Journal of Affective Disorders 208 (2017) 460–466

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Amygdala and dlPFC abnormalities, with aberrant connectivity and habituation in response to emotional stimuli in females with BPD

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ARTICLE INFO

Keywords:
Borderline personality disorder
Imaging
Amygdala
Disgust
Functional connectivity
Habituation

ABSTRACT

Background: Little is known about the frontolimbic abnormalities thought to underlie borderline personality disorder (BPD). We endeavoured to study regional responses, as well as their connectivity and habituation during emotion processing.

Methods: 14 BPD patients and 14 normal female controls (NC) controlled for menstrual phase underwent emotion-induction during an fMRI task using standardised images in a block design. We then performed psychophysiological interaction (PPI) analysis to investigate functional connectivity.

Results: BPD patients reported more disgust in questionnaires compared to controls. Relative to NC, they showed reduced left amygdala and increased dorsolateral prefrontal cortex (dlPFC) activation to all emotions collapsed versus neutral. Habituation of ventral striatal activity to repeated emotional stimuli was observed in controls but not in BPD. Finally, in the context of disgust (but not other emotions) versus neutral, BPD patients displayed enhanced left amygdala coupling with the dlPFC and ventral striatum.

Limitations: Strict inclusion criteria reduced the sample size.

Conclusions: In summary, BPD showed abnormal patterns of activation, habituation and connectivity in regions linked to emotion regulation. Amygdala deactivation may be mediated by abnormal top-down regulatory control from the dorsolateral prefrontal cortex. Aberrant emotion processing may play a unique role in the pathophysiology of BPD.

1. Introduction

Borderline personality disorder (BPD) is defined by emotional dysregulation at its core and further comprises interpersonal difficulties, impulsivity, aggressive outbursts and dissociative symptoms. The disorder often involves patients experiencing profound distress, functional impairment, diminished quality of life (IsHak et al., 2013) and is associated with high suicidality and societal costs (Wagner et al., 2014). Further, it is characterised by its perceived lack of a legitimate neurobiological basis clinically (Dudas, 2014), making progress in understanding its pathophysiology particularly important. Whilst some progress understanding BPD has been made over recent years (Leichsenring et al., 2011), characterising its precise neurobiological correlates and mechanisms has been challenging. The majority of fMRI research to date in BPD has focused on abnormal limbic and amygdala responses to a range of emotive and aversive stimuli, auditory scripts and images (Schmahl et al., 2003). Initial reports appeared consistent with the hypothesis of amygdala hyper-responsiveness to unpleasant stimuli (Herpertz et al., 2001). Subsequent studies implicated a more dispersed complex of regions across the prefrontal cortex and limbic system together with a dual frontolimbic pathology model (Tebartz van Elst et al., 2003) suggesting a 'failure of top down control' (Silbersweig et al., 2007). However, fMRI study findings and methods have not been consistent (Ruocco et al., 2013), and whilst many studies reported

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http://dx.doi.org/10.1016/j.jad.2016.10.043
Received 6 June 2016; Received in revised form 12 September 2016; Accepted 22 October 2016
Available online 27 October 2016
0165-0327/

limbic changes, several studies failed to replicate the initially reported amygdala hyperactivation. One meta-analysis (Ruocco et al., 2013) of 10 studies involving 225 subjects with BPD found an overall decrease amygdala activation whilst a more recent meta-analysis (Schulze et al., 2016) conversely found increased amygdala activation in response to unpleasant stimuli. These meta-analyses have suggested key abnormalities in both frontal (including dorsolateral prefrontal cortex (dlPFC) and limbic (amygdala, hippocampus, anterior cingulate cortex (ACC)) areas consistent with overall frontolimbic dysfunction.

Whilst such fMRI studies have explored different aversive emotions, behavioural studies have indicated specific deficits related to disgust, and this emotion has received limited attention. For instance, studies have shown BPD subjects make more errors recognising negative human facial emotions (Daros et al., 2014; Schulze et al., 2016), and this impairment may be more prominent to disgust compared to other negative emotions such as fear (Nicol et al., 2014). Recognising emotional cues in others may be an important skill for BPD subjects given its role in effective social functioning, disgust recognition deficits have been put forward as a potential explanatory mechanism for the problems subjects typically experience in developing and maintaining stable relationships (Veague and Hooley, 2014). Focusing on one's own self, including one's own body lead to an increase both in self-disgust and self-harm urges in BPD (Abdul-Hamid et al., 2014). Disgust processing errors have further been linked to suicidality, which is notably 50 times higher in BPD compared to the general population (Association, 2001). In a study of non-BPD, non-depressed patients, only errors recognising disgust and not other emotions was found to be significantly different between patients with and without previous suicide attempts (Richard-Devantoy et al., 2013). Emerging evidence has suggested connectivity between frontolimbic brain regions could also be aberrant and responsive to Dialectical Behavioural Therapy (Schmitt et al., 2016). Although frontolimbic dysfunction has been indicated to underlie BPD, the specific role of disgust, habituation and aberrant brain connectivity in its pathophysiology is less clear.

Here we investigate the neural correlates of emotional processing in BPD and further examine altered habituation which has received limited attention (Goodman et al., 2014). We compared BPD and matched normal controls in a functional MRI (fMRI) block design task comparing emotion-inducing images specifically with neutral images. We also included other positive and negatively valenced images for comparison purposes. In-line with recent meta-analysis findings (Ruocco et al., 2013), we first hypothesized that BPD subjects would have lower amygdala activity to negative stimuli relative to neutral imagery compared to normal controls. Secondly, we hypothesized that disgust would be associated with reduced amygdala-prefrontal connectivity in BPD compared to normal controls consistent with impaired emotional regulation.

2. Patients and methods

2.1. Participants

14 females with BPD and 14 female normal controls (NC) participated. Patients were recruited from the local personality disorder service and the controls via local advertisements. To control for known sex-specific differences related to processing emotion (Domes et al., 2010; McRae et al., 2008), processing disgust (Schienle et al., 2005) and effects of the menstrual cycle (Protopopescu et al., 2005), only females were recruited and wherever possible, scanned only during their follicular phase. All subjects were assessed and screened with strict criteria by a trained, experienced psychiatrist using structured diagnostic interview schedules (MINI International Neuropsychiatric Interview, (Sheehan et al., 1997)) and Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II (First et al., 1995)). Only subjects who fulfilled DSM IV-TR criteria for BPD were included. Those that met diagnostic criteria for other personality disorders were excluded. Further exclusion criteria included current major depressive disorder or lifetime history of any formally diagnosed psychotic illness or substance dependence identified in the MINI. Isolated subthreshold symptoms of a depressive, personality or psychotic disorder were allowed. Universal exclusion criteria also included those less than 18 years of age, MR-scanning incompatibility, and positive pre-scanning recreational urine drug screen. The local NHS research ethics committee approved this research (Cambridgeshire 4 Research Ethics Committee, NHS National Research Ethics Service, reference number: 09/H0305/10). Written informed consent was obtained from each participant. All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

2.2. Measuring disgust and psychiatric indices

Subjects completed standardised measures of depression (Beck Depression Inventory (BDI (Beck et al., 1996)); Hamilton Depression Rating Scale (HDRS (Hamilton, 1960)), anxiety (State and Trait Anxiety Inventory; STAI (Spielberger, 1983)), dissociation (Cambridge Depersonalisation Scale; CDS (Sierra and Berrios, 2000)) as well as the Borderline subscale of the Personality Assessment Inventory (PAI-BOR (Morey, 1991)) and body mass index (BMI). We assessed disgust using both general disgust (modified Disgust Scale Revised, m-DSR (Olatunji et al., 2007)) and self-disgust questionnaires (Self-disgust Scale (SDS) (Overton et al., 2008)).

2.3. Emotion induction task

We employed a block-design fMRI task using standardised intermixed emotion-inducing images from five emotional categories from the International Affective Picture System (disgust, anger, sad, happy and neutral) (Lang et al., 1999). A Novel Image Series was presented before redisplaying the same pictures in a Repeated Image Series to assess for altered habituation (Fig. 1). Repetitive emotional stimuli were presented to more closely mimic real-world experiences and maximise ecological validity. 50 trials of novel and repeated images were shown, both series consisting of a total of 10 unique images per emotional valence. Images were displayed in blocks of 5 sequential images of the same valence. Blocks of different emotional valences were randomised so that different emotion blocks were intermixed within the same series whilst this randomised order was kept constant across participants to control for effects of different duration latencies between first seeing an image and its repetition. For each trial, an emotion-inducing image was displayed for 6 s, before subjects were given 2 s to respond to a simple task as to whether the preceding picture was ‘inside or outside’ in order to assess task engagement. Then, a fixation cross was displayed for a further 2 s to provide an inter-trial interval before the next emotion-induction image was shown. The inter-stimulus-interval was not jittered. Trials were repeated as described until the experiment was complete.

2.4. Neuroimaging acquisition & analysis

A 3T Siemens Magnetom TrioTim syngo MR B17 scanner was used with a 12-channel head coil using a tilted plane acquisition at the Wolfson Brain Imaging Centre in Cambridge. T2-weighted echo planar images (EPI) using interleaved slices were acquired. Parameters were TR=2000 ms, TE=30 ms, flip angle 78 degrees, matrix size 64×64, with 32 slices created with a slice thickness of 3 mm (in-plane resolution 3 mmx3 mmx3 mm). Analysis was performed using Statistical Parametric Mapping 8 (Wellcome Department of Cognitive Neurology, London, United Kingdom http://www.fil.ion.ucl.ac.uk/spm). Images were realigned and spatially normalised to standard