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Inhibition errors in borderline personality disorder with psychotic-like symptoms

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Abstract

Background: The aim of this study was to examine whether patients with borderline personality disorder (BPD) have deficits in cognitive inhibition as measured with an anti-saccade eye task similar to patients with schizophrenia (Sz). Furthermore, we investigated whether these inhibition errors were more prominent among BPD patients with psychotic-like symptoms than among BPD patients without these symptoms.
Methods: An anti-saccade task was administered in 32 BPD patients (among them, 20 had with psychotic-like symptoms), 21 patients with recent onset schizophrenia (Sz), and 25 healthy controls (HC). The percentage inhibition errors in the anti-saccade task were the primary outcome variable, in addition, the percentage of anticipatory errors was measured.
Results: Sz patients showed more inhibition errors than HC and BPD ($p<.001$ and $p<.05$ resp.), whereas BPD patients scored in between Sz and HC. The difference with HC was significant as well ($p<.05$). BPD patients with psychotic-like symptoms showed more inhibition errors than BPD patients without these symptoms ($p<.05$). BPD patients showed more anticipatory errors than HC ($p<.001$), whereas Sz patients did not ($p<.26$).
Conclusion: The data demonstrate that inhibition deficits, as measured with anti-saccadic eye movement task, may be characteristic among BPD patients and in a larger extent in patients with psychotic-like symptoms. This inhibition deficit was distinct from a general predisposition to response impulsively as measured by anticipatory errors, which was found in the whole group of BPD patients. Psychotic-like symptoms may be an important target dimension for future BPD research and treatment.

Keywords: Borderline personality disorder; Impulsivity; Inhibition; Psychosis; Saccades; Schizophrenia

1. Introduction

Borderline personality disorder (BPD) is a complex psychiatric disorder characterized by a pervasive pattern of instability in interpersonal relationships, self-image, affect and impulse control (American Psychiatric Association, 1994). Self-destructing behavior is a key feature of BPD, resulting in suicide rates of 8–10% (Work Group on Borderline Personality Disorder, 2001). BPD usually starts in early adulthood and is estimated to occur in about 1% of the population, most predominantly in women (Torgersen et al., 2001). Although BPD is the most common personality disorder in psychiatric settings, our understanding of its neurobiological basis is still limited (Skodol et al., 2002).

Recent neuroimaging research suggests that a dysfunctional frontolimbic network plays an important part in the pathophysiology of BPD. This network encompasses the amygdala, the hippocampus, the anterior cingulate cortex, and the orbitofrontal

Abbreviations: BPD, Borderline personality disorder; BPD+PSYCH, Borderline personality disorder with psychotic-like symptoms; BPD−PSYCH, Borderline personality disorder without psychotic-like symptoms; EOG, electro-oculography; HC, healthy controls; LED, light-emitting diodes; ANOVA, analyses of variance PFC=prefrontal cortex; SCID-1, structural clinical interview for DSM-IV axis I (SCID-I); Sz, schizophrenia.

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and dorsolateral prefrontal cortex (Lieb et al., 2004; Schmahl and Bremner, 2006). Data on executive dysfunction in BPD is still limited and findings are conflicting. Supportive evidence is that BPD patients, when compared to healthy subjects, have longer response times on the Porteus maze task and the trail-making test. Furthermore BPD patients exhibited more errors on the Stroop color-word test (Swirsky-Sacchetti et al., 1993). Other studies, however could not always replicate these findings, which suggests clinical and neurobiological heterogeneity in BPD (Kunert et al., 2003; Sprock et al., 2000).

The present study was designed to further examine a specific domain of executive functioning in BPD by focusing on a task that assesses inhibition. We used in particular the anti-saccade task, in which participants visually fixate a central stimulus that is replaced by a sudden onset target that appears either to the left or the right. The participants are required to inhibit a reflexive pro-saccade to the peripheral target and to execute an alternative, voluntary eye-movement to the opposite direction: an anti-saccade (Hutton and Ettinger, 2006). The neural circuitry behind saccadic eye movements is well understood (Munoz and Everling, 2004). Lesion studies show a particular involvement of the dorsolateral prefrontal cortex (DLPFC) and the anterior cingulate cortex (ACC) in the performance on the anti-saccade task (Gaymard et al., 1998; Milea et al., 2003; Paus et al., 1993; Pierrot-Deseilligny et al., 2003; Ploner et al., 2005).

The first aim of this study was to examine whether patients with borderline personality disorder (BPD) have deficits in cognitive inhibition as measured with an anti-saccade eye task, in similar to patients with schizophrenia (Sz). Inhibition abnormalities in the anti-saccade task have consistently been found in the schizophrenia spectrum, especially in patients with negative symptoms, and are even regarded as an endophenotype (Broerse et al., 2001; Hutton and Ettinger, 2006; Turetsky et al., 2007). Since anti-saccadic errors have been found in other patient groups as well (e.g. ADHD, Bipolar disorder, Huntington's disease), Hutton and Ettinger (2006) concluded that 'anti-saccade errors are increased in neuropsychiatric disorders that implicate frontal lobe dysfunction.' Previous research showed that BPD patients made more errors in response inhibition in the Wisconsin Card Sorting test (Lenzenweger et al., 2004; Swirsky-Sacchetti et al., 1993) and more slowing and errors of omission on the go/no-go task (Dinn et al., 2004). In addition, BPD traits have been related to response inhibition in a stop-signal task as well (Nigg et al., 2005). As BPD has been related with frontal dysfunction, we expected BPD patients to have more deficits than healthy controls. We added schizophrenia patients as a patient comparison group, because the deficit has been well documented for schizophrenia. Moreover, this comparison gives an indication of the extent of the putative inhibition deficit.

In addition to inhibition errors, the number of 'too fast', impulsive responses was measured. Since BPD patients generally exhibit impulsive behavior (Moeller et al., 2001), we did expect to find a faster anticipatory response style. Recently, it has been found that BPD patients show more problems in learning from their own errors (de Bruijn et al., 2006).

Another important characteristic of BPD is the proneness to develop psychotic-like symptoms. In fact, the term 'borderline' was actually put forward, because clinicians believed that such patients lie on the border of psychotic functioning (Knight, 1953). However, the criterion "transient, stress-related severe dissociative symptoms or paranoid ideation" was incorporated in the classification for BPD not until the publication of DSM-IV in 1994. The presence of psychotic-like symptoms in BPD is of clinical importance as well. The prevalence of major psychotic disorders is low, but transient psychotic-like symptoms ('quasi'-hallucinations, ideas of reference or paranoid ideation) in response to stress occur in about 40% of BPD patients (Zanarini et al., 1990). The tendency to develop such psychotic-like symptoms is persistent over time (Antikainen et al., 1995) and is considered to be associated with chronic impairment (Stone, 1993).

As schizophrenia and BPD share the vulnerability to develop psychotic symptoms, our second research question focuses on the relationship between psychotic symptoms and inhibition deficits. We expect that cognitive deficits would be more prominent in the subgroup with psychotic-like symptoms, because of the clinical concordance. We hypothesized *a priori* that BPD-patients with psychotic-like symptoms would show more inhibition errors than BPD patients without these symptoms.

2. Methods

2.1. Participants

We recruited 32 patients with Borderline Personality disorder (BPD) and 21 with recent-onset schizophrenia (Sz) from the in- and out-patient clinics of the two participating centers (Radboud University Nijmegen Medical Centre and GGNEt Apeldoorn). We recruited 25 healthy controls (HC) without a personal and family history of psychiatric disorders through advertisements in newspapers. Since the group of BPD patients consisted mainly of women and the schizophrenia group of men, we choose to include both men and women in the control group. Furthermore, age between 18 and 50 was an inclusion criterion in all groups.

The clinical diagnosis of the patients was confirmed by a trained research physician with the Structural Clinical Interview for DSM-IV axis I (SCID-I) and axis II (SCID-II) disorders (First et al., 1995; Spitzer et al., 1992). Since schizotypal traits are related to anti-saccade performance, we excluded patients with a co-morbid schizotypal personality disorder (Gooding et al., 2005). During the psychiatric interview, extra attention was focused on psychotic-like symptoms. The existence of psychotic-like symptoms in the past year was assessed on the basis of the cognitive section of the Revised Diagnostic Interview for Borderline (DIB-R) (Zanarini et al., 1989). Examples of psychotic-like symptoms are transient paranoid or somatic delusions, hallucinations or depersonalization. Among the 32 patients with BPD, 20 appeared to have had a pattern of several, consistent psychotic-like episodes related to stress in the past year (BPD+PSYCH), although none of them had any psychotic symptoms just before or during the

measurement. 12 BPD patients reported not to have had any of such symptoms (BPD−PSYCH) 'Recent onset Schizophrenia' was defined as patients with schizophreniform disorder or schizophrenia disorder, less than 1 year after first onset of positive symptoms (see Table 1 for demographic characteristics). The three groups did not differ with respect to age ($F=2.79$, $df=2,74$, $p=.07$), but they differed significantly in sex distribution, with more females in the BPD group and more males in the schizophrenia group ($\chi^2=27.4$, $df=2$, $p<.001$).

Neurological, ophthalmologic and vestibular disorders were exclusion criteria, as well as comorbidity with alcohol- or substance dependence or major depressive disorder according to SCID-I. If there was a self-reported use of any cannabis, illicit drugs or frequent alcohol (>3 units/day) in the week before measurements, appointments were rescheduled. None of the subjects had used alcohol, benzodiazepines or any other psychotropic drugs in the 12 h before measurement. The subjects' daily medication use is presented in Table 1. All medication was stopped 12 h before measurements. Subjects were further asked to abstain from caffeine and nicotine 6 h before measurement, although it was reported that inhibitory dysfunction in anticipatory saccades appeared to be unrelated to smoking (Olincy et al., 2003).

Approval for this study was obtained from the local ethics committee. All subjects gave written informed consent and were paid €10,-/h.

2.2. Laboratory procedures

The subjects were seated in a darkened room, 50 cm from a bar containing three equally spaced horizontal light-emitting diodes (LED). A chin/forehead rest was used to prevent head movements. Target lights were located at 15°, right and left from the central fixation point. Horizontal eye movements were recorded by electro-oculography (EOG) with electrodes attached on the outer canthi. A ground electrode was placed at the forehead. Low pass filters were set at 500 Hz. Windaq Acquisition software and interface and a universal psychophysiological amplifier were used to record the EOG signal and stimulus presentations.

4 series of 40 trials each were presented to the subjects. The task order was: pro-saccade/anti-saccade/anti-saccade/pro-saccade. Each trial consisted of the illumination of the central LED for randomly 1000–1200 ms, followed by the simultaneous extinguishment of the central LED and the illumination of one of the peripheral LEDs for 800 ms without overlap. The peripheral target light appeared left or right in a random order. The instruction of the pro-saccade task was to make an eye movement to the illuminated peripheral LED. The instruction of the anti-saccade task was to make an eye movement in the direction *opposite* to the LED. Subjects were instructed to respond as fast and accurate as possible.

Table 1
Demographic characteristics

	N	Sex (M/F)	Age (mean, SD/ median)	Medication use [a]
Healthy subjects	25	14/11	25.7 (5.5/24.0)	None ($n=25$).
Schizophrenia patients [b]	21	17/4	27.0 (9.1/25.0)	None ($n=4$), AAP ($n=3$), CAP ($n=14$)
BPD patients	32	3/29	29.4 (5.9/28.0)	
BPD patients with psychotic-like symptoms	20	1/19	29.5 (6.3/30.5)	None ($n=11$), SSRI ($n=6$), AAP ($n=2$), TCA ($n=2$), CAP ($n=2$)
BPD patients without psychotic-like symptoms	12	2 /10	27.6 (6.1/27.0)	None ($n=7$), SSRI ($n=4$). SNRI ($n=1$)

BPD = Borderline Personality Disorder. *N*=number of patients. SSRI = selective serotonin inhibitor. TCA = tricyclic anti-depressant. AAP = Atypical anti-psychotic. CAP = classical antipsychotic. SNRI = Serotonin-norepinephrine reuptake inhibitor.
[a] Medication use was not allowed 12 h before measurements.
[b] =8 patients with schizophreniform disorder, 13 patients with schizophrenia.

2.3. EOG analysis

EOG segments were analyzed with interactive custom made software. The eye movements were visually assessed, blinded to group status, and divided in different response categories: 'correct response' (a linear eye movement >80 ms after baseline in the correct the direction — depending on (pro-saccade or anti-saccade) task instruction), 'inhibition error' (reflexive saccade to the same side as the stimulus) and 'anticipatory saccade' (anticipatory response in either direction between <500 ms before baseline and <80 ms after baseline). Trials with eye blinks, missing eye movements and movement artifacts were removed from the analyses.

2.4. Statistical analysis

Dependent measures were the percentages of inhibition errors, anticipatory (too early) errors, percentage of correct responses and latency times.

All dependent variables were analyzed in two steps. First, the effect of the factor group (BPD, Sz, HC) was compared with an ANOVA, followed by post-hoc tests (Fisher's LSD). Secondly, differences between the BPD group with and without psychotic-like symptoms (BPD+PSYCH and BPD−psych respectively) were tested with ANOVA. Since sex was differently distributed in the groups, it was included as a between-subject factor in all analyses. Pearson correlations were used to investigate the relationship between inhibition and anticipatory errors. The level of significance was set at $p<.05$ (two-tailed). SPSS 14.0 software was used.

3. Results

3.1. Demographics

The demographic data are presented in Table 1. Its statistical evaluation showed that the three groups did not differ significantly with respect to age, however, the sex distribution was not equal in all groups ($\chi^2=27.4$, $df=2$, $p<.001$). There were more females than males in the BPD group, and more

Table 2
Eye movements in pro-saccade task

	% anticipatory responses (mean, SD)	% correct responses (mean, SD)	Latency time correct responses (ms) (mean, SD)
Healthy subjects	2.2 (2.4)	92.6 (5.1)	179.6 (22.8)
Schizophrenia patients	4.8 (4.7)	77.5 (12.6)	204.1 (51.2)
BPD patients	6.5 (4.9)	86.3 (12.7)	190.9 (30.6)
BPD with psychotic-like symptoms	6.9 (5.1)	84.4 (14.7)	188.6 (28.4)
BPD without psychotic-like symptoms	5.8 (4.7)	89.1 (6.9)	194.9 (35.0)

males than females in the schizophrenia group (Table 1). Therefore, sex was included as a between subject-factor in the subsequent analyses.

Tables 2 and 3 show the descriptive statistics of the pro-saccade and anti-saccade task (percentages correct responses and errors, and latencies for the correct responses and inhibition errors).

3.2. Introductory analyses

We removed unusable trials due to missing eye movements, eye blinks or artifacts. The percentage of unusable trials was higher in Sz than in the other groups (3.9% vs both 1.8%),. but in the ANOVA the group differences were not significant (F=2.71, df=2,72, p=. 07).

In the pro-saccade task, the ANOVA with the percentage of correct responses as dependent variable revealed a main group effect (BPD, Sz, HC) (F=6.9, df=2,72, p<.01). Post hoc tests indicated that both BPD and Sz patients made less correct responses than HC (both p<.01). The difference between Sz and BPD patients was not significant (p=.97). In the anti-saccade task, the ANOVA with the number of correct responses as dependent variable revealed a main group effect as well (F=13.6, df=2,72, p=.07). HC had more correct responses than both Sz patients (p<.001) and BPD patients (p<.001). The two patient groups did not differ to this respect (p=.08).

The ANOVA with 'latency time of the correct responses' as the dependent variable did not reveal a group effect in the pro-saccade task (F=2.14, df=2,72, p=0.12), but a significant group effect in the anti-saccade task (F=6.2, df=2,72, p<.01). Sz patients had longer initiation times than HC (p<0.01) and BPD patients (p<.01). The latter two did not differ from each other (p=.59). Latency times of BPD+PSYCH patients did not differ from BPD−PSYCH patients (p=.87 and .52 for the pro-saccade and anti-saccade task respectively).

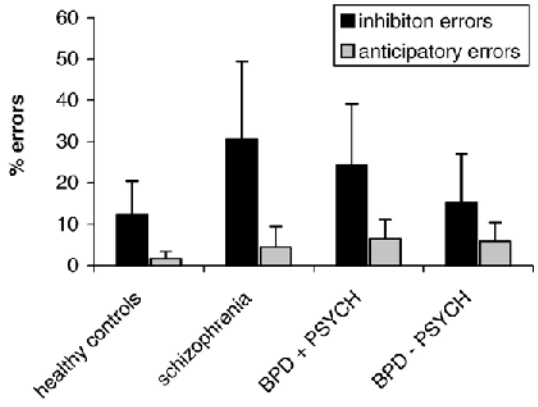

Fig. 1. Percentage inhibition errors in anti-saccade task and pooled anticipatory errors in pro-saccade and anti-saccade task (Standard deviation shown in figure). 'BPD+PSYCH' and 'BPD−PSYCH' refers to the presence and absence of psychotic-like symptoms respectively.

3.3. Inhibition errors

The primary outcome measure of this study was the percentage of inhibition errors in the anti-saccade task; the ANOVA revealed a significant group effect (F=10.3, df=2,72, p<.001). The data are depicted in Fig. 1. Sz patients had more errors than HC (p<.001) and BPD patients (p<0.05). The difference between BPD patients and HC was significant as well (p<0.05). The effect for sex was not significant (p=.92).

Subsequent analysis revealed that BPD patients with psychotic-like symptoms had more inhibition errors than BPD patients without psychotic-like symptoms (F=10.2, df=1,28, p<.01). The effect for sex within the BPD groups was significant as well (F=7.42, df=1,28, p<.05). An additional post hoc ANOVA analysis revealed that BPD+PSYCH patients did not differ from the Sz patients (p=.41), while BPD−PSYCH differed significantly from Sz (p<.01). When the analyses on inhibition errors were restricted to only females or to only medication-naïve patients, the results were essentially similar, though p-values were higher due to loss of power.

Table 3
Eye movements in anti-saccade task

	% inhibition errors (mean, SD)	% anticipatory responses (mean, SD)	% correct responses (mean, SD)	Latency time inhibition errors (ms) (mean, SD)	Latency time correct responses (ms) (mean, SD)
Healthy subjects	12.3 (8.2)	1.1 (1.3)	86.6 (6.5)	187.4 (45.1)	271.6 (68.4)
Schizophrenia patients	30.4 (18.9)	4.2 (5.4)	63.3 (16.4)	256.8 (104.0)	358.6 (139.1)
BPD patients	20.8 (14.3)	5.8 (4.7)	71.3 (16.5)	218.9 (67.4)	284.4 (62.4)
BPD with psychotic-like symptoms	24.3 (14.7)	5.7 (4.4)	68.4 (17.6)	226.9 (81.7)	282.0 (62.5)
BPD without psychotic-like symptoms	15.0 (12.0)	6.0 (5.3)	76.0 (14.0)	204.4 (24.7)	287.9 (64.9)

3.4. Anticipatory errors

The percentage of anticipatory errors did not differ between the pro- and anti-saccade task (F=1.98, df=1,65, p=.16), therefore the data of both tasks were pooled in further analyses.

In the ANOVA with percentage of anticipatory errors as dependent variable, a significant group effect was found (F=4.60, df=2,72, p<.05); the post-hoc tests showed that BPD patients had higher percentages of anticipatory errors than healthy controls (p<.01), while the differences between Sz and BPD (p=.13) and HC (p=.30) were not significant. There was no difference between BPD patients with and without psychotic-like symptoms (p=.70). In addition, there was no significant correlation between the percentage of anticipatory and inhibition errors (r=0,23, p=.25).

4. Discussion

In the present study, we demonstrated that BPD patients scored in between schizophrenia and healthy controls on an inhibition task (hypothesis I). Moreover, BPD patients with psychotic-like symptoms had significantly more inhibition errors than BPD patients without these symptoms (hypothesis II). The BPD patients with psychotic-like symptoms had a similar rate of inhibition errors as patients with Sz, whereas BPD patients without psychotic-like symptoms resembled healthy controls. The inhibition deficit was distinct from a general predisposition to respond impulsively, which was found in the whole group of BPD patients.

There may be similar underlying dopaminergic alterations in BPD and schizophrenia. Recently, an essential role for dopamine in BPD pathophysiology has been proposed in that dopaminergic pathways projecting to the PFC may be involved in disturbed cognitive perceptual responses and planned behaviors in BPD (Friedel, 2004). Psychotic-like symptoms have been regarded as one of the clinical dimensions in the neurobiological research of BPD (Skodol et al., 2002). Moreover, antipsychotic drugs have secured a position in the pharmacological treatment of BPD (Grootens and Verkes, 2005).

Our results raise the question whether the anti-saccade error is a specific marker for schizophrenia or a marker for psychosis in general. These deficits has also been found in patients with bipolar disorder (Sereno and Holzman, 1995; Tien et al., 1996). In addition, the association between psychotic-like symptoms and inhibition errors has been found earlier in a groups of students with questionnaire-identified schizotypy (Gooding, 1999; O'Driscoll et al., 1998).The percentage of inhibition errors and latency times found in the schizophrenia group are in line with percentages previously found by others (Broerse et al., 2001; Everling and Fischer, 1998). Of importance is the fact that the Sz patients in our sample had a recent onset of the syndrome. Our results show that inhibition abnormalities can be established in early stages of the syndrome in patients without a history of long-term medication.

Another way of interpreting the shared high number of inhibition errors of both BPD and Sz in the anti-saccade task is to take the developmental perspective, because both BPD and Sz have an early age of onset. In healthy subjects, there is a clear relation between age and anti-saccadic performance, in that a dramatic improvement in the performance of the anti-saccade task has been found between from age 5 to15 (Fischer et al., 1997; Luna et al., 2001; Munoz et al., 1998). The ability to inhibit prepotent responses is viewed as a direct result of structural and functional maturation of the prefrontal cortex and its connections, that gradually improves through childhood and adolescence (Munoz et al., 1998). One might suggest a disturbed functional development of the PFC or associated neurocircuitry in both Sz and a subgroup of BPD patients, a hypothesis which is in line with previous findings (de Bruijn et al., 2006; De la Fuente et al., 1997; Lyoo et al., 1998; Soloff et al., 2000, 2003; Tebartz et al., 2003; Tu et al., 2006). Since normal anti-saccadic performance reflects normal PFC development, the poor performance on this task has been regarded as a biological marker for several neuropsychiatric disorders. Not necessarily only biological, but also psychological events may interfere with normal brain development in BPD. Therefore, it is interesting to examine the relationships between severe negative life events, disinhibition and psychotic-like symptoms in BPD in the future.

Next to inhibition errors, we found a higher percentage of anticipatory errors in BPD patients in comparison to healthy subjects. In contrast to the inhibition deficit, subtyping for the presence or absence of psychotic symptoms did not differ with regard to the number of anticipatory errors. The tendency to make 'false alarms' can be viewed as a form of disinhibition as well. However, it is not an automatic response to a stimulus that is inhibited, but a disinhibition of a motor response to an internal cue. The absence of a correlation between anticipatory and inhibition defects indicates that the two error types are essentially different. It is an interesting question whether anticipatory errors reflect clinical impulsivity, which is traditionally viewed as a core feature of BPD. Since 31 of 32 BPD patients of our sample were positive for the DSM-IV criterion for impulsiveness ('at least two potentially self-damaging impulsive behaviors'), it was not possible to further analyze the association between the anticipatory response style and clinical impulsivity.

As expected, the pro-saccade task revealed no differences between the three groups in latency time. However, the low percentage of correct responses – especially in the two patient groups – is atypical in comparison to previous reports (Broerse et al., 2001).We think our strict definition of 'correct response' may have attributed to this: next to eye movements in the wrong direction, we labeled all trials with non-linear eye movements (with 'steps') or with a latency outside the timeframe 80–500 ms as incorrect.

A possible limitation to our findings is the effect of drug treatment. Although recent literature suggests that anti-saccade errors in schizophrenia remain even after drug treatment, it is possible that medication effects did occur in our study (Harris et al., 2006). However, in an extra post hoc omnibus analysis with different drug types as co-factor, we did not find any effects of medication, suggesting that recent use of medication did not confound the findings of our study. Moreover, acute drug effects were excluded because there was a 12-hour medication-free period prior to the assessments. In addition, the

latency and duration times did not indicate that sedative effects were present. Another possible limitation is the sex distribution of the three groups. Our sample reflected the rather typical sex distribution of a male preponderance of Sz and a female preponderance of BPD. To adjust for this as much as possible, we run all our analyses including sex as a cofactor. The outcomes of our analyses do not show that the differences in sex jeopardize our conclusions.

In conclusion, our data suggest that inhibition deficits may be characteristic among BPD patient with psychotic-like symptoms, but do not reflect the whole group of BPD patients. The resemblance with schizophrenia is striking and possibly implicates a shared involvement of dopaminergic pathways in the dorsolateral PFC and/or ACC. Therefore our results are in line with a prefrontal-dysfunction hypothesis for BPD. Psychotic-like symptoms may be an important target dimension for future BPD research and treatment.

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