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Striatal activity in borderline personality disorder with comorbid intermittent explosive disorder: Sex differences

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ABSTRACT

Borderline Personality Disorder (BPD) is associated with behavioral and emotional dysregulation, particularly in social contexts; however, the underlying pathophysiology at the level of brain function is not well understood. Previous studies found abnormalities in frontal cortical and limbic areas suggestive of poor frontal regulation of downstream brain regions. However, the striatum, which is closely connected with the medial frontal cortices and plays an important role in motivated behaviors and processing of rewarding stimuli, has been understudied in BPD. Here we hypothesized that, in addition to frontal dysfunction, BPD patients may show abnormal striatal function. In this study, 38 BPD patients with intermittent explosive disorder (BPD-IED) and 36 healthy controls (HC) participated in the Point Subtraction Aggression Paradigm (PSAP), a computer game played with a fictitious other player. ^{18}Fluoro-deoxyglucose positron emission tomography (FDG-PET) measured relative glucose metabolism (rGMR) within caudate and putamen in response to aggression-provoking and non-provoking versions of the PSAP. Male BPD-IED patients had significantly lower striatal rGMR than all other groups during both conditions, although male and female BPD-IED patients did not differ in clinical or behavioral measures. These sex differences suggest differential involvement of frontal-striatal circuits in BPD-IED, and are discussed in relation to striatal involvement in affective learning and social decision-making.

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1. Introduction

Borderline Personality Disorder (BPD) is a chronic illness characterized by behavioral disinhibition, including impulsivity, aggression and affective lability (Sanislow et al., 2000, 2002). Impulsive aggression and affective dysregulation/instability are core traits of BPD (Siever, Torgersen et al., 2002; Skodol, Siever et al., 2002; McGlashan, Grilo et al., 2005), and contribute substantially to the morbidity and mortality associated with BPD. Impulsive aggression in BPD can manifest in a variety of behaviors, including destruction of property, assault, domestic violence, self-injurious and suicidal behavior, or substance abuse (New, Gelernter et al., 1998).

Although earlier research supported a higher prevalence of BPD among women, as reflected in the 3:1 female to male ratio reported in the most recent edition of the DSM (DSM-IV-TR) (APA, 2000), more recent data suggest that there are no sex differences in the prevalence of BPD (Grant, Chou et al., 2008). The available data also suggest that there are no gender differences in BPD with regard to self-harm behaviors such as self-cutting and presenting levels of psychological distress (Sansone and Sansone, 2011). However, there appear to be gender differences with regard to personality traits (with men having higher rates of explosive temperaments and high levels of novelty seeking), Axis I (with men having higher rates of substance abuse whereas women are more likely to suffer eating, mood, anxiety, and posttraumatic stress disorders) and Axis II comorbidity (with men more likely than women to have antisocial personality traits), and treatment utilization histories (men are more likely to have had treatment for substance abuse whereas women are likely to have used more pharmacotherapy and psychotherapy) (Sansone and Sansone, 2011).

Brain imaging studies in BPD (see New at al. for a review (New et al., 2008)) have shown abnormalities in structure, function and connectivity of medial frontal cortical and limbic regions. These findings have been interpreted as decreased frontal top-down

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control of limbic areas involved in affective responsiveness and impulsive aggression, resulting in disinhibited behavior and increased impulsive aggression (New et al., 2009). However, the striatum, which is closely connected with the medial frontal cortices and plays an important role in motivated behaviors and processing of rewarding stimuli (Ernst and Fudge, 2009), has been understudied in BPD.

The striatum, which is part of the basal ganglia, is composed of the caudate nucleus and putamen (Ernst and Fudge, 2009). Corticostriatal pathways have been implicated in motivated goal-directed behavior (Ernst and Fudge, 2009; Hollerman et al., 1998; Kawagoe et al., 1998; O'Doherty, 2004; Schultz and Romo, 1988), habit learning, economic and social decision-making (de Quervain et al., 2004; Rilling et al., 2008). The striatum is activated by primary (Gottfried et al., 2003; O'Doherty et al., 2001; Pagnoni et al., 2002) and secondary (Delgado et al., 2000; Kirsch et al., 2003; Knutson et al., 2001) reinforcement, including maternal (Bartels and Zeki, 2004) and romantic love (Aron et al., 2005), suggesting a role in processing socially rewarding cues. Dysregulation of the basal ganglia and corticostriatal networks has been associated with aggressive behavior (Amen et al., 1996; Cummings, 1993; Mendez et al., 1989; Richfield et al., 1987; Soderstrom et al., 2002), schizophrenia (Buchsbaum et al., 1982; Sheppard et al., 1983), unipolar and bipolar depression (Baxter et al., 1985; Buchsbaum et al., 1986), generalized anxiety disorder (Wu et al., 1991), obsessive compulsive disorder (Baxter et al., 1987; Martinot et al., 1990) and alcoholism (Volkow et al., 1994).

However, only four studies have examined striatal activity or structure in BPD. One study using ^{18}Fluoro-deoxyglucose (FDG) positron emission tomography (^{18}FDG-PET) showed hypometabolism throughout thalamo-cortico-basal ganglia circuits in BPD (De La Fuente et al., 1997), although another study found no differences in basal ganglia metabolism with ^{18}FDG-PET during resting state in BPD patients compared to controls (Salavert et al., 2011). Another study showed lower α-[11C]methyl-L-tryptophan (α-[11C]MTrp) trapping in corticostriatal pathways, suggesting decreased serotonin synthesis capacity, in BPD (Leyton et al., 2001). Finally, significantly increased right and left putamen volumes were observed in male BPD subjects with substance use disorders (Brambilla et al., 2004).

In the present study, we aimed to extend these earlier findings by comparing volume and striatal activity using ^{18}FDG-PET in a group of BPD patients selected for serious impulsive aggression (meeting criteria for intermittent explosive disorder-revised (IED-R)) and healthy controls (HCs) in an aggression provocation behavioral paradigm (New et al., 2009). We aimed to determine whether striatal dysfunction is present in BPD patients during the provocation of aggression and whether it correlates with behavioral and self-reported impulsive aggression. We also aimed to explore any possible gender effects or gender by diagnosis interaction on striatal volume and activity.

We hypothesized that BPD-IED patients and HCs would differ in striatum metabolism during aggression provocation. However, the direction of hypothesized group differences was unclear in light of the ambiguity in the literature.

2. Method

2.1. Participants

Participants and the diagnostic assessments for this study were described in detail previously (New et al., 2009) and are briefly described here. Although we previously published ^{18}FDG-PET data from this sample, the analyses focused on the amygdala and prefrontal cortex, and the striatal data was not examined. We previously published a whole brain statistical probability mapping analysis that specifically focused on differences between the provoked and non-provoked conditions, and did not analyze males and females separately, as no sex differences were discovered in amygdala and prefrontal cortex. Briefly, 38 patients who met DSM-IV criteria for BPD and IED-R (BPD-IED) (22 male, 16 female) and 36 healthy controls (HC; 18 male, 18 female) with no personal or first-degree family history of psychiatric disorders were included. We chose to study a subset of BPD patients meeting criteria for IED-R to find a homogeneous group of subjects with clinically significant impulsive aggression. Groups were sex- and age-matched (mean age: BPD-IED 30.5 years, SD 8.5; HC 28.4 years, SD 7.1; (New et al., 2009)). All participants gave informed consent and the study was approved by the Mount Sinai School of Medicine Institutional Review Board.

All subjects were medically healthy and free of psychiatric medication for at least 2 months and substance abuse or dependence for 6 months. All subjects had negative urine toxicology screens on each testing day (1 HC and 2 BPD-IED excluded for positive test), and females had negative pregnancy tests on each scan day (one female, BPD-IED, was excluded for a positive test). Three subjects (1 HC, 2 BPD-IED) were excluded because they did not believe the task deception.

Axis I diagnoses were made by a psychologist using the Structured Clinical Interview for DSM-IV Disorders (First et al., 1996) and Axis II with the Structured Interview for DSM-IV Personality Disorders (Pfohl B, 1997). Exclusion criteria were schizophrenia, schizophrenia-related psychotic disorders, bipolar I disorder, or current major depressive disorder (MDD). BPD-IED patients with a past history of MDD or posttraumatic stress disorder (PTSD) were not excluded, because of the high comorbidity with these disorders and a goal of selecting a representative sample of patients with BPD (Grilo et al., 2000). Subjects were also assessed with the Module for Intermittent Explosive Disorder-Revised (Coccaro, 1989); see (New et al., 2009).

All subjects completed the Barratt Impulsivity Scale-II (BIS-II) (Barratt, 1965), Affective Lability Scale (ALS) (Harvey et al., 1989), Beck Depression Inventory (BDI) (Beck et al., 1961), Overt Aggression Scale-Modified (OAS-M, including three subscales: aggression, irritability, and suicidality) (Yudofsky et al., 1986), and State-Trait Anger Expression Inventory (STAXI) (Spielberger, 1988). Subjects completed the Buss-Durkee Hostility Inventory (BDHI) (Buss and Durkee, 1957) or the Buss-Perry Aggression Questionnaire (BPAQ—an updated BDHI) (Buss and Perry, 1992); a composite score was calculated, using *Z* scores (t-BUSS) (See Table 1).

2.2. The Point Subtraction Aggression Paradigm (PSAP)

The PSAP was used to provoke aggressive behavior in study subjects (Cherek et al., 1997). Subjects played a computer game with a fictitious partner with the goal of earning points, which were exchanged for money. Unbeknownst to the participant, there was no live opponent. Subjects were instructed to play by pressing one of three buttons: pressing the A button 100 times earned 1 point; pressing the B button 10 times subtracted a point from the "opponent" (the aggressive response, since no points were earned by the subject for B presses); and pressing the C button would protect the subject for a period from having points subtracted by the "opponent" (no net gain or loss of points).

In the *non-provoking* condition, the "opponent" at no time subtracted points from the participant. In the *provoking* condition, the "opponent" subtracted points from the participant approximately every 62.5 s. All participants were debriefed about the task deception upon study completion.