correlates of maternal and romantic love. *Neuroimage.* **21**(3), 1155-1166.
- Beblo, T., Driessen, M., Mertens, M., Wingenfeld, K., Piefke, M., Rullkoetter, N., Silva-Saavedra, A., Mensebach, C., Reddemann, L., Rau, H., Markowitsch, H.J., Wulff, H., Lange, W., Berea, C., Ollec, I., Woermann, F.G. (2006). Functional MRI correlates of the recall of unresolved life events in borderline personality disorder. *Psychol Med* 36(6), 845-56.
- Bowlby, J. (1973). Attachment and loss. Seperation: Anxiety and anger. Basic Books: New York
- Buchheim, A., Erk, S., George, C., Kachele, H., Ruchsow, M., Spitzer, M., Kircher, T. and Walter, H. (2006a). Measuring attachment representation in an FMRI environment: a pilot study. *Psychopathology*. **39**(3), 144-152.
- **Buchheim, A. and George, C.** The representational function of attachment disorganization in borderline personality disorder und anxiety disorder. In *Disorganization of Attachment and Caregiving*.(eds. J. Solomon and C. George). The Guildford Press: New York.
- **Buchheim, A., George, C., Kachele, H., Erk, S. and Walter, H.** (2006b). Measuring adult attachment representation in an fMRI environment: concepts and assessment.

 *Psychopathology. 39(3), 136-143.
- Conklin, C. Z., Bradley, R. and Westen, D. (2006). Affect regulation in borderline personality disorder. *J Nerv Ment Dis.* **194**(2), 69-77.

- **Davis, M. and Whalen, P. J.** (2001). The amygdala: vigilance and emotion. *Mol Psychiatry*. **6**(1), 13-34.
- De La Fuente, J. M., Goldman, S., Stanus, E., Vizuete, C., Morlan, I., Bobes, J. and Mendlewicz, J. (1997). Brain glucose metabolism in borderline personality disorder. *J Psychiatr Res.* **31**(5), 531-541.
- 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. and Wexler, B. E. (2003). Amygdala hyperreactivity in borderline personality disorder: implications for emotional dysregulation. *Biol Psychiatry*. 54(11), 1284-1293.
- **Petersen, M., Herrmann, J., Stahl, K., Zwaan, M., Meier, S., Hill, A., Osterheider, M. and Petersen, D.** (2000). Magnetic resonance imaging volumes of the hippocampus and the amygdala in women with borderline personality disorder and early traumatization. *Arch Gen Psychiatry.* **57**(12), 1115-1122.
- **Duncan, J. and Owen, A. M.** (2000). Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends Neurosci.* **23**(10), 475-483.
- **Duvernoy, H.** (1999). *The human brain*. Springer: New York.
- Ebner-Priemer, U. W., Badeck, S., Beckmann, C., Wagner, A., Feige, B., Weiss, I., Lieb, K. and Bohus, M. (2005). Affective dysregulation and dissociative experience in female patients with borderline personality disorder: a startle response study. *J Psychiatr Res*. 39(1), 85-92.
- Fonagy, P., Leigh, T., Steele, M., Steele, H., Kennedy, R., Mattoon, G., Target, M. and Gerber, A. (1996). The relation of attachment status, psychiatric classification, and response to psychotherapy. *J Consult Clin Psychol.* **64**(1), 22-31.

- **Fonagy, P., Target, M. and Gergely, G.** (2000). Attachment and borderline personality disorder. A theory and some evidence. *Psychiatr Clin North Am.* **23**(1), 103-122, vii-viii.
- **George, C., Kaplan, N. and Main, M.** (1984/1985/1996). The Adult Attachment Interview (Unpublished Manuscript). University of California, Berkley.
- **George, C. and West, M.** (2001). The development and preliminary validation of a new measure of adult attachment: the adult attachment projective. *Attach Hum Dev.* **3**(1), 30-61.
- George, C. and West, M. (2003). The Adult Attachment Projective: Measuring individual differences in attachment security using projective methodology In *Comprehensive Handbook of psychological assessment*, Vol. 2 (ed. M. Hilsenroth), pp. 431-448. Wiley & Sons: New Jersey.
- George, C., West, M. and Pettem, O. (1999). The Adult Attachment Projective:

 Disorganization of Adult Attachment at the level of representation. In *Attachment disorganization* (eds. J. Solomon and C. George), pp. 462-507. Guilford: New York.
- Gillath, O., Bunge, S. A., Shaver, P. R., Wendelken, C. and Mikulincer, M. (2005).

 Attachment-style differences in the ability to suppress negative thoughts: exploring the neural correlates. *Neuroimage*. **28**(4), 835-847.
- Gunderson, J. G., Daversa, M. T., Grilo, C. M., McGlashan, T. H., Zanarini, M. C., Shea,
 M. T., Skodol, A. E., Yen, S., Sanislow, C. A., Bender, D. S., Dyck, I. R., Morey, L. C.
 and Stout, R. L. (2006). Predictors of 2-year outcome for patients with borderline
 personality disorder. Am J Psychiatry. 163(5), 822-826.
- Herpertz, S. C., Dietrich, T. M., Wenning, B., Krings, T., Erberich, S. G., Willmes, K.,

 Thron, A. and Sass, H. (2001). Evidence of abnormal amygdala functioning in

 borderline personality disorder: a functional MRI study. *Biol Psychiatry*. **50**(4), 292-298.

- Herpertz, S. C., Kunert, H. J., Schwenger, U. B. and Sass, H. (1999). Affective responsiveness in borderline personality disorder: a psychophysiological approach. *Am J Psychiatry*. **156**(10), 1550-1556.
- **Irle, E., Lange, C. and Sachsse, U.** (2005). Reduced size and abnormal asymmetry of parietal cortex in women with borderline personality disorder. *Biol Psychiatry.* **57**(2), 173-182.
- Leibenluft, E., Gobbini, M. I., Harrison, T. and Haxby, J. V. (2004). Mothers' neural activation in response to pictures of their children and other children. *Biol Psychiatry*. **56**(4), 225-232.
- Lemche, E., Giampietro, V.P., Surguladze, S.A., Amaro, E.J., Andrew, C.M., Williams, S.C., Brammer, M.J., Lawrence, N., Maier, M.A., Russell, T.A., Simmons, A., Ecker, C., Joraschky, P., Phillips, M.L. (2006). Human attachment security is mediated by the amygdala: evidence from combined fMRI and psychophysiological measures. *Hum Brain Mapp* 27(8): 623-35
- Levy, K. N., Meehan, K. B., Kelly, K. M., Reynoso, J. S., Weber, M., Clarkin, J. F. and Kernberg, O. F. (2006). Change in attachment patterns and reflective function in a randomized control trial of transference-focused psychotherapy for borderline personality disorder. *J Consult Clin Psychol.* 74(6), 1027-1040.
- Lieb, K., Zanarini, M. C., Schmahl, C., Linehan, M. M. and Bohus, M. (2004). Borderline personality disorder. *Lancet.* **364**(9432), 453-461.
- **Linehan, M. M., Tutek, D. A., Heard, H. L. and Armstrong, H. E.** (1994). Interpersonal outcome of cognitive behavioral treatment for chronically suicidal borderline patients. *Am J Psychiatry*. **151**(12), 1771-1776.
- Main, M. and Goldwyn, R. (1995). Adult Attachment Classification System (Unpublished Manuscript). University of California, Department of Psychology, Berkley

- Nitschke, J. B., Nelson, E. E., Rusch, B. D., Fox, A. S., Oakes, T. R. and Davidson, R. J. (2004). Orbitofrontal cortex tracks positive mood in mothers viewing pictures of their newborn infants. *Neuroimage*. **21**(2), 583-592.
- Ochsner, K. N. and Gross, J. J. (2005). The cognitive control of emotion. *Trends Cogn Sci.* **9**(5), 242-249.
- **Putnam, K. M. and Silk, K. R.** (2005). Emotion dysregulation and the development of borderline personality disorder. *Dev Psychopathol.* **17**(4), 899-925.
- Ridderinkhof, K. R., van den Wildenberg, W. P., Segalowitz, S. J. and Carter, C. S. (2004).

 Neurocognitive mechanisms of cognitive control: the role of prefrontal cortex in action selection, response inhibition, performance monitoring, and reward-based learning. *Brain Cogn.* **56**(2), 129-140.
- Schmahl, C. G., Elzinga, B. M., Vermetten, E., Sanislow, C., McGlashan, T. H. and Bremner, J. D. (2003). Neural correlates of memories of abandonment in women with and without borderline personality disorder. *Biol Psychiatry*. **54**(2), 142-151.
- **Schmahl, C. G., Vermetten, E., Elzinga, B. M. and Bremner, J. D.** (2004). A positron emission tomography study of memories of childhood abuse in borderline personality disorder. *Biol Psychiatry*. **55**(7), 759-765.
- Schnell, K., Dietrich, T., Schnitker, R., Daumann, J., Herpertz, S.C. (2007). Processing of autobiographical memory retrieval cues in borderline personality disorder. *J Affect Disord* **97**(1-3), 253-9.
- Skodol, A. E., Siever, L. J., Livesley, W. J., Gunderson, J. G., Pfohl, B. and Widiger, T. A. (2002). The borderline diagnosis II: biology, genetics, and clinical course. *Biol Psychiatry*. **51**(12), 951-963.

- Soloff, P. H., Meltzer, C. C., Greer, P. J., Constantine, D. and Kelly, T. M. (2000). A fenfluramine-activated FDG-PET study of borderline personality disorder. *Biol Psychiatry*. **47**(6), 540-547.
- **Talairach, J. and Tournoux, P.** (1988). *Co-Planar Stereotactic Atlas of the human brain.* .

 Thieme: Stuttgart.
- **Tebartz van Elst, L., Hesslinger, B., Thiel, T., Geiger, E., Haegele, K., Lemieux, L., Lieb, K., Bohus, M., Hennig, J. and Ebert, D.** (2003). Frontolimbic brain abnormalities in patients with borderline personality disorder: a volumetric magnetic resonance imaging study. *Biol Psychiatry.* **54**(2), 163-171.
- **Tebartz van Elst, L., Thiel, T., Hesslinger, B., Lieb, K., Bohus, M. and Hennings, J.** (2001). Subtle prefrontal neuropathology in a pilot magnetic resonance spectroscopy study in patients with borderline personality disorder *J Neuropsychiatry Clin Neurosci.* **13**, 511-514.
- Westen, D., Nakash, O., Thomas, C. and Bradley, R. (2006). Clinical assessment of attachment patterns and personality disorder in adolescents and adults. *J Consult Clin Psychol.* **74**(6), 1065-1085.
- Zanarini, M. C., Frankenburg, F. R., Hennen, J., Reich, D. B. and Silk, K. R. (2006).

 Prediction of the 10-year course of borderline personality disorder. *Am J Psychiatry*.

 163(5), 827-832.

Neural correlates of attachment dysregulation in BPD

Table legends

Table 1

Two-group-comparison of clinical scales

Table 2

Transcript examples of a "resolved" and two "unresolved" stories to the AAP picture "Cemetery"

Table 3

FMRI results. All results: p < 0.001 uncorrected for multiple comparisons at voxel level, p < 0.05 at cluster level; * p < 0.05 corrected for region of interest; BA, Brodmann area; x,y,z, respective coordinates of MNI template

Neural correlates of attachment dysregulation in BPD

Figure legends

Figure 1

Upper part: Picture "Departure" from the Adult Attachment Projective © (George et al. 1999)

Lower part: Picture "Cemetery" from the Adult Attachment Projective © (George et al. 1999)

Figure 2

Results of the fMRI analysis. A significant AAP effect (increasing activation along the task) was found in the amygdala for both, unresolved controls and patients, but not in the resolved controls. A significant AAP effect in the medial prefrontal cortex was observed in both control groups, whereas the DLPFC exhibits an AAP effect only in the group of unresolved controls. All regions were significant in the respective interaction analyses (see table 3). Images of statistic parametric mapping are projected onto sections of the standard T1 template of SPM 2. Plots of contrast estimates for each condition were shown on the right. Green bars, resolved controls; blue bars, unresolved controls; red bars, unresolved patients.

Table 1

| | C | | H | 3 | CxB |
|-------------------------------|--------|------|--------|------|--------|
| Clinical scales | Cont | rol | Borde | | |
| | Total | | Total | | |
| | (n=17) | | (n=13) | | U-test |
| | М | SD | M | SD | p |
| Clinical scales | | | | | |
| GSI (SCL-90) | .22 | .22 | 1.5 | .51 | .000 |
| Barrett Impulsivity Scale | 67.4 | 10.0 | 85.2 | 10.4 | .000 |
| Dissociative Experience Scale | 4.2 | 3.9 | 15.7 | 16.3 | .001 |

Exact two-tailed Mann-Whitney U-test

Table 2

Resolved AAP story (Control) Unresolved AAP story (Control) "An elder man in the graveyard. The man is standing "A man is standing besides a grave. His wife has recently died. in front of his mother's tombstone. As he accidentally She died suddenly in a car accident. The man is totally in visited his hometown he also visited the graveyard and despair. Once a week he is visiting her grave. He finds it lays down a bunch of flowers to his mother. He is difficult to say goodbye. He often talks to her. He thinking about the past, how things had been when she communicates with her about whether he is doing things the was still alive, what she had pointed out to him for his right way and how hard it is for him to raise his three children live. He is very centered upon the past remembering all by himself. And how helpless the children are to have lost many things and at the same time he is gathering their mother too early. It's my impression that he needs a lot courage for the future since he knows that life is of time to come to terms with the situation". transient. He is keeping to this task for a while; then he returns to his apartment lost in thought. The next day he is leaving his hometown after having visited some of his old friends and some of mother's neighbors to talk to". *Unresolved AAP story (Borderline patient)* "On a graveyard a man is standing by a grave he had been searching for many years. It's the grave of his parent, who gave their son up for adoption. Their son wants to finally say farewell to his biological parents and he wants to know where his roots are to be found. He is staying on the graveyard for a while, then moves on to an inn and gets drunk until the next evening hoping that in this way he could bury his past just like his parents are buried there. He feels suicidal and like an orphan with no roots. He will never return. He wants to erase the bad past with an adoptive family".

Words representing attachment dysregulation are underlined

Table 3. FMRI results

| region | ВА | | Z | х | у | Z |
|-----------------------------------------------------------|---------|--------|--------------|----------|----------|-----------|
| all CTRLs | | D | 4.51 | 24 | -3 | -27 |
| amygdala dorsolateral prefrontal cortex | 46 | R R | 4.51 3.54 | 24 48 | -3 24 | -27 15 |
| medial prefrontal cortex | 9 | 11 | 4.09 | -3 | 33 | 33 |
| | | | | | | |
| CTRLs resolved superior temporal sulcus | 39 | L | 4.24 | -51 | -60 | 21 |
| superior temporar sulcus | 55 | _ | 7.27 | 01 | 00 | 21 |
| CTRLs unresolved | | | | | | |
| amygdala | 40 | R | 4.60 | 24 | 3 | -27 |
| dorsolateral prefrontal cortex | 46 6 | R R | 3.71 | 48 21 | 27 15 | 15 |
| superior frontal gyrus | 0 | ĸ | 4.26 | 21 | 15 | 63 |
| all unresolved (CTRLs and PATs) | | | | | | |
| amygdala | | R | 4.42 | 24 | 3 | -24 |
| superior temporal sulcus | 39 | R | 3.87 | 57 | -51 | 12 |
| medial prefrontal cortex | 8 | R | 3.85 | 3 | 21 | 45 |
| PATs unresolved | | | | | | |
| amygdala | | R | 3.66 | 21 | -6 | -21 |
| anterior cingulate cortex | 32 | R | 3.70 | 3 | 21 | 33 |
| cingulate gyrus | 24 | R | 3.58 | 3 | -18 | 42 |
| superior temporal sulcus | 39 | R | 3.99 | 60 | -57 | 15 |
| all CTRLs > PATs unresolved | | | | | | |
| medial prefrontal cortex | 8 | L | 2.92* | -6 | 36 | 39 |
| CTDL a reached DATe was a bed | | | | | | |
| CTRLs resolved > PATs unresolved medial prefrontal cortex | 8 | L | 2.83* | -6 | 36 | 39 |
| mediai premontai cortex | 0 | _ | 2.03 | -0 | 30 | 39 |
| all unresolved (CTRLs and PATs) > CTRLs res | olved | | | | | |
| amygdala | | R | 3.15* | 27 | 3 | -21 |
| CTRLs unresolved > CTRLs resolved | | | | | | |
| amygdala | | R | 3.41* | 27 | 3 | -24 |
| dorsolateral prefrontal cortex | 46 | R | | 48 | 27 | 15 |
| · | | | | | | |
| PATs unresolved > CTRLs resolved | | _ | | | | |
| amygdala | | R | 2.88* | 21 | -6 | -21 |
| CTRLs unresolved > PATs unresolved | | | | | | |
| dorsolateral prefrontal cortex | 46 | R | 3.11* | 48 | 24 | 15 |
| medial prefrontal cortex | 8 | L | 2.44* | -6 | 36 | 39 |
| | | | | | | |





