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ORIGINAL PAPER

Orbitofrontal cortex and impulsivity in borderline personality disorder: an MRI study of baseline brain perfusion

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Abstract Behavioral and neuroimaging studies in patients with borderline personality disorder (BPD) have associated orbitofrontal cortex (OFC) dysfunction with distinct symptom clusters such as impulsivity. It is unclear, however, whether abnormal patterns of OFC activity are also present during resting-state conditions and whether OFC dysfunction is specifically associated with impulsivity in BPD. This study tested the hypothesis that BPD patients would exhibit changes of OFC baseline perfusion and explored the relationship between regional cerebral blood flow and distinct BPD symptom clusters, such as impulsivity, dissociation tension and depressive symptoms. Using continuous arterial spin labeling magnetic resonance imaging at 3 Tesla, we investigated 16 women with BPD according to DSM-IV criteria and 16 healthy female control participants during resting-state conditions. Between-group comparisons were conducted using an analysis of variance ($p < 0.05$ cluster corrected). Compared to controls, BPD patients exhibited decreased blood flow in the medial OFC, whereas increased blood flow was found in the left and right lateral OFC. Correlation analyses revealed a positive relationship between medial and lateral orbitofrontal blood flow and impulsivity scores, whereas measures of dissociation tension and depression did not exhibit a significant correlation with OFC perfusion. These data suggest that dysfunction of medial and lateral regions of the OFC could specifically mediate symptoms of impulsivity in BPD.

Keywords Borderline personality disorder · CBF · Impulsivity · MRI · Perfusion imaging · Orbitofrontal cortex

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Introduction

Dysfunctional affect regulation, deliberate self-harming behavior, interpersonal instability, severe dissociative states and impulsivity are clinical core symptoms in patients with borderline personality disorder (BPD) [1]. The precise functional neuroanatomy underlying these symptoms is unclear at present; however, a growing body of behavioral and neuroimaging research has emphasized a pivotal functional role of the frontal cortex in BPD [2–5]; see also references [6–8] for comprehensive reviews. More specifically, it has been hypothesized that a dysfunction of the orbitofrontal cortex (OFC) and its cortical and subcortical connections could mediate several core symptoms in BPD patients—a notion that is in excellent accordance with several critical functions of the OFC, such as affective control, behavioral inhibition and the regulation of emotional and

social behavior [9–12]. In support of this hypothesis, neuroimaging studies in BPD have revealed abnormalities of OFC volume [13, 14], metabolism [15, 16] and activation [2, 4, 5, 17]. In this context, it is noteworthy that the majority of functional neuroimaging studies so far have employed task-based protocols to elicit brain activation patterns in BPD. It is however possible that OFC metabolism in BPD is already altered in the absence of explicit experimental stimulation and that this baseline dysfunction could also determine task-related activation responses. Moreover, whether OFC dysfunction may account for distinct symptom clusters characterizing BPD is still an incompletely resolved issue. For instance, neuropsychological studies have shown behavioral similarities between BPD patients and patients with lesions in the OFC, suggesting that OFC dysfunction could be specifically related to symptoms of impulsivity [18]. Accordingly, hypometabolism of the medial OFC has been previously related to impulsivity in BPD [16], and a recent study of brain structure has reported an association between impulsivity measures and volume of the lateral OFC [19]. In contrast, OFC dysfunction in BPD has been recently attributed to depressive symptoms but not to impulsivity [4].

The objectives of this study were twofold: First, we tested the hypothesis that BPD patients would exhibit abnormal brain activity within the OFC and its known cortical and subcortical connections [11, 20]. To this end, we investigated neural function in BPD using a resting-state imaging approach. We chose to assess regional cerebral blood flow (CBF) since this parameter is quantifiable, tightly coupled to neural function and metabolism [21] and relatively stable over time [22]. In this study, we investigated CBF differences between BPD patients and healthy controls by means of a non-invasive magnetic resonance imaging (MRI) technique based on perfusion images obtained with continuous arterial spin labeling (CASL) [23–27]. We primarily expected lower OFC CBF in BPD patients, in accordance with previous resting-state single photon emission computed tomography (SPECT) and positron emission tomography (PET) studies in BPD and related disorders characterized by poor impulse control [15, 16, 28]. However, given one previous resting-state FDG report showing medial prefrontal hypermetabolism in female BPD patients [29], we did not a priori exclude the possibility of increased CBF in our patient sample. The second objective was to explore the relationship between CBF and distinct symptom clusters in BPD, that is, impulsivity, dissociation tension and depressive symptoms, as indicated by validated psychometric instruments [30–32]. Specifically, we predicted a negative relationship between OFC blood flow and impulsivity, as suggested by neuropsychological and neuroimaging data linking deficient impulse control to OFC dysfunction [11, 16, 18, 19, 33].

Methods

Participants

We studied 16 female participants recruited among the in- and outpatients of the Department of Psychiatry and Psychotherapy III, University of Ulm, Germany, meeting DSM-IV criteria for BPD. All patients were part of a previously reported sample [34]. Diagnostic assessments using the German versions of the Structured Clinical Interview for DSM-IV (axis I and axis II disorders) were performed by clinically trained and experienced raters (R.C.W. and N.D.W.) for patients and controls. All patients were on a stable drug regime for at least 2 weeks prior to scanning. Medication, either as monotherapy or as a combination included antidepressants [escitalopram ($n = 5$ patients), fluoxetine ($n = 2$), sertraline ($n = 1$), venlafaxine ($n = 3$) and agomelatin ($n = 1$)], mood stabilizers [lamotrigine ($n = 10$), topiramate ($n = 1$)] and antipsychotics [quetiapine ($n = 7$), aripiprazole ($n = 2$)]. Only patients who presented without acute suicidal ideation and patients with a sufficiently stable physical condition to undergo the MRI scanning process were recruited for the study. Patients with a history of a neurological disorder, a history of head trauma or learning disabilities were excluded from the study. Further exclusion criteria were lifetime diagnoses of schizophrenia, bipolar disorder, attention-deficit/hyperactivity disorder (ADHD) and alcohol and illicit drug abuse within 6 months prior to study participation. Given the reports of neural differences in BPD patients with and without post-traumatic stress disorder (PTSD) [8], we chose to include only patients who did not meet current criteria for PTSD. Axis I disorders in the BPD cohort included five patients with lifetime major depressive disorder, six with past drug and alcohol abuse, eight with current major depression, four with an eating disorder (two with bulimia nervosa, two with an eating disorder not otherwise specified) and one patient with a current anxiety disorder not otherwise specified.

Overall, BPD symptoms in the patient group were assessed using the short version (23 items) of the Borderline Symptom List (BSL-23) [35]. Self-reported impulsivity was assessed in all participants using the German version of the Barratt Impulsiveness Scale (BIS) [30]. Apart from the BIS total score, subscale scores according to three second-order factors [30] were calculated for attentional impulsivity (BIS-A; i.e., inability to focus attention on a task at hand), motor impulsivity (BIS-M; i.e., acting without thinking and acting impetuously) and non-planning impulsivity (BIS-N; i.e., lack of future planning and orientation). BPD patients and controls completed the Beck Depression Inventory (BDI) [31] and were complementary rated by means of the Hamilton Depression Rating

Table 1 Demographics and psychometric scores for healthy controls and patients with borderline personality disorder (BPD)

	Controls ($n = 16$)		BPD patients ($n = 16$)		p value
	Mean	SD	Mean	SD	
Age (years)	27.6	8.1	27.8	6.4	0.96
Education (years)	13.3	1.8	12.8	1.7	0.43
EHI	86.3	12.8	84.7	14.5	0.75
BIS	55.8	8.6	71.8	9.4	0.000
BIS-A	14.2	3.1	21.7	4.3	0.000
BIS-M	20.6	3.0	22.1	3.2	0.17
BIS-N	21.0	4.7	27.9	5.6	0.000
BDI	1.8	2.7	35.9	9.6	0.000
HAMD	0.7	1.5	14.7	5.5	0.000
DTS	n.a.	n.a.	37.3	28.7	n.a.
BSL-23	n.a.	n.a.	59.5	18.8	n.a.

n.a. indicates not applicable, *EHI* Edinburgh Handedness Inventory, *BIS* Barratt Impulsiveness Scale, *BIS-A* BIS attention, *BIS-M* BIS motor, *BIS-N* BIS nonplanning, *BDI* Beck depression inventory, *HAMD* Hamilton Depression Rating Scale, *BSL-23* borderline symptom list, *DTS* Dissociation Tension Scale

Scale (HAMD) [36]. Dissociative symptoms were assessed using the Dissociative Tension Scale (DTS) [32]. Detailed demographic and psychometric data are shown in Table 1.

The healthy control group consisted of 16 unmedicated right-handed female participants (7 participants were part of a previously reported healthy control group [34]) matched for age, education and handedness. Participants with a neurological or a psychiatric disorder according to DSM-IV-TR criteria, substance abuse or dependence were excluded. Further exclusion criteria were a positive family history for psychiatric disorders and a history of seizures or major head trauma. The study was approved by the local Research Ethics Committee (University of Ulm, Germany) and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Written informed consent was obtained from all participants following a complete description of the study.

MRI data acquisition

CASL brain volumes were obtained with a 3 Tesla "Magnetom Allegra" (Siemens, Erlangen, Germany) MRI system equipped with a head volume coil at the Department of Psychiatry and Psychotherapy III at the University of Ulm, Germany. MRI scanning was carried out in darkness, and the participants were explicitly instructed to keep their eyes closed, not to think about something special, not to fall asleep and move as little as possible. Adherence to these instructions was verified by verbal contact immediately after the scan and as part of a post-scanning exit interview.

CASL uses magnetically labeled arterial blood water to endogenously trace and quantify CBF as a surrogate marker reflecting underlying neural activity [25]. Unlike techniques measuring CBF, such as SPECT or positron emission tomography PET, CASL is a non-invasive method with excellent spatial and temporal resolution properties that make this technique particularly appealing for both basic and clinical neuroscience research of brain perfusion physiology [26]. Importantly, unlike blood oxygen level–dependent (BOLD) functional MRI (fMRI), CASL delivers a quantitative assessment of cerebral perfusion and appears to be better suited to investigate slow changes in neural activity that could otherwise be biased by scanner drifts. Moreover, CASL shows a high stability over long-time scales (over minutes up to days and weeks) [37] and generates data that are statistically independent over time under the null hypothesis, that is, data that do not possess autocorrelation [38, 39]. Eventually, CASL-based perfusion contrast can be assessed using MR pulse sequences that are resistant to susceptibility effects, thus offering an important advantage for imaging, for example, orbitofrontal regions or inferior temporal areas [27, 40].

Technical details on the CASL sequence used in this study can be found elsewhere [25]. In brief, the labeling plane was 8 cm beneath the centre of the imaging sections. Twenty radio-frequency (RF) pulses of 100 ms duration and gap of 7.5 ms were used for labeling. Mean duration of each control or labeling image acquisition was 2,142.5 ms. A delay of 1 s between the end of the labeling pulses and image acquisition should reduce transit-related effects. Off-resonance artifacts were controlled by a sinusoidally amplitude-modulated version of the labeling pulse. T2*—weighted interleaved label and control images were acquired using a gradient echo-planar imaging (EPI) sequence (matrix 64 × 64 pixels, repetition time 4 s, echo time 16 ms, bandwidth 3.005 Hz/Px). Eighteen transversal slices were positioned along the anterior commissure/posterior commissure (AC–PC) line (slice thickness 5 mm, 1.5 mm gap). In-plane resolution was 3.44 × 3.44 mm. The perfusion block for all participants comprised 80 acquisitions of labeled and control images, with a duration of 5 min, 28 s. Prior to the perfusion scan, correct head positioning was assessed with a localizer scan, followed by whole-brain shimming.

CASL data analysis

Preprocessing and statistical analyses were performed using Statistical Parametric Mapping (SPM5, Wellcome Department of Cognitive Neurology, London, UK; www.fil.ion.ucl.ac.uk) in combination with software implemented in MATLAB 7.3 (MathWorks, Natick, MA) for use as a toolbox under SPM5. The toolbox code is based on a MATLAB script by H. Y. Rao and J. J. Wang from the Center for Functional Imaging at the University of Pennsylvania (http://cfn.upenn.edu/perfusion/software.html) that implements a single-compartment CASL perfusion model for reconstructing images of raw perfusion and quantified regional CBF in units of ml/100 g tissue/min [25]. The individual images underwent realignment to the first image to correct for head movement, reslicing and generation of perfusion-weighted images by pair-wise subtraction of the label and control images, followed by conversion to quantified CBF. This procedure also incorporated the calculation of a mean EPI by averaging across all acquired EPI images. The CBF images were normalized to the canonical Montreal Neurological Institute (MNI) space by applying the transformation matrices from the normalization of the individual high-resolution T1-weighted MR images to a standard T1 template of $2 \times 2 \times 2$ mm^3 voxel. Prior to normalization, the individual T1 images had been co-registered onto the average EPI. The normalized CBF images were then smoothed with a three-dimensional 10 mm full-width at half-maximum Gaussian kernel. In general linear model voxel-wise 1st level analyses, the time course of the volume mean was used as a covariate to reduce spatially coherent noise [41]. The CBF images were scaled to a grand mean of 50. No temporal filtering was involved. Within this 1st level analysis, mean CBF images were computed for each subject.

Group comparisons between controls and patients were conducted at the 2nd level using the 1st level individual mean CBF maps, and an analysis of variance (ANOVA) model, where age, BDI and HAMD scores [16] as well as the individual mean CBF values [42] were included as covariates of no interest. The 2nd level analyses were constrained to a network of interest including the medial and lateral OFC and regions projecting to or receiving projections from the OFC [10, 11]. The anatomical mask computed for this purpose included the bilateral superior, inferior, middle and medial OFC, the anterior cingulate cortex (ACC), the posterior cingulate cortex (PCC), the bilateral middle and inferior frontal gyri, the bilateral insula, the bilateral amygdala, the bilateral caudate nucleus and the bilateral parahippocampal cortex, as defined by the Automatic Anatomical Labelling (AAL) Atlas [43]. Inference of meaningful local group differences on the 2nd level was based on an uncorrected voxel threshold of $p < 0.005$ and a cluster correction threshold of $p < 0.05$ [44]. Stereotaxic coordinates of significant between-group differences are reported from activation maxima within a given cluster according to the MNI template.

Correlations between CBF and clinical symptom clusters

For the patient group, Spearman correlations were calculated between CBF values and psychometric scores obtained by the DTS, BDI, BIS total score and the BIS subscales (BIS-A, BIS-M, BIS-N). Correlations were computed using the psychometric variables and the extracted CBF values from clusters of interest emerging from the between-group comparisons (see below). The mean CBF cluster values were extracted using MarsBar [45] and subsequently processed off-line using the Statistica software package (Version 6.0, StatSoft Inc., Tulsa, OK, USA). As nominal level of significance, a level of $p < 0.05$ was defined and adjusted for multiple comparisons using the Benjamini–Hochberg–Yekutieli procedure [46] to control the false discovery rate (FDR adjusted p-level = 0.0264).

Results

Psychometric scores

The BIS total score and the BIS-A and BIS-N subscores were significantly higher in patients, whereas the BIS-M score did not significantly differ between patients and controls. BDI and HAMD scores were significantly higher in patients compared to controls; see Table 1.

CBF between-group analyses

Compared to controls, BPD patients exhibited decreased CBF in the medial OFC (Brodmann area [BA] 10: $x = 4$, $y = 54$, $z = -2$; $Z = 2.94$, cluster extent [k] = 56 voxels, Cohen's $d = 1.14$) and increased CBF in the left and right lateral OFC (left BA 11: $x = -26$, $y = 44$, $z = -4$; $Z = 3.79$, $k = 144$ voxels, Cohen's $d = 1.67$; right BA 11: $x = 32$, $y = 44$, $z = -6$; $Z = 3.16$, $k = 60$ voxels, Cohen's $d = 1.44$); see Fig. 1.

Correlations between CBF and clinical symptom clusters

A positive correlation was found between the BIS total score and CBF in the medial ($\rho = 0.50$, $p = 0.024$), left lateral ($\rho = 0.58$, $p = 0.009$) and right lateral OFC ($\rho = 0.64$, $p = 0.004$). BIS-A scores were positively

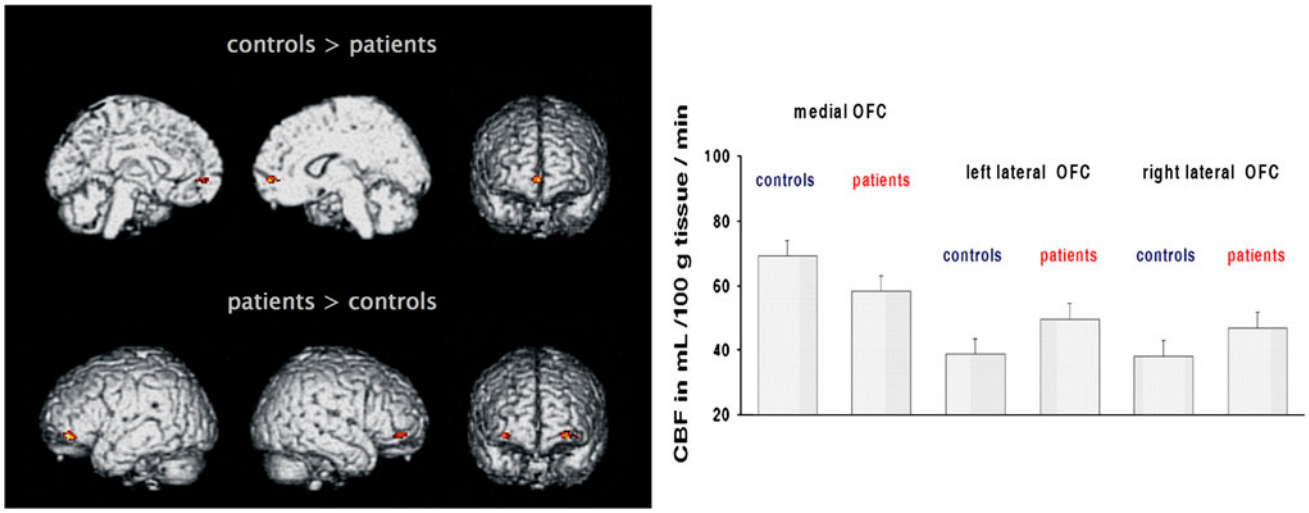

Fig. 1 *Left* Regions exhibiting decreased (contrast: controls > patients) and increased (contrast: patients > controls) CBF in patients with BPD compared to healthy controls. Results derived from the between-group ANOVA ($p < 0.005$, uncorrected for height, $p < 0.05$ cluster corrected). *Right* Extracted CBF values (means and standard error) from medial and lateral orbitofrontal cortex (OFC) clusters

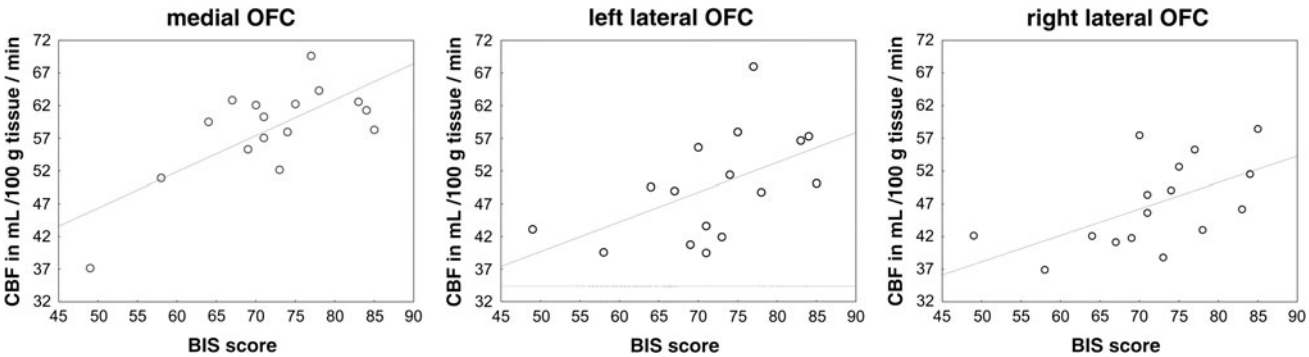

Fig. 2 Correlation plots between medial and lateral orbitofrontal CBF and BIS sum scores

correlated with CBF in the medial ($\rho = 0.60$, $p = 0.007$) and left lateral ($\rho = 0.54$, $p = 0.020$) OFC. BIS-N scores were positively correlated with CBF in the left ($\rho = 0.55$, $p = 0.014$) and right lateral ($\rho = 0.55$, $p = 0.012$) OFC; see Fig. 2 and Table 2, supplementary data for detailed statistics.

There were no significant correlations between BIS-M scores and orbitofrontal CBF. Correlations between medial or lateral orbitofrontal CBF and scores of dissociation tension and depression were not significant (see also Table 2, supplementary data).

Discussion

This study investigated resting-state CBF and its relationship to distinct symptom clusters in individuals with BPD. Two main findings emerged: First, patients exhibited abnormal CBF in the medial and lateral regions of the OFC. Second, we found a significant relationship between measures of impulsivity and medial/lateral OFC blood flow, whereas correlations between OFC blood flow and measures of dissociation tension and depression were not significant.

The findings of aberrant OFC blood flow are in line with several functional neuroimaging studies that have shown abnormal function of the OFC in patients with BPD with and impulsivity-related personality disorders [2, 5, 16, 17, 28]. The pattern of OFC dysfunction, however, suggests that resting-state brain perfusion physiology in BPD is characterized by both decreased and increased orbitofrontal blood flow in anatomically distinct areas of the OFC. In this regard, previous studies of brain function in BPD have repeatedly demonstrated increases and decreases of activation, providing evidence for a complex pattern of neural dysfunction elicited by experimentally controlled tasks [2–

5, 47]. Considering the extant resting-state data on CBF and metabolism in BPD, findings from FDG PET have predominantly suggested decreased medial prefrontal and orbitofrontal metabolism [3, 15, 16], although metabolic increases have been also occasionally reported [29]. Similarly, a report of resting-state CBF, as studied by SPECT, has emphasized reduced frontotemporal blood flow in a sample of patients with BPD or anti-social personality disorder without evidence for CBF increases [28]. Methodological differences, such as the measurement of cerebral metabolism vs. CBF, or sample characteristics, such as the inclusion of patients with other impulsivity-related axis II disorders [28], may at least partly account for the fact that the BPD sample presented here exhibited increased lateral OFC blood flow in contrast to patterns of predominantly reduced metabolism or CBF. Nevertheless, our results suggest that altered resting-state CBF in patients is characterized by a regionally specific dysfunction of distinct OFC regions, in line with our initial prediction, and in good accordance with behavioral data suggesting a functional deficit of the OFC in BPD [18]. Moreover, we were able to demonstrate a significant relationship between OFC blood flow and impulsivity, as measured by the BIS, whereas correlations with other symptom dimensions, such as dissociation tension and depressive symptoms, did not yield significant results. These data are in excellent agreement with the hypothesis that disrupted function of the OFC may specifically play a role in the expression of impulsivity in BPD [16, 18] and that other symptom dimensions, for example, dissociation, pain sensitivity or self-injurious behavior could be mediated by different neural substrates [48–50]. For instance, an involvement of insular activation has been repeatedly shown in the context of dissociative symptoms [48, 49], whereas neural correlates involved in altered pain sensitivity have been shown to comprise dorsolateral prefrontal, parietal and cingulate regions [50].

Apart from their potential clinical relevance, the findings of our study are also in accordance with recent reports linking trait impulsivity to distinct regions of the OFC. For instance, two studies of OFC volume have shown a relationship between lateral OFC gray matter and BIS total scores [19, 33], along with differential correlations between BIS subscores and left and right lateral OFC, respectively. In this regard, our observation that attentional impulsivity is associated with left lateral OFC blood flow is consistent with what has been recently reported for left OFC volume in a BPD patient sample [19]. Conversely, nonplanning impulsivity was specifically related right OFC blood flow, in line with findings from a healthy population [33]. Given the correlation patterns found in our patient sample, it is possible that distinct orbitofrontal loci could differentially mediate certain dimensions of impulsivity in BPD, that is, attentional versus nonplanning aspects of impulsive behavior. However, this hypothesis clearly needs to be substantiated by complementary behavioral data obtained by comprehensive neuropsychological testing.

The observation of increased lateral and decreased medial OFC blood flow deserves further attention. Neuroanatomically, inputs to and outputs from the medial OFC can be segregated from connections to lateral parts of the OFC, where medial areas connect mediolateral temporal, cingulate, parahippocampal and dorsolateral prefrontal regions, in contrast to the multisensory inputs to the lateral OFC and its connections with the ventrolateral prefrontal cortex [20]. Accordingly, evidence from animal studies in conjunction with behavioral and neuroimaging findings in humans has proposed several models of medial versus lateral OFC function [11, 51, 52]. For instance, it has been suggested that the medial OFC could subserve the monitoring of reward reinforcers, whereas lateral OFC regions may mediate the evaluation of punishers and the subsequent modification of behavior [11]. Other putative functions of the lateral OFC may include the suppression of previously rewarded behavior, as suggested by some authors [51]. With respect to the findings of our study, it appears possible that the decreased medial OFC perfusion in contrast to the increased lateral OFC blood flow could also reflect different functional properties of the OFC. The differential correlation patterns between medial and lateral OFC blood flow versus attentional and nonplanning aspects dimensions of impulsivity might at least partly support this assumption. For instance, studies on delay discounting and decision-making processes have emphasized contributions of the lateral OFC to nonplanning impulsivity [53, 54]. In addition, both medial and lateral regions of the OFC have been implicated in reward processing, with the medial OFC being involved in immediate in contrast to delay-independent choices [55]. It is thus conceivable that a dysbalance between medial and lateral OFC function, as we have shown for BPD patients, may lead to dysfunctional processing of reinforcers and reward values and consequently to impulsive, risky and less predictable behavior.

Contrary to our expectations, we did not find a negative relationship between impulsivity scores and medial OFC blood flow, that is, that lower medial orbitofrontal CBF would be associated with increased impulsivity. Similar unexpected findings have been recently reported by a volumetric study relating brain volume to impulsivity in BPD and healthy individuals [19]. It is possible that the positive relationship between medial OFC blood flow and attentional impulsivity could be related to different levels of arousal [56] or that it may signify decreased levels of intrinsic alertness [57] in BPD compared to healthy controls. In this respect, it is unclear how the study-specific settings, that is, the absent experimental stimulation, could

have contributed to our findings. Alternatively, it is also possible that the positive relationship between impulsivity and medial OFC blood flow could also reflect different functional activation responses in the presence or absence of explicit stimulation, as suggested previously [58]. Thus, higher phasic activity elicited by experimental stimulation could be associated with the expression of increased impulsivity, in contrast to low tonic activity during resting-state conditions. Directly testing this hypothesis will however need further studies using resting-state imaging in conjunction with an event-related functional neuroimaging protocol.

A crucial aspect of our study is that the data were obtained under resting-state conditions. Thus, given the absence of an experimentally manipulated task, we speculate that OFC dysfunction could signal a relatively stable neural signature of BPD independent of situations of specific social interactions [59] or explicit affective processing [4, 60]. On the other hand, the question whether the findings of the present study could be regarded as specific for BPD must remain open at this stage of research. MRI perfusion studies in other clinical populations have repeatedly demonstrated abnormal patterns of CBF, for example, in patients with major depressive disorder, schizophrenia and neurodegenerative disorders [26]. Yet so far, clear-cut and diagnosis-specific patterns of CBF changes have not been established. The fact that CASL is a relatively young technique compared to PET, SPECT or even BOLD fMRI [27], might partly account for the lack of these both scientifically and clinically relevant data. Future studies using direct clinical comparisons are necessary to determine whether our findings are specific for BPD or whether they may also apply to other diagnostic groups characterized by mood instability or deficient impulse control [61, 62]. Also, it should be kept in mind that the present findings have been obtained under resting-state conditions, and as such, they do not necessarily imply an intact function of other brain regions when challenged by experimental manipulation. Indeed, brain regions such as the ACC, the ventro- and dorsolateral prefrontal cortices, the insula and the amygdala have been repeatedly shown to exhibit abnormal activation in BPD patients [2, 6, 8, 50, 63, 64]; see also reviews by [6, 8]. In this regard, it is important to note that in contrast to the present CASL study, the vast majority of fMRI findings in BPD so far have been obtained by means of task-based techniques and thus, interactions with experimental material have to be taken into account [58]. A main strength of a resting-state approach is its advantage to study brain function unbiased by experimentally controlled stimulation. However, this approach may not have the potential to reveal brain activation changes associated with an active processing of cognitive, social or affective demands. Taking setting-specific conditions of our study into account, it is possible that regions outside the OFC, such as, for example, the amygdala, might appear intact when studied under resting-state conditions but may show abnormal activation during conditions of experimental stimulation. Again, directly testing this hypothesis will need further research using resting-state imaging together with task-based fMRI protocols.

Potential limitations of this study include the limited patient sample size and the presence of comorbid axis I disorders in our patient sample. However, most BPD patients have an additional axis I disorder such as depression [65, 66], and thus, fully excluding participants with a co-ocurrent axis I disorder may reduce generalizability to the larger BPD population. Moreover, we focused on a female population to avoid stratification effects, which are critical confounds in this type of research [67], and thus, the findings of our study need to be confirmed in male BPD patients. Eventually, all patients were medicated, and although we found regionally very circumscribed effects of abnormal OFC perfusion, we cannot fully rule out OFC-specific modulatory effects of psychotropic medication.

In conclusion, the results of the present study suggest abnormal resting-state CBF of medial and lateral regions of the OFC in female BPD patients without comorbid PTSD. Both medial and lateral OFC blood flow were associated with measures of impulsivity, indicating a critical role of the OFC in the expression of this symptom cluster in BPD patients. In addition, the regional dissociation between medial and lateral areas of the OFC suggests that distinct orbitofrontal loci of dysfunction could subserve distinct domains of behavioral impairment. Potential implications for further research in BPD and other impulse control disorders include the availability of a stable and quantifiable physiological unit of brain activity, which could be used to assess neural changes after specific clinical interventions, for example, psychotherapy [68]. In addition, task-based investigations of brain function in BPD may acknowledge the fact that differences of baseline brain perfusion physiology do exist in BPD, and these changes could potentially interact with stimulus-related activation responses.

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Conflict of interest The authors declare that they have no conflict of interest.

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