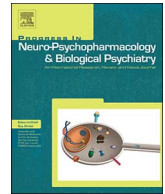


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Resting-state functional connectivity of neurotransmitter producing sites in female patients with borderline personality disorder



Gerd Wagner^a, Annegret Krause-Utz^{b,c,d}, Feliberto de la Cruz^a, Andy Schumann^a,
Christian Schmahl^{b,1}, Karl-Jürgen Bär^{a,*,1}

^a Psychiatric Brain and Body Research Group Jena, Department of Psychiatry and Psychotherapy, University Hospital Jena, Philosophenweg 3, Jena 07743, Germany

^b Department of Psychosomatic Medicine and Psychotherapy, Central Institute of Mental Health (CIMH), Mannheim, Germany

^c Institute of Clinical Psychology, Leiden University, Leiden, Netherlands

^d Leiden Institute for Brain and Cognition, Leiden University, Leiden, Netherlands

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ABSTRACT

Impulsive behavior, difficulties in controlling anger and suicidal behavior are typical patterns of affective/behavioral dysregulation in patients with borderline personality disorder (BPD). Previous functional MRI studies in the resting state condition demonstrated altered functional connectivity (FC) between the anterior cingulate cortex (ACC) and the frontoparietal executive control network (ECN), which was significantly associated with impulsivity in BPD. Impulsivity is often defined as a function of inhibitory control, strongly relying on the proper functioning of the fronto-cingulo-striatal network. Noradrenergic, dopaminergic and serotonergic neurotransmitter systems are assumed to be involved in different forms of impulsive behavior and inhibitory control. In our previous study, we investigated the FC of the main monoamine-producing nuclei within the midbrain and brainstem, which were functionally integrated in specific resting-state networks. In the present study we investigated the resting-state FC of midbrain/brainstem nuclei in 33 unmedicated female patients with BPD and 33 matched healthy controls. We further related altered functional connectivity of these nuclei to the patient's degree of impulsivity. The main finding was that BPD patients showed stronger FC from the noradrenergic locus coeruleus (LC) to the ACC. Functional connectivity between the LC and ACC was positively associated with the degree of motor impulsivity in the total group. Controlling for aggression, a stronger FC was also found between serotonergic nucleus centralis superior (NCS) and the frontopolar cortex (FPC) in patients compared to controls. Furthermore, patients showed a weaker “anti-correlation” from the substantia nigra (SNc) to the left dorsolateral prefrontal cortex (DLPFC). The observed enhanced LC-ACC FC in BPD and its association with the motor impulsivity might be indicative of a noradrenergic dysfunction in the neural inhibitory control network, whereas the significant relationship between NCS-FPC FC and aggression points toward serotonergic contribution to prefrontal control of aggressive reactions.

1. Introduction

Impulsive behavior and difficulties in controlling anger and aggression as well as repeated non-suicidal self-injury and suicidal behavior are typical patterns of affective and behavioral dysregulation in patients with borderline personality disorder (BPD) (Linehan, 1993). Neuroimaging studies in BPD have consistently described increased amygdala activation during exposure to emotionally arousing pictures compared to healthy controls, suggesting enhanced emotional reactivity (Donegan et al., 2003; Schulze et al., 2011, 2016). Blunted activation was also found in the anterior cingulate cortex (ACC) and in

the dorsolateral prefrontal cortex (DLPFC) in BPD during paradigms requiring affective control (Malhi et al., 2013; Wingenfeld et al., 2009).

Additionally, studies focusing on resting-state functional connectivity (RSFC) in BPD revealed abnormal connectivity of limbic, medial frontal structures and of the ACC. For example, increased RSFC was demonstrated between the amygdala and the insula, putamen and orbitofrontal cortex (OFC) as well as decreased RSFC between the dorsal ACC (dACC) and the posterior cingulate cortex (PCC) (Krause-Utz et al., 2014). The latter is a core region of the default mode network (DMN). Abnormal RSFC between medial PFC/ACC and the frontoparietal executive control network (ECN) was detected and was

* Corresponding author at: Department of Psychiatry and Psychotherapy, University Hospital Jena, Philosophenweg 3, Jena 07743, Germany.

E-mail address: Karl-Juergen.Baer@med.uni-jena.de (K.-J. Bär).

¹ Both authors contributed equally.

significantly associated with impulsivity in BPD (Das et al., 2014). Furthermore, recent meta-analysis of rs-fMRI studies corroborated these findings by demonstrating the important role of abnormal ACC connectivity in BPD (Visintin et al., 2016).

Impulsivity is a personality trait and often defined as a function of inhibitory control, an important component of executive functions (Clark et al., 2006). On the other hand, impulsivity has many other facets, so the homogeneity of this construct has been challenged (Robbins et al., 2012; Stahl et al., 2014). For example, the ability to deal with reward contingencies (“motivational impulsivity”) and the ability to reflect about one’s own decisions (“reflection impulsivity”) are also considered to be important components of impulsivity (Robbins et al., 2012; Stahl et al., 2014).

Considering this multidimensionality, impulsivity is thought to be a core feature and a specific neurobiological predisposition of several neuropsychiatric conditions such as BPD or attention deficit hyperactivity disorder (ADHD). Different dimensions of impulsivity can be assessed by several task-based measures such as the stop-signal reaction-time (SSRT) or Go/No-Go tasks for inhibitory control or using delay discounting tests for reward anticipation.

Using self-report measures, impulsivity can be assessed, for example, by means of the Barratt Impulsivity Scale (BIS) (Stanford et al., 2009). Interestingly, neuropsychological measures of impulsivity only partially overlap with impulsivity as assessed by self-report. Stahl et al. (2014) reported that there was no evidence for a relation between the behavioral impulsivity and the self-reported impulsivity, potentially indicating different underlying constructs.

This fact may explain the often-reported dissociation between self-report measurements, in which BPD patients consistently showed higher impulsivity scores than healthy controls and often-unaffected performance in neuropsychological tests (Sebastian et al., 2014).

On the other side, neuropsychological deficits and fMRI activation differences associated with response inhibition in BPD were consistently demonstrated in fronto-limbic regions if the cognitive task was modulated by negative emotions (Sebastian et al., 2014).

Previous neuroimaging studies, which explicitly investigated the relationship between impulsivity, as assessed by using BIS and neural activation, demonstrated that BPD patients exhibited a significantly negative correlation between ventral striatal activation and BIS-11 (Barratt Impulsivity Scale Version 11) scores during loss anticipation responses. This might suggest impaired prediction of aversive outcomes in highly impulsive patients (Herbort et al., 2016). Mortensen et al. (2016) observed in BPD patients increased activation in the dorsal ACC during cue primes in an uncertainty paradigm. The authors interpreted this result in terms of a strong preparedness of patients to respond and thus indicating abnormal impulsivity in BPD. Very recently, Soloff et al. (2017) detected that self-reported impulsivity in BPD as assessed by BIS-11 was positively correlated with the activation in the dorsal ACC, OFC, basal ganglia (BG), and DLPFC during the affective Go No-Go task. Interestingly, the degree of aggression was negatively correlated with the activation in the OFC and BG. Regarding the neurochemical basis of impulsivity, noradrenergic, dopaminergic and serotonergic neurotransmitter systems are assumed to be involved in different forms of impulsive behavior and inhibitory control (Bari and Robbins, 2013; Chamberlain and Sahakian, 2007). Main findings stem from studies investigating the action of psychostimulants mostly influencing catecholamine neurotransmission. For example, atomoxetine, a selective noradrenaline (NA) reuptake inhibitor improves response inhibition in the stop-signal task in both rats and humans (Eagle et al., 2008). The serotonergic system was linked to impulsivity by investigating aggression and suicidal behavior (Manchia et al., 2017; Mann et al., 2001). Serotonin depletion was found to increase impulsive aggression in men (Bjork et al., 2000) and women (Marsh et al., 2002). Koch et al. (2007) demonstrated a 43% higher brainstem serotonin transporter availability in a 123I-ADAM SPECT study in unmedicated patients with BPD when compared to controls, which was significantly correlated with

impulsivity as assessed by the BIS. Regarding the dopaminergic system, Buckholtz et al. (2010) showed in a PET study in healthy subjects that individual differences in D2/D3 autoreceptor binding in the ventral tegmental area (VTA) and substantia nigra of the midbrain were associated with the expression of impulsivity as assessed by the BIS-11.

In a recent study, we used rs-fMRI and graph theoretical analysis to elucidate the RSFC and network organization of the monoamine-producing midbrain/brainstem nuclei in a large sample of healthy subjects (Bär et al., 2016). We demonstrated that serotonergic brainstem nuclei, i.e. the nucleus raphes dorsalis (DRN) and the nucleus centralis superior (NCS), as well as the dopaminergic ventral tegmental area (VTA) and substantia nigra pars compacta (SNc), are functionally integrated within the DMN. In contrast, the locus coeruleus was part of a network comprising regions such as the DLPFC, VLPFC and the parietal cortex corresponding to the ECN.

The present study addressed two major goals. Firstly, we aimed to investigate the RSFC of the main monoamine-producing neurotransmitter nuclei in the midbrain/brainstem in patients with BPD using rs-fMRI. We mainly hypothesized altered FC of the serotonergic DRN/NCS with DMN regions as well as altered noradrenergic LC-RSFC to regions of the ECN. Due to its involvement in impulsivity, we also investigated putative alterations in the FC of the dopaminergic midbrain nuclei in BPD. The second main goal of the present study was to relate the degree of impulsivity to the strength of the RSFC of the midbrain/brainstem nuclei showing altered FC.

2. Methods

2.1. Participants

Thirty-three females who met the criteria for BPD according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) were recruited from the inpatient service of the Central Institute of Mental Health in Mannheim, Germany. On average, patients were 26.7 ± 6.4 years old and were free of psychotropic medication for at least two weeks prior to study. Thirty-three female control subjects matched for age were recruited through local newspaper advertisement. The mean age was 26.4 ± 6.2 years.

All participants underwent diagnostic assessments including the Structured Interview for DSM-IV Axis I (SCID-I) and the International Personality Disorder Examination (IPDE, Loranger, 1999) by trained diagnosticians. The exclusion criteria for the patient group were: current major depression, lifetime diagnoses of psychotic disorder, bipolar affective disorder, mental retardation, developmental disorder, and life threatening suicidal crisis. Exclusion criteria for the control group were: lifetime diagnoses of psychiatric or somatic disorders. One patient had a current attention deficit hyperactivity disorder (ADHD) diagnosis. Eight patients fulfilled the diagnostic criteria for alcohol/substance abuse. Further demographic and clinical data are shown in the Table 1.

Impulsivity was assessed by means of the German version of BIS-11 (Preuss et al., 2008). BIS-11 consists of 30 items, each rated on a four-point Likert scale (1 = ‘rarely/never’ to 4 = ‘always’) and can be divided into the subscales Motor Impulsiveness (11 items, measures the tendency to engage in spontaneous behavior), Attentional Impulsiveness (8 items, measures the tendency to make quick decisions), and Non-Planning Impulsiveness (11 items, assesses the lack of concerns for the consequences of one’s actions). The study has been approved by the local ethics committee of the Medical Faculty of Heidelberg University. All subjects gave full consent one day in advance.

2.2. MRI procedure

All participants were informed about the study and scanning procedure. The functional and structural magnetic resonance data were collected on a 3T whole body system equipped with a 12-element head matrix coil (MAGNETOM TIM Trio, Siemens). The whole measurement

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