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Effects of serotonin-2A receptor binding and gender on personality traits and suicidal behavior in borderline personality disorder

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Abstract

Impulsivity and aggressiveness are personality traits associated with a vulnerability to suicidal behavior. Behavioral expression of these traits differs by gender and has been related to central serotonergic function. We assessed the relationships between serotonin-2A receptor function, gender, and personality traits in borderline personality disorder (BPD), a disorder characterized by impulsive-aggression and recurrent suicidal behavior. Participant comprised 33 BPD patient and 27 healthy controls (HC), were assessed for Axis I and II disorders with the Structured Clinical Interview for DSM-IV and the International Personality Disorders Examination, and with the Diagnostic Interview for Borderline Patients-Revised for BPD. Depressed mood, impulsivity, aggression, and temperament were assessed with standardized measures. Positron emission tomography with [¹⁸F]altanserin as ligand and arterial blood sampling was used to determine the binding potentials (BP_{ND}) of serotonin-2A receptors in 11 regions of interest. Data were analyzed using Logan graphical analysis, controlling for age and non-specific binding. Among BPD subjects, aggression, Cluster B co-morbidity, antisocial PD, and childhood abuse were each related to altanserin binding. BP_{ND} values predicted impulsivity and aggression in BPD females (but not BPD males), and in HC males (but not HC females.) Altanserin binding was greater in BPD females than males in every contrast, but it did not discriminate suicide attempters from non-attempters. Region-specific differences in serotonin-2A receptor binding related to diagnosis and gender predicted clinical expression of aggression and impulsivity. Vulnerability to suicidal behavior in BPD may be related to serotonin-2A binding through expression of personality risk factors.

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Keywords

Impulsivity; Aggression; Temperament; Novelty Seeking; Harm Avoidance; Positron emission tomography (PET); Suicidal behavior

1. Introduction

Personality traits such as impulsivity and aggression are associated with vulnerability to suicidal behavior, independent of diagnoses. Within a stress-diathesis model of suicide, they are considered heritable traits of temperament that are components of a neurobiological diathesis to suicide at times of stress (Mann et al., 1999; Mann, 2003). Temperamental impulsivity and aggression are diagnostic characteristics of Cluster B Personality Disorders, especially Antisocial and Borderline Personality Disorders (BPD), which are notable for high rates of attempted and completed suicide (McGirr et al., 2007). We study the relationship between personality traits and suicidal behavior in the context of BPD. Patients with BPD are characterized by a marked reactivity of mood, impulsive behavior across multiple life domains, behavioral aggression, unstable interpersonal relationships, and recurrent suicidal behavior. With a community prevalence of 0.7%–5.9% (depending on method of study) and a suicide completion rate up to 10%, BPD is a clinically relevant model for studying the neurobiology of suicidal behavior (Paris and Zweig-Frank, 2001; Paris, 2010).

The research literature has demonstrated an inverse relationship between measures of central serotonergic function and suicidal behavior in diverse patient populations (Mann, 2003). In Major Depressive Disorder (MDD), BPD, Intermittent Explosive Disorder and other impulsive personality disorders (PDs), trait impulsivity and impulsive-aggression are inversely related to serotonergic indices, independent of suicidal behavior (Oquendo and Mann, 2000). In these clinical disorders, impulsivity, aggression and suicidal behavior may be mediated by diminished serotonergic neurotransmission in specific neural networks regulating mood and behavior.

Neuroimaging studies have demonstrated structural volume loss (using magnetic resonance imaging (MRI)) and hypometabolism (using positron emission tomography (PET)) in BPD subjects compared with healthy controls, especially in orbital and medial areas of the prefrontal cortex (PFC) and anterior cingulate gyrus (De La Fuente et al., 1997; Soloff et al., 2003; Tebartz van Elst et al., 2003; Hazlett et al., 2005). Diminished gray matter in the anterior cingulate (Brodmann area (BA) 24) and orbital cortex (BA 10), and increased white matter volumes in prefrontal BA 47 correlate with increased impulsivity, irritability and assaultiveness (Hazlett et al., 2005). Impulsive subjects with BPD (and other impulsive PDs) have diminished metabolic responses to fenfluramine (FEN) and meta-chlorophenylpiperazine (m-CPP) in related prefrontal areas, suggesting a role for diminished serotonergic function in these behavioral disorders (Siever et al., 1999; Soloff et al., 2000; New et al., 2002).

Post-mortem studies of suicide victims report increased post-synaptic serotonin-1A and serotonin-2A receptor binding, and decreased serotonin transporter binding in areas of the

prefrontal cortex (especially ventral lateral and orbital frontal PFC) (Arango et al., 1995; Mann, 2003; Currier and Mann, 2008). These results suggest diminished serotonergic agonism and compensatory postsynaptic up-regulation in areas of the brain involved in the regulation of mood and impulsive behavior. However, platelet studies have also found increased numbers of serotonin-2A receptors on platelets of suicide attempters (Biegon et al., 1990; Pandey et al., 1995), and a positive correlation between platelet serotonin-2A receptor number, aggression, and lethality of suicide attempt. Gene expression of serotonin-2A receptors and serotonin transporter sites may mediate suicide risk factors such as impulsive-aggression in PD subjects (McBride et al., 1994; Coccaro et al., 1996; Coccaro et al., 1997).

PET neuroimaging studies have reported dysregulation of the serotonin-2A receptor in subjects with attempted or completed suicide *independent of diagnosis* (Audenaert et al., 2001; van Heeringen et al., 2003), and in patients with MDD and BPD *independent of suicidal behavior* (Biver et al., 1997; Yatham et al., 2000; Messa et al., 2003; Meyer et al., 2003; Mintun et al., 2004; Bhagwagar et al., 2006; Soloff et al., 2007). The emerging literature in normal volunteers demonstrates a relationship between serotonin-2A receptor binding and personality traits such as neuroticism and dysfunctional attitudes, which relate to the vulnerability to mood disorders (Meyer et al., 2003; Frokjaer et al., 2008). These vulnerability traits are also highly characteristic of subjects with BPD (O'Leary et al., 1991; Clarkin et al., 1993; Wilberg et al., 1999; Trull et al., 2003).

We previously reported increased binding to the serotonin-2A receptor in female BPD suicide attempters (Soloff et al., 2007), and subsequently found significant gender effects among healthy volunteers on the relationship between serotonin-2A binding and psychological traits, including aggression (Soloff et al., 2010). In the current study, a new cohort of male BPD subjects are added to an expanded sample of female BPD subjects to test the hypothesis that gender has a significant effect on the relationships among serotonin-2A binding, personality traits and suicidal behavior in BPD.

2. Methods

This study was approved by the Institutional Review Board of the University of Pittsburgh, and participants gave written informed consent. Participants were recruited from outpatient clinics, the community, and from the first author's longitudinal study of BPD. Axis I and II disorders were diagnosed with the Structured Clinical Interview for DSM IV (SCID) (First et al., 2005) and the International Personality Disorders Examination (IPDE) (Loranger, 1999), and BPD with the Diagnostic Interview for Borderline Patients-Revised (DIB-R) (Zanarini et al., 1989). BPD subjects were required to have the highest score (3) on the Impulse Action Patterns section of the DIB-R. Severity of BPD psychopathology was assessed by the DIB Section Score total (DIB Total) (Gunderson et al., 1981). This value is the sum of the five DIB Section scores (Social Adaptation, Impulse Action Patterns, Affects, Psychosis, and Interpersonal Relations), which, in turn, reflect the sum of the 29 scored statements on the DIB. Patients were excluded for a past or current diagnosis of schizophrenia, schizoaffective disorder, delusional disorder, bipolar I or II disorders, psychotic depression, or organic mood disorder. Control subjects had no current or lifetime

Axis I or II diagnoses. Final diagnoses were determined by consensus of raters using all available data. Aggression was assessed using the Brown-Goodwin Lifetime History of Aggression (LHA) (Brown and Goodwin, 1986), depressed mood on the Beck Depression Inventory (BDI) (Beck et al., 1961), and trait impulsiveness on the Barratt Impulsiveness Scale–Version 11 (BIS) (Barratt and Slaughter, 1998). The 240-item Temperament and Character Inventory (TCI) was used to assess Novelty Seeking (NS), Harm Avoidance (HA), Reward Dependence (RD), and Persistence (P) (Cloninger et al., 1994). A history of childhood abuse was obtained by interview at intake. The Abuse History is a 19-item questionnaire that assesses physical and sexual abuse separately, including questions concerning severity of abuse (method, medical and legal consequences), perpetrators, duration (age at onset/ offset), frequency of episodes, and subjective effects on life (Soloff et al., 2002). All subjects had a physical examination, were physically healthy, and were free of oral contraceptives and all psychoactive medication for a minimum of 2 months. All were free of street drugs and alcohol for at least 5 days before the PET scan (confirmed by urinalysis). Female subjects had a negative pregnancy test. Subjects were requested to eat a low tryptophan breakfast and no caffeine the day of the scan.

2.1. MRI and PET Imaging

A brief summary of the neuroimaging acquisition and analysis methods is provided below, with further detail available in Soloff et al. (2010). Magnetic resonance imaging (MRI) was performed before the PET study using a 1.5-Tesla Signa scanner (GE Healthcare, Milwaukee, WI, USA). A Spoiled Gradient Recalled (SPGR) structural MR Image was acquired for MRI/PET co-registration, region definition and correction of the PET results for cerebrospinal fluid (CSF) dilution arising from cerebral atrophy and partial volume averaging. Screening for neuroradiological abnormalities was based on T2 and proton density MRI.

PET scanning was performed using a Siemens/CTI ECAT HR+ scanner (2D mode, 63 image planes, 152-mm axial field-of-view). The 5HT_{2A} receptor antagonist, [¹⁸F]altanserin, was synthesized using previously described methods (Lemaire et al., 1991; Price et al., 2001a,b). PET data were reconstructed by filtered back-projection with corrections for deadtime, attenuation, radioactive decay and scatter to yield a final image resolution of about 6 mm.

Before PET imaging, an intravenous catheter was placed in an antecubital vein for radiotracer injection. A short catheter was inserted into a radial artery to enable dynamic arterial blood sampling for input function determination (Bailer et al., 2004). Head motion was minimized using thermoplastic mask immobilization. A windowed transmission scan (⁶⁸Ge/⁶⁸Ga) was performed for attenuation correction. The [¹⁸F]altanserin was administered as a slow bolus over 20 s (Table 1). A 90-min dynamic PET acquisition (17 frames: 2×30 s, 2×1 min, 2×1.5 min, 3×3 min, 1×5 min, 7×10 min) began at injection along with blood sampling. Thirty-five arterial blood samples were collected over 90 min (20 collected over the first 2 min). Five additional blood samples were collected at 2, 10, 30, 60 and 90 min post-injection in order to determine the concentration of radiolabeled metabolites, relative to

total plasma radioactivity. These data were used to generate the metabolite-corrected input function for data analysis.

The PET and MRI data were co-registered using automated algorithms, as previously described (Soloff et al., 2010). Regions of interest (ROIs) were manually defined, without knowledge of diagnosis, across several planes of the SPGR MRI using a modified version of ROITool (CTI PET Systems). Nine ROIs were relevant to psychopathology in BPD. These included the medial orbital frontal cortex (MOF: BA 11), medial frontal cortex (MFC: BA 9/10), lateral orbital frontal cortex (LOF: BA 45/47), anterior cingulate (ANC: BA 32) and its subdivisions the pregenual cingulate (PRG: BA 24/32) and subgenual cingulate (SUG: BA 25). The hippocampus (HIP) was sampled as a discrete ROI and also as part of the medial temporal cortex (MTC, including the hippocampal-amygdala complex). The basal ganglia (BG) ROI included the putamen and globus pallidus. Two control regions that represent cortical and limbic regions not involved in our hypothesis were the occipital cortex (OCC: BA 18) and thalamus (THL). The cerebellum was used as a reference region for nondisplaceable uptake (V_{ND} or CER_V_T).

The ROIs were applied to the dynamic PET images to generate regional time-activity curves. These data were analyzed using the Logan graphical method, applied across the 12 to 90 min integration intervals (Logan et al., 1990; Meltzer et al., 1999; Meltzer et al., 1998; Bailer et al., 2004). Justification for the Logan analysis of [^{18}F]altanserin PET data has been provided in detail previously, and includes consideration of validity, sensitivity, and reliability of implementation (Price et al., 2001b; Bailer et al., 2004; Soloff et al., 2010). The regional volume of distribution (V_T) values used in the current work reflects radioactivity concentration in brain that arises from [^{18}F]altanserin and that is free, nonspecifically bound, and specifically bound in brain, as well as nonspecific uptake that arises from radiometabolites and radioactivity in the vasculature. The cerebellum was used as the reference region as it was assumed to reflect minimal levels of specific binding consistent with earlier studies that indicated that it provided a reasonable estimate of the nondisplaceable volume of distribution (or V_{ND}) accounting for the overestimation of the nonspecific component as a result of blood-brain barrier (BBB)-permeable radiometabolites (Price et al., 2001a,b). Accordingly, the cerebellar V_T values were used to correct the regional [^{18}F]altanserin V_T values to obtain regional specific binding potential measures, i.e., $BP_{ND} = (V_T - V_{ND})/V_{ND} = (V_T/V_{ND}) - 1$. For each ROI, binding potentials (BP_{ND}) were analyzed for the left and right hemispheres to identify lateralized effects, and as a pooled sample. The BP_{ND} values were corrected for atrophy-related CSF dilution, using MRI-based correction factors that varied from 0 to 1 (where 1 indicates no CSF dilution), as routinely applied in our facility (Meltzer et al., 1999).

2.2. Statistical analyses

Demographic and clinical data were examined using t -test and χ^2 procedures as indicated. The relationship between binding potentials (BP_{ND}) in each ROI and diagnostic group was first explored using analysis of covariance (ANCOVA), adjusting for age. As [^{18}F]altanserin binding is not entirely absent in cerebellum, cerebellar distribution volumes (V_{ND} or CER_V_T) were compared between groups (Dwivedi and Pandey, 1998; Staley et al., 2001).

Cerebellar binding (CER_{VT}) was included as a covariate in all analyses that involved both male and female subjects as we found significant gender differences in CER_{VT} values among our BPD subjects. Body-mass index (BMI) did not differ significantly between groups by diagnosis or gender and was not included as a covariate. Effects of gender on BP_{ND} values and group $\times$ gender interactions were assessed using two-way ANCOVA (diagnosis, gender) adjusting for age and CER_{VT} . The relationships between serotonin-2A receptor binding and psychological traits, measured as continuous variables, were first analyzed using partial correlation coefficients to identify significant linear relationships between the scale scores and BP_{ND} values in each ROI while adjusting for age and CER_{VT} . BP_{ND} values that had significant partial correlations with scale scores were then entered in linear regression models with ROI, age and CER_{VT} as independent variables, and psychological traits as dependent variables. To examine the effects of gender, partial correlation coefficients were calculated separately within the four combinations of gender and diagnostic status and entered in regression models with age co-varied. Relationships between categorical clinical characteristics in BPD subjects and BP_{ND} values were assessed by ANCOVA, with age and CER_{VT} as covariates. Partial correlation coefficients are reported in the text and regression analyses in Table 3 (for models with $p < 0.05$). Analyses using lateralized ROIs were subjected to Bonferroni's correction ($p < 0.025$). The female sample included 14 BPD and 11 control subjects studied with identical methods in an earlier report (Soloff et al., 2007). Sample sizes for analyses vary due to some incomplete psychological test data. Analyses were conducted with IBM SPSS Statistics version 20.0.

3. Results

3.1. Sample characteristics (Table 1)

The study sample included 33 BPD (20 female, 13 male), and 27 healthy control subjects (HC: 12 female, 15 male), with no significant differences in age, gender, race, or BMI. One female BPD subject failed to complete the altanserin study. A current Axis I depression (MDE, Dysthymia, or Depression NOS) was diagnosed in 20 BPD subjects (60.6%), a comorbid Cluster B diagnosis in 13 (39.4%), and Antisocial PD in eight subjects (24.2%). A current diagnosis of alcohol abuse or dependence was found in six BPD subjects (18.2%), while 12 (36.4%) had other current substance use diagnoses. A history of childhood abuse was reported in 17 BPD subjects (51.5%), but in no healthy controls. Medically significant suicide attempts were reported in 21 BPD subjects (63.6%).

BPD subjects had significantly more depressed mood and aggression compared with control subjects (all $p < 0.001$), but not more trait impulsiveness. On the four TCI temperament scales, BPD subjects endorsed significantly higher scores than healthy controls on the NS total score and three subscales (Exploratory Excitability, Impulsiveness, Disorderliness), two subscales of HA (Fear of Uncertainty, Fatigability), and two subscales of RD (Attachment and Dependence). Control subjects had significantly higher scores on the HA Shyness subscale. There were no differences between groups in Persistence.

3.2. Injected [^{18}F]altanserin dose

The mean injected [^{18}F]altanserin dose was very similar for both groups and associated with low but variable co-injected unlabeled or “cold” mass (Table 1). The specific activities were variable (BPD: 17.9 ± 38.5 Ci/ μmole ; HC: 62.9 ± 9.9 Ci/ μmole), and this was attributed to several factors including the inherent variability in the amount of carrier fluoride produced in the target irradiation process, variations in detector sensitivities between analytical instrumentation systems used to determine specific activity measures, and a production process upgrade during the study timeframe that increased radiochemical yield by about three-fold. The difference in co-injected cold mass is not believed to account for the study findings (see Section 4). The fraction of unchanged [^{18}F]altanserin was similar for both subject groups across the 2, 10, 30, 60 and 90 min timepoints (BPD: 0.95 ± 0.07 , 0.83 ± 0.06 , 0.63 ± 0.07 , 0.52 ± 0.07 , 0.45 ± 0.07 ; HC: 0.97 ± 0.03 , 0.87 ± 0.04 , 0.70 ± 0.07 , 0.56 ± 0.07 , 0.50 ± 0.07). These values were also similar across gender, although two BPD males had about 25% lower metabolism at 2–30 min, relative to the BPD mean values in this parameter (data not shown).

3.3. Serotonin-2A receptor binding: BPD vs. HC

There were no significant differences between BPD and HC subjects in CER_{V_T} with age co-varied; however, BPD females had significantly greater CER_{V_T} than BPD males ($F(1,29) = 13.7$, $p = 0.001$). Serotonin-2A receptor binding (BP_{ND}) was significantly greater in BPD subjects than in HC in the hippocampus ($F(1,55) 5.38$, $p = 0.024$), and Lt. HIP ($F(1,55) 7.93$, $p = 0.007$), with age and CER_{V_T} co-varied. These results remained significant when depressed mood was co-varied. Similarly, there were no significant differences in BP_{ND} values for hippocampus (or Lt. HIP) between BPD subjects with and without co-morbid depression. BPD suicide attempters had greater binding in the hippocampus ($F(1,43) 8.71$, $p = 0.005$) and Lt. HIP ($F(1,42) 8.01$, $p = 0.007$) with age and CER_{V_T} co-varied, compared with HC.

3.4. Effects of co-morbidity (Table 2)

BPD subjects with Cluster B co-morbidity had significantly diminished binding in the basal ganglia, medial temporal cortex, and medial orbital frontal cortex compared with BPD subjects without Cluster B co-morbidity, with age and CER_{V_T} co-varied. This result was related to co-morbidity with Antisocial PD (ASPD), a Cluster B disorder. BPD subjects with co-morbid ASPD, compared with those with no ASPD, also had significantly diminished BP_{ND} values in the basal ganglia and medial temporal cortex, but also in the anterior cingulate, pregenual cingulate, and left thalamus. Axis I depression, current substance use diagnoses, and attempter status were not related to serotonin-2A receptor binding in any pooled ROI. A history of childhood abuse was associated with increased binding in the medial orbital frontal cortex, with age and CER_{V_T} co-varied.

3.5. Psychological traits (Table 3)

Among BPD subjects, aggression, was negatively associated with BP_{ND} values in the medial orbital frontal cortex ($r = -0.49$, $p = 0.008$) and Rt. MOF ($r = -0.54$, $p = 0.003$), but not in any

ROI among HC subjects. BPD severity was positively associated with BP_{ND} values in Lt. MOF ($r=0.48, p=0.009$). Impulsiveness was not associated with binding in either group.

Although BPD subjects endorsed higher NS Total scores than HC, there was no relationship between this temperament and BP_{ND} values among BPD subjects. Among HC subjects, NS Total scores were positively related to BP_{ND} values in occipital cortex ($r=0.55, p=0.015$) and Lt. OCC ($r=0.52, p=0.02$). Subscales of HA that significantly discriminated between BPD and control groups were analyzed separately but did not survive post-hoc Bonferroni correction.

Among HC, the HA Total score was positively associated with BP_{ND} values in hippocampus ($r=0.46, p=0.04$). Among HA subscales, Fear of Uncertainty was positively associated with BP_{ND} values in LOF ($r=0.73, p<0.001$), Lt. LOF ($r=0.61, p=0.006$), and Rt. LOF ($r=0.71, p=0.001$), MFC ($r=0.61, p=0.005$), Lt. MFC ($r=0.54, p=0.017$), and Rt. MFC ($r=0.54, p=0.007$), and Rt. subgenual cingulate ($r=0.56, p=0.013$). Fatigability was associated with BP_{ND} values in Lt. MTC ($r=0.58, p=0.01$). RD and P were not related to BP_{ND} values among BPD subjects. Among control subjects, RD was predicted by BP_{ND} values in the Rt. PRG ($r=0.52, p=0.02$). Regression models were significant in each case.

3.6. Gender considerations

There were 28 male (13 BPD and 15 HC), compared with 32 female subjects (20 BPD, 12 HC), with no significant differences between groups in age, race, or BMI. Similarly, there were no significant differences between male and female BPD groups in depressed mood, aggression, trait impulsiveness, or BPD severity. The proportion of BPD subjects with histories of childhood abuse and suicide attempts did not differ significantly by gender. Among HC subjects, there were no significant gender differences in depressed mood or trait impulsiveness; however, healthy males endorsed more aggression than healthy females ($t=2.98, df=21.5, p=0.007$).

3.7. Serotonin-2A receptor binding: gender effects

Significant group $\times$ gender interactions on BP_{ND} values were found in the hippocampus, lateral orbital frontal cortex, medial temporal cortex, and occipital cortex, with age and CER_{VT} co-varied. In each case, *female* BPD subjects had *greater* BP_{ND} values relative to their controls, while *male* BPD subjects had *diminished* BP_{ND} values relative to their controls.

Among female BPD subjects, BP_{ND} values were significantly *increased* relative HC in the hippocampus ($F(1,28)=13.52, p=0.001$) and Lt. HIP ($F(1,28)=12.54, p=0.001$), MTC ($F(1,28)=4.53, p=0.042$) and Lt. MTC ($F(1,28)=10.10, p=0.004$), occipital cortex ($F(1,28)=5.80, p=0.023$) and Rt. OCC ($F(1,28)=6.08, p=0.02$). Differences between male BPD and HC did not survive Bonferroni correction.

These analyses were repeated for suicide attempters. Results must be considered exploratory due to small sample sizes. Female attempters ($n=13$) had *increased* BP_{ND} values compared with female controls ($n=12$) in every pooled contrast, with age co-varied. Significant differences were found in the hippocampus ($F(1,22)=16.54, p=0.001$), Lt. HIP (F

(1,22)=12.57, $p=0.002$) and Rt. HIP ($F(1,22)=8.27$, $p=0.009$), Lt. MTC ($F(1,22)=8.14$, $p=0.009$), occipital cortex ($F(1,22)=8.54$, $p=0.008$), Lt. OCC ($F(1,22)=5.87$, $p=0.024$) and Rt. OCC ($F(1,22)=10.23$, $p=0.004$). However, BP_{ND} values in female BPD attempters ($n=13$) differed from those in non-attempters ($n=6$) only in the Rt. OCC ($F(1,16)=6.16$, $p=0.025$).

Male attempters ($n=7$) had *diminished* BP_{ND} values compared with male controls ($n=15$) in every pooled contrast with age co-varied. Significant differences were noted in occipital cortex ($F(1,19)=6.50$, $p=0.02$) and Lt. OCC ($F(1,19)=7.53$, $p=0.013$). However, there were no significant differences between male BPD attempters ($n=7$) and non-attempters ($n=6$).

3.8. Serotonin-2A receptor binding: male vs. female BPD (Table 4)

BP_{ND} values were increased among female BPD subjects in every pooled and lateralized contrast compared with values among males, with age and CER_{VT} co-varied. Significant differences between groups were noted in the basal ganglia (also Lt. BG and Rt. BG), Rt. MFC, medial temporal cortex (and Rt. MTC), and occipital cortex (Fig.1). Similarly, BP_{ND} values were significantly increased in female attempters ($n=13$) compared with male attempters ($n=7$) in the hippocampus (and Rt. HIP), Rt. MFC, and occipital cortex (also Lt. OCC and Rt. OCC) (Table 4). There were no significant differences between male and female HC in any pooled or lateralized ROI, with age and CER_{VT} co-varied.

3.9. Gender, psychological traits, and serotonin-2A binding

Among male BPD subjects, there were no significant relationships between BP_{ND} values and trait impulsiveness, aggression, or BPD severity. In marked contrast, among female BPD subjects, trait impulsiveness was negatively related to BP_{ND} values in medial frontal cortex (beta ($\pm$ s.e.)=133.8 (19.0), [c.i.=93.08,174.42], $p=0.02$), (also Lt. MFC (beta ($\pm$ s.e.)=128.3 (18.7), [c.i.=88.3, 168.3], $p=0.032$), and Rt. MFC (beta ($\pm$ s.e.)=126.4 (18.3) [c.i.=87.2, 165.7], $p=0.034$)). Aggression was negatively related to BP_{ND} values in MOF (beta ($\pm$ s.e.)=36.4(8.8) [c.i.=17.6, 55.2], $p=0.009$), and Rt. MOF(beta ($\pm$ s.e.)=35.5(7.3), [c.i.=19.8, 51.1], $p=0.003$). BPD severity was positively related to binding in the basal ganglia (beta ($\pm$ s.e.)=25.7 (5.1) [c.i.=14.7, 36.6], $p=0.04$), and medial frontal cortex (beta ($\pm$ s.e.)=-1.7 (14.6) [c.i.=-32.7, 29.4], $p=0.03$). Impulsiveness and aggression were not related to binding in either male or female control subjects.

4. Discussion

In this mixed gender sample, we found significant differences in serotonin-2A receptor binding between BPD and HC subjects, but only among females. Female BPD subjects had increased binding, and BPD males had decreased binding in every contrast compared with their controls, and with each other, with significant differences in specific ROIs. Increased serotonin-2A binding among female BPD subjects implies diminished serotonergic agonism, with postsynaptic up-regulation, and increased receptor number (or, alternatively, increased receptor affinity). The reverse is presumed for BPD males. Variations in serotonergic receptor function in specific ROIs may mediate gender differences in the clinical presentations of BPD.

BPD is a heterogeneous syndrome, diagnosed more frequently among women than men in clinical settings. Women with BPD typically present with internalizing disorders such as self-injury, identity disturbance, eating disorders, and posttraumatic stress disorder. In contrast, men with BPD are characterized by symptoms of externalized impulsivity and aggression including antisocial behavior, intermittent explosive disorder, and substance use (Zanarini et al., 1998; Johnson et al., 2003; Zlotnick et al., 2002; Beauchaine et al., 2009). Some investigators argue that BPD and ASPD share a common genetic etiology, and that symptomatic differences derive from gene $\times$ sex interactions. One proposed model involves dopaminergic and serotonergic mediation of trait impulsivity, in interaction with specific environmental risk factors, such as childhood abuse (Beauchaine et al., 2009).

We found that co-morbidity with Cluster B PDs, ASPD, and increased aggression among BPD subjects were associated with diminished binding in specific ROIs, with considerable overlap in affected areas, suggesting the possibility of common neurobiological mediation. These ROIs include fronto-limbic regions involved in the regulation of mood and behavior (including medial orbital frontal and medial temporal cortex, anterior cingulate and basal ganglia). Dysregulation of serotonergic function in these fronto-limbic regions may adversely affect executive cognitive functions required for adaptive coping, such as response inhibition, decision-making, and imagining future outcomes (Peters, 2011).

Rylands et al. (2012) recently reported diminished cortical serotonin-2A receptor binding associated with high levels of impulsive-aggression among *male* non-clinical subjects who also met criteria for BPD and/or ASPD. Highly aggressive subjects also had increased serotonin transporter availability in the brain stem, which was positively correlated with measures of impulsivity and childhood adversity. The authors suggest that impulsive-aggression may be mediated through the effects of early childhood adversity on the expression of serotonin transporter sites in the brain stem, and serotonin-2A receptor availability in the cortex. We also found a negative association between serotonin-2A receptor binding and aggression, but in *female*, not male, subjects with BPD. In our sample, early childhood abuse was associated with increased serotonin-2A receptor binding in the medial orbital frontal cortex, an area involved in the regulation of emotion and behavior. Childhood abuse is an etiological factor in the development of BPD.

These results differ from our earlier report, where we found no relationship between aggression and BP_{ND} values among 14 female BPD subjects (Soloff et al., 2007). In the current study, this relationship was significant (and robustly so) only for female BPD subjects (MOF: $p=0.009$, Rt. MOF: $p=0.003$). The methods used in the two studies are identical. We found no outliers among LHA values in the six new female BPD cases; however, mean LHA values ($\pm$ s.d.) (19.4 ± 2.9) were lower than among the 14 previously acquired cases (24.6 ± 4.7). We attribute the difference in results between studies to the increased sample of relatively low aggression BPD female subjects in the current study. That is, low levels of aggression are associated with increased binding in the MOF (and Rt. MOF) among female BPD subjects.

We found no significant relationships between aggression and BP_{ND} values among control subjects. A recent report by da Cunha-Bang et al. (2013) also found that trait aggression and

trait impulsivity were not associated with serotonin-2A receptor binding in the frontal cortex of psychiatrically healthy individuals. Decreased binding in the medial orbital frontal cortex in BPD subjects may be a vulnerability trait for aggression in this clinical disorder, or a reflection of state severity not seen in healthy subjects. The disposition to impulsive-aggression may be a genetically mediated endophenotypic trait that is expressed in abnormalities of serotonergic function in regulatory circuits of the PFC (McCloskey et al., 2009). Variations in serotonin-2A binding may play a role in state expression of this trait (Rosell et al., 2010).

We found no significant difference in trait impulsivity in BPD and control subjects, and no relationship to serotonin-2A receptor binding for either group in any ROI. Trait impulsivity, as defined by the BIS, is a broad personality construct, with both cognitive and behavioral expressions, including many non-pathological behaviors. In studies of BPD, impulsive-aggression (assessed by LHA) correlates with other measures of aggression, but not with measures of impulsivity (Critchfield et al., 2004). We found no significant correlation between measures of aggression (LHA) and impulsivity (BIS).

We found gender differences in the relationships between personality traits and serotonin-2A receptor binding in both BPD and control subjects. Among BPD females, but not BPD males, BP_{ND} values were related to impulsivity, aggression and BPD severity in discrete ROIs. Among male, but not female, control subjects, BP_{ND} values were related to impulsivity and aggression. The anatomical localization of peak effects in these contrasts differed markedly by gender in both BPD and control subjects.

BPD subjects had significantly *greater* BP_{ND} values compared with controls in the hippocampus, a result attributable to *increased* binding among BPD females and *decreased* binding among BPD males relative to their own controls. Diminished volume of the hippocampus is the most widely replicated morphometric finding in MRI studies of BPD, and it is associated with histories of childhood abuse, an important factor in the etiology of the disorder and a risk factor for suicide (Driessen et al., 2000; Schmahl et al., 2003; Tebartz van Elst et al., 2003; Brambilla et al., 2004; Soloff et al., 2008; Sala et al., 2011). The hippocampus processes declarative, episodic and working memory, and through connections to the medial orbital frontal cortex and anterior cingulate, facilitates “future thinking” and decision-making (Wall and Messier, 2001; Peters and Buchel, 2010). A loss of the ability to envision positive outcomes in crisis situations increases the likelihood of suicidal behavior (Williams and Broadbent, 1986; Pollock and Williams, 2001).

Finally, in the contrast between BPD attempters and non-attempters, we found no significant differences in binding values among males, and only one marginally significant result among females. Although based on small samples, these results challenge the notion that serotonin-2A receptor binding has a *direct* relationship to suicidal behavior in BPD. We propose that the effect of serotonin-2A receptor binding on attempt behavior in BPD is *indirect*, i.e., related to an association with co-morbid Cluster B PD, ASPD, aggression, and a history of childhood abuse.

4.1. Limitations

Gender differences in central serotonergic function have been related to the vulnerability to mood disorders, eating disorders, impulsive-aggression, and suicidal behavior. Several hypotheses have been advanced to explain these effects, including gender-specific differences in serotonergic agonism or, alternatively, differential effects of sex hormones on gene expression affecting receptor number and/or affinity. We demonstrated gender effects on serotonin-2A receptor binding and the relationship to select personality traits in BPD; however, the etiology of these effects is beyond the scope of this work.

Sex hormones may have an effect on serotonin-2A receptor binding in both female and male subjects, though the studies are few in number and inconsistent in outcomes. Increased cortical binding to the serotonin-2A receptor has been reported in some small sample studies of postmenopausal women following replacement hormone therapy (Moses et al., 2000; Kugaya et al., 2003), though not in other studies of hormonal contraception or replacement therapy (Frokjaer et al., 2008). A positive correlation between cortical serotonin-2A receptor binding and plasma estradiol levels has been reported in healthy men, with no independent effects for testosterone (Frokjaer et al., 2010). Future studies should sample sex hormones at the time of PET study to control for this variable.

This study focused solely on the potential role of serotonin-2A receptor binding in mediating specific personality traits in BPD; however, BPD is a very heterogeneous syndrome, characterized by diverse personality traits such as emotion dysregulation, impulsivity and aggression, and many clinical symptoms including dissociation, psychoticism, and altered pain perception. Other neurotransmitter systems have been implicated in the pathogenesis of these diverse presentations, including endogenous opioids, the glutamatergic NMDA receptor, and the neuropeptides oxytocin and vasopressin (Grosjean and Tsai, 2007; New et al., 2008; Stanley and Siever, 2009; Prossin et al., 2010). Our findings suggest a role for serotonin-2A receptor binding in mediating aggression and impulsivity, which are core characteristics of BPD, but cannot explain the diversity of symptoms in this complex syndrome.

Technical limitations concerning the Logan graphical method and quantification of binding measures in small structures are acknowledged and described elsewhere in detail. (Soloff et al., 2010). Similarly, we acknowledge that [^{18}F]altanserin is not completely selective and binds to serotonin-2C as well as serotonin-2A receptors, though, given equal concentrations, serotonin-2A binding would account for greater than 95% of radiotracer binding due to a 20-fold greater affinity of altanserin for the serotonin-2A receptor (Tan et al., 1999).

The amount of non-radioactive altanserin (“cold mass”) that is co-injected with the [^{18}F]altanserin can potentially bias results if there is a significant disparity between groups. The co-injected “cold mass” competes for the same receptor site as the radiolabeled altanserin. We found no statistically significant differences between BPD and HC groups for either injected [^{18}F]altanserin dose (mCi) or mass of co-injected “cold” altanserin (μg) (Table 1).

The [^{18}F]altanserin plasma-free fraction (f_p) that is inversely related to plasma protein binding was not measured in this study. Differences in f_p are expected to give rise to differences in the cerebellar V_{ND} (CER_V_T) values, but no such differences were evident between BPD and HC subjects (with age covaried). It is possible that this may have played a role in differences in CER_V_T observed for BPD females relative to BPD males, but such a difference was addressed by including CER_V_T as a covariate in all analyses. In a study of healthy volunteers, Frokjaer et al. (2008) previously reported that there was no significant correlation between f_p or nonspecific radiotracer binding and neuroticism or any of its constituent trait scores.

4.2. Conclusions

We found significant differences in serotonin-2A receptor binding in BPD vs. HC subjects, and in the relationships between binding potentials, impulsivity and aggression in specific ROIs. Gender effects were notable, as BP_{ND} values predicted impulsivity and aggression in BPD females (but not BPD males), and in HC males (but not HC females). Comorbidity with Cluster B PDs, ASPD, and increased aggression among BPD subjects was associated with diminished binding in specific ROIs, with considerable overlap in affected areas; however, serotonin-2A receptor binding did not discriminate suicide attempters from nonattempters. A history of childhood abuse was also related to diminished altanserin binding among BPD subjects.

Region-specific differences in serotonin-2A receptor binding that are related to diagnosis, gender, and history of childhood abuse may mediate the clinical expression of aggression and impulsivity in BPD. We propose that serotonin-2A binding is *indirectly* related to the vulnerability to suicidal behavior in BPD through expression of personality risk factors such as aggression and impulsivity. Reducing impulsive-aggression, through serotonergic medication or psychotherapy, may reduce the risk of suicidal behavior in BPD.

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Figure 1.
Serotonin-2A receptor binding in male vs. female BPD subjects.

Table 1**Characteristics of Study Sample**

	BPD	Control	<i>t/df/P⁽¹⁾</i>
<i>N</i> (f,m)	33 (20f,13m)	27 (12f,15m)	
Age (mean,s.d.)	27.5 (7.2)	28.8 (8.2)	-.36, <i>df</i> = 58, <i>P</i> . ns
BMI (mean, s.d.)	24.2 (5.2)	24.6 (3.1)	.34, <i>df</i> = 54, <i>P</i> .n.s.
[¹⁸ F]ALT dose (mCi) *	10.3 (0.7)	10.5 (0.5)	-1.41, <i>df</i> =57, <i>P</i> .n.s.
Inject. cold mass (ug) **	1.8 (2.4)	2.7 (2.5)	-1.41, <i>df</i> =56, <i>P</i> . n.s.
Psychological Assessments			
Beck Depr.Inv.	25.6 (11.8)	1.13 (1.5)	-11.22, <i>df</i> =30.1, <i>P</i> . <0.001
Impulsivity (BIS)	75.6 (5.4)	73.6 (3.2)	-1.73, <i>df</i> = 49.3, <i>P</i> . n.s.
Aggression (LHA)	23.1 (5.1)	14.7 (3.3)	-7.27, <i>df</i> = 57, <i>P</i> . <0.001
Novelty Seeking Total	19.9 (4.8)	15.9 (5.2)	-2.69, <i>df</i> =43, <i>P</i> . = 0.01
-NS Excitability	5.7 (1.5)	4.5 (2.1)	-2.22, <i>df</i> =42, <i>P</i> . = 0.032
-NS Impulsiveness	5.6 (1.7)	4.4 (1.9)	-2.27, <i>df</i> =43, <i>P</i> . = 0.028
-NS Disorderliness	5.3 (1.5)	3.7 (1.6)	-3.46, <i>df</i> =43, <i>P</i> . = 0.001
Harm Avoidance Total	14.1 (4.6)	13.2 (3.8)	-.71, <i>df</i> =43, <i>P</i> . ns
-HA Fear Uncertainty	4.0 (1.7)	1.7 (1.1)	-5.52, <i>df</i> =43, <i>P</i> . = <0.001
-HA Shyness	2.6 (.83)	3.9 (1.3)	4.12, <i>df</i> =43, <i>P</i> . = <0.001
-HA Fatiguability	4.0 (1.1)	2.6 (1.5)	-3.60, <i>df</i> =43, <i>P</i> . = 0.001
Reward Dep. Total	12.6 (3.1)	11.1 (3.0)	-1.62, <i>df</i> =43, <i>P</i> .ns.
-RD Attachment	4.3 (1.3)	3.5 (.87)	-2.45, <i>df</i> =43, <i>P</i> . = 0.018
-RD Dependence	2.9 (1.6)	1.9 (1.6)	-2.28, <i>df</i> =43, <i>P</i> . = 0.028
Persistence Total	4.0 (2.4)	3.0 (1.5)	1.65, <i>df</i> =43, <i>P</i> . ns.

⁽¹⁾ Student's *t* test, 2 tailed. / *df* = degrees of freedom / *p* value.

* [¹⁸F]altanserin ([¹⁸F]ALT) = injected dose, BPD *n*=32 (one subject did not complete study).

** Injected cold mass = non-radioactive altanserin, BPD *n* =31 (one sample lost)

Table 2Effects of Co-morbidity on BP_{ND} values in BPD subjects *

Co-morbidity	Yes BP _{ND} (mean,sd)	No BP _{ND} (mean,sd)	Statistic <i>F/df/P.</i>
A. Cluster B (N)	13	17	
Basal ganglia	0.23 (0.13)	0.34 (0.13)	6.55,df=1,26, <i>P</i> .= 0.02
Med. temp. cortex	0.38 (0.12)	0.47 (0.13)	5.37,df=1,26, <i>P</i> .= 0.03
Med. orb. frontal	1.63 (0.44)	1.89 (0.23)	6.29,df=1,26, <i>P</i> .= 0.02
B. ASPD (N)	8	22	
Basal ganglia	0.17 (0.11)	0.34 (0.12)	10.21,df=1,26, <i>P</i> .= 0.004
-----Lt. BG	0.15 (0.16)	0.35 (0.14)	9.83,df=1,26, <i>P</i> .= 0.004
-----Rt.BG	0.19 (0.12)	0.32 (0.13)	6.02,df=1,26, <i>P</i> .= 0.02
Med. Temp. Cortex	0.34 (0.10)	0.46 (0.13)	6.01, df=1,26, <i>P</i> .= 0.02
Anterior Cingulate	1.28 (0.28)	1.61 (0.24)	6.16, df=1,26, <i>P</i> .= 0.02
-----Rt. ACC	1.16 (0.26)	1.58 (0.25)	8.75, df=1,26, <i>P</i> .= 0.007
Pregenual Cingulate	1.22 (0.27)	1.54 (0.25)	8.31, df=1,26, <i>P</i> .= 0.008
-----Rt. PRG	1.16 (0.26)	1.50 (0.27)	8.91, df=1,26, <i>P</i> . = 0.006
Thalamus	0.13 (0.16)	0.26 (0.16)	4.04, df=1,26, <i>P</i> . = 0.055
-----Lt. Thalamus	0.13 (0.13)	0.24 (0.10)	7.99, df=1,26, <i>P</i> .= 0.009
C. Childhood Abuse (N)	16	15	
Med. orb. frontal	1.83 (0.32)	1.70 (0.39)	4.56, df=1,27, <i>P</i> . = 0.04

*
age and CER_VT co-varied,

Table 3

Effects of serotonin-2A receptor binding on psychological traits.

	BPD	Control
<i>N</i>	23	21
Regression Model	beta $\pm$ s.e [95% c.i.], <i>P</i> [*] (<i>R</i> ²)	beta $\pm$ s.e [95% c.i.],
<i>P</i> [*] (<i>R</i> ²)		
LHA		
---med. orbital frontal	-7.52 $\pm$ 2.55 [-12.74, -2.31] ^{**} (0.44)	n.s.
---Rt. MOF	-7.22 $\pm$ 2.20 [-11.72, -2.72] ^{**} (0.47)	n.s.
BPD severity		
---Lt. MOF	7.24 $\pm$ 2.72 [1.67, 12.82] [*] (0.25)	n.s.
Novelty Seeking Total		
----occipital cortex	n.s.	21.52 $\pm$ 7.95 [4.74, 38.30] [*] (0.49)
----Lt. OCC	n.s.	14.29 $\pm$ 5.68 [2.30, 26.27] [*] (0.46)
Harm Avoidance Total		
----hippocampus	n.s.	16.07 $\pm$ 7.42 [0.40, 31.73] [*] (0.43)
HA: Fear of Uncertainty		
----lateral orbital frontal	n.s.	3.84 $\pm$.86 [2.02, 5.65] ^{***} (0.69)
----Lt. LOF	n.s.	2.78 $\pm$.88 [0.91, 4.64] ^{**} (0.57)
----Rt. LOF	n.s.	3.38 $\pm$.81 [1.68, 5.09] ^{***} (0.67)
----medial frontal cortex	n.s.	2.21 $\pm$.69 [0.75, 3.66] ^{**} (0.58)
----Lt. MFC	n.s.	1.55 $\pm$.59 [0.31, 2.79] [*] (0.52)
----Rt. MFC	n.s.	2.44 $\pm$.80 [0.76, 4.11] ^{**} (0.56)
----subgenual cing.	n.s.	2.35 $\pm$ 1.01 [0.22, 4.48] [*] (0.48)
----Rt. SUG	n.s.	2.52 $\pm$.91 [0.61, 4.45] [*] (0.53)
HA: Fatigability		
---Lt. med. temporal c.	n.s.	8.97 $\pm$ 3.09 [2.46, 15.49] ^{**} (0.40)
Reward Dependence Total		
---Rt. pregenual cingulate	n.s.	7.06 $\pm$ 2.84 [1.07, 13.03] [*] (0.39)
Persistence Total		

* *P* < 0.05,** *P* < 0.01,*** *P* < 0.001. Age and CER_VT co-varied.

Table 4Gender effects on serotonin-2A receptor binding in BPD females vs. males ^(*)

	Female	Male	Statistic
A. BPD Subjects	19	13	<i>F/df/P.</i>
ROI	BP _{ND} (mean,sd)	BP _{ND} (mean,sd)	
basal ganglia	0.35 (0.13)	0.20 (0.09)	8.47, df=1,28, <i>P.</i> = 0.007
---Lt. BG	0.35 (0.17)	0.20 (0.12)	6.46, df=1,28, <i>P.</i> =0.02
---Rt. BG	0.34 (0.12)	0.19 (0.10)	7.14, df=1,28, <i>P.</i> = 0.01
med. temporal c.	0.47 (0.13)	0.35 (0.11)	6.89, df=1,28, <i>P.</i> = 0.01
---Rt. MTC	0.46 (0.14)	0.34 (0.11)	5.87, df=1,28, <i>P.</i> = 0.02
occipital cortex	1.47 (0.29)	1.25 (0.25)	4.53, df=1,28, <i>P.</i> = 0.04
Rt. med. frontal c.	2.04 (0.37)	1.70 (0.34)	8.23, df=1,28, <i>P.</i> = 0.008
B. BPD Attempters	Female	Male	Statistic
	13	7	<i>F/df/ P.</i>
ROI	BP _{ND} (mean,sd)	BP _{ND} (mean,sd)	
hippocampus	.47 (0.13)	.35 (0.10)	10.12, df=1,16, <i>P.</i> = 0.006
---Rt. HIP	.47 (0.14)	.32 (0.08)	6.10, df=1,16, <i>P.</i> = 0.02
occipital cortex	1.51 (0.31)	1.20 (0.19)	9.19, df=1,16, <i>P.</i> = 0.008
---Rt.OCC	1.55 (0.33)	1.25 (0.23)	7.37, df=1,16, <i>P.</i> = 0.015
---Lt. OCC	1.47 (0.30)	1.15 (0.20)	9.17, df=1,16, <i>P.</i> = 0.008
Rt. med. frontal c.	2.03 (0.40)	1.68 (0.38)	6.48, df=1,16, <i>P.</i> = 0.022

^(*) Age and CER_VT co-varied