

Elevated Monoamine Oxidase-A Distribution Volume in Borderline Personality Disorder Is Associated With Severity Across Mood Symptoms, Suicidality, and Cognition

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Abstract

BACKGROUND—Monoamine oxidase-A (MAO-A) is a treatment target in neurodegenerative illness and mood disorders that increases oxidative stress and predisposition toward apoptosis. Increased MAO-A levels in prefrontal cortex (PFC) and anterior cingulate cortex (ACC) occur in rodent models of depressive behavior and human studies of depressed moods. Extreme dysphoria is common in borderline personality disorder (BPD), especially when severe, and the molecular underpinnings of severe BPD are largely unknown. We hypothesized that MAO-A levels in PFC and ACC would be highest in severe BPD and would correlate with symptom magnitude.

METHODS— $[^{11}\text{C}]$ Harmine positron emission tomography measured MAO-A total distribution volume (MAO-A V_T), an index of MAO-A density, in severe BPD subjects ($n = 14$), moderate BPD subjects ($n = 14$), subjects with a major depressive episode (MDE) only ($n = 14$), and healthy control subjects ($n = 14$). All subjects were female.

RESULTS—Severe BPD was associated with greater PFC and ACC MAO-A V_T compared with moderate BPD, MDE, and healthy control subjects (multivariate analysis of variance group effect: $F_{6,102} = 5.6$, $p < .001$). In BPD, PFC and ACC MAO-A V_T were positively correlated with mood symptoms (PFC: $r = .52$, $p = .005$; ACC: $r = .53$, $p = .004$) and suicidality (PFC: $r = .40$, $p = .037$; ACC: $r = .38$, $p = .046$), while hippocampus MAO-A V_T was negatively correlated with verbal memory ($r = -.44$, $p = .023$).

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DISCLOSURES

Drs. Meyer, Wilson, and Houle have received operating grant funds for other studies from Eli-Lilly, GlaxoSmithKline, Bristol Myers Squibb, Lundbeck, and SK Life Sciences in the past 5 years. Dr. Meyer has consulted to several of these companies, as well as Takeda, Sepracor, Trius, Mylan, and Teva. Dr. Links received an honorarium from Lundbeck within the past 5 years. None of these companies participated in the design or execution of this study or in writing the manuscript. All other authors report no biomedical financial interests or potential conflicts of interest.

CONCLUSIONS—These results suggest that elevated MAO-A V_T is associated with multiple indicators of BPD severity, including BPD symptomatology, mood symptoms, suicidality, and neurocognitive impairment.

Keywords

Borderline personality disorder; Harmine; Imaging; Monoamine oxidase-A; Positron emission tomography; Suicidal behavior

Psychiatric illnesses are often conceptualized as comprising multiple clusters of target pathologies that co-segregate across different disorders (1). Consistent with this perspective, monoamine oxidase-A (MAO-A) is an important target in neurodegenerative illness, due to its role in apoptosis (2,3), and in affect dysregulation, due to the association of elevated MAO-A levels in the prefrontal cortex (PFC) and anterior cingulate cortex (ACC) with depressive symptoms (4–7). MAO-A is an enzyme located on outer mitochondrial membranes in glia and monoamine-releasing neurons that increases oxidative stress, influences predisposition toward intrinsic apoptosis, and metabolizes monoamines (3). In brain tissue, greater MAO-A levels are correlated with elevated MAO-A activity (8), and an index of MAO-A density, the MAO-A distribution volume (MAO-A V_T), can be measured with [^{11}C] harmine positron emission tomography (PET) (9). [^{11}C] Harmine is a selective, reversible PET radiotracer that binds to the center of the active pocket of the MAO-A enzyme with high affinity (10).

Borderline personality disorder (BPD), especially when severe, is a major burden on public health and health care systems due to its high prevalence, occurring in 10% of outpatient psychiatric cases and 20% of psychiatric inpatient cases (11). A core feature of BPD is affect dysregulation with accompanying episodes of severe dysphoria that drive expression of other BPD symptoms, including intense anger, dysfunctional interpersonal interactions, and recurrent suicidal behavior (12,13). Severe dysphoria in BPD is highly clinically relevant because it is associated with need for inpatient care (14), although other dimensions of the illness, such as neurocognitive impairment, also contribute to BPD severity (15). Severe BPD is associated with greater functional impairment (16,17), dysregulated emotional responses to negative stimuli (18), and increased suicidality (17), which together contribute to the clinical burden of BPD.

The principal aim of the present investigation was to measure MAO-A V_T in BPD with moderate or severe symptoms. One model of emotional dysregulation in BPD highlights a deficient regulatory control system localized to the PFC and ACC (19) that is based on PET studies showing reduced engagement of these regions (20–24). In support of this model, meta-analysis of functional neuroimaging studies pinpoints hypoactivity of the ACC and dorsal regions of the PFC as central to the abnormal neurocircuitry underlying negative emotionality in BPD, although specific pathologies therein have not been identified (25). Depressive behaviors in rodents, such as those observed in chronic social defeat or chronic restraint stress paradigms, are associated with greater MAO-A messenger RNA and activity in the PFC (26,27). Moreover, depressive and anxious behaviors in rodents, particularly in the context of altered social environments, are associated with increased gene expression and

reduced degradation of brain MAO-A (28,29). Since affect dysregulation emerges from impaired social interaction and is core to worsened presentations of BPD (30,31), the primary study hypothesis was that PFC and ACC MAO-A V_T would be most elevated in severe BPD, particularly in relation to mood symptoms and suicidality, and elevated to a lesser extent in moderate BPD. Given that several of the functions attributed to MAO-A, including generation of oxidative stress and induction of apoptosis, are processes implicated in neurocognitive impairment (32), a secondary aim was to investigate MAO-A V_T in functional regions linked to verbal memory ability in BPD. Therefore, the secondary hypothesis was that MAO-A V_T would be elevated in the hippocampus when verbal memory impairment is more severe.

METHODS AND MATERIALS

Participants

Fifty-six female subjects completed the study protocol: 14 with severe BPD, 14 with moderate BPD, 14 with a major depressive episode (MDE) and no BPD, and 14 healthy control subjects. In clinical settings, female subjects comprise up to 74% of BPD cases (33). Hence, we restricted our analysis to women to focus on the type of BPD presentation most likely to come to clinical attention. Healthy and MDE control subjects were selected based on matching age and sex to the BPD samples. All subjects in the study were female and age-matching between control subjects and BPD samples was within 3 years. Samples had a similar proportion of women aged 41 to 51 years in each group to control for the effect of perimenopause on MAO-A V_T ($\chi^2_3 = .6, p = .63$) (34). Each participant provided written consent after study procedures had been explained. All study components were approved by the Research Ethics Board for Human Subjects at the Centre for Addiction and Mental Health, Toronto, Canada.

BPD Subjects—BPD participants were recruited from out-patient dialectical behavior therapy clinics (39.3%), inpatient psychiatric wards (17.9%), outpatient tertiary care (17.9%), and outpatient primary/secondary care (25.0%). BPD was diagnosed following clinical assessment and use of the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II) (35) by a psychiatrist experienced in the assessment and treatment of personality disorders (N.J.K.), who also administered the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (36). The BPD diagnosis was consistent with the diagnosis given to subjects by their tertiary care center treatment providers. BPD participants also met diagnostic criteria for current MDE. We included current MDE as an inclusion criterion to maximize generalizability of results, given that approximately 90% of female BPD cases have comorbid major depressive disorder (37). To rule out confounds of other major mood or psychotic disorders, exclusion criteria for BPD subjects included past history of mania, hypomania, or psychotic illness. Exclusion criteria also included use of medications in the past 3 months that are known or hypothesized to interfere with MAO-A levels, such as MAO-A inhibitors, mood stabilizers (e.g., lithium, valproic acid, carbamazepine), and psychostimulants (38). In contrast to some imaging markers, MAO-A levels are insensitive to monoamine reuptake inhibition; for example, selective serotonin reuptake inhibitors (SSRIs) do not affect MAO-A V_T (5). Therefore, use of recent

antidepressants that do not target MAO-A was permitted. As BPD is frequently associated with inpatient care, eight BPD participants, mostly recruited from inpatient settings, had been taking prescription psychotropic medications during the month before PET scanning, which included SSRIs (eight subjects), selective serotonin/norepinephrine reuptake inhibitors (one subject), atypical antipsychotics (three subjects), and benzodiazepines (three subjects).

MDE Subjects—MDE subjects were screened with the SCID-I and SCID-II, which was verified by subsequent consultation with a psychiatrist (JHM). MDE subjects were sex- and age-matched within 2 years to the BPD participants. MDE subjects had no lifetime history of additional psychiatric illness and had not taken antidepressant medication within the previous 2 weeks. Forty-three percent had never taken antidepressant treatment.

Healthy Subjects—Healthy subjects were also screened with the SCID-I and SCID-II by an experienced rater and verified by review with a psychiatrist (JHM). Healthy subjects were sex- and age-matched within 3 years to the BPD participants. Healthy subjects had no history of psychiatric illness or psychotropic medication use.

Healthy and MDE subjects were a subset of participants from previously published studies in our laboratory (5,39). All study participants were nonsmoking and provided negative urine drug screen tests on assessment and PET scanning days. Additionally, all study subjects refrained from the use of alcohol the night before PET scanning and drinking tea, coffee, or caffeinated beverages on the day of PET scanning.

Image Acquisition

Each participant underwent a single [^{11}C] harmine PET scan. Intravenous [^{11}C] harmine (370 MBq [10 MCi]) was administered as a bolus at the start of each PET scan. An automatic blood sampling system measured arterial blood radioactivity continuously for the first 22 minutes. Manual samples were obtained at 2.5, 7.5, 15.0, 20.0, 30.0, 45.0, 60.0, and approximately 90.0 minutes after injection. Whole blood and plasma radioactivity were measured as previously described (9). Fifteen frames lasting 1 minute each were acquired, followed by 15 frames of 5 minutes each. [^{11}C] Harmine was of very high radiochemical purity ($99.0 \pm .9\%$) and high specific activity ($109.5 \pm 67.0 \text{ GBq [} 2958.6 \pm 1811.1 \text{ MCi]}/\mu\text{mol}$) at the time of injection. PET images were obtained using a high-resolution research tomograph PET camera (in-plane resolution; full-width at half maximum, 3.1 mm; 207 axial sections of 1.2 mm) (Siemens Molecular Imaging, Knoxville, Tennessee) as described elsewhere (5).

Image Analysis

Each participant also underwent magnetic resonance imaging (MRI) on a 1.5T GE scanner (fast spoiled gradient echo T1-weighted image; x, y, z voxel dimensions: .78, .78, and 1.5 mm) (GE Medical Systems, Milwaukee, Wisconsin) for the region of interest (ROI) analysis. The ROIs were determined utilizing a semi-automated method, where regions of a template MRI were transformed onto the individual MRI based on a series of transformations and deformations that matched the template image to the individual co-registered MRI followed

by segmentation of the individual MRI to select the gray matter voxels, as previously reported (5,40).

The PFC and ACC were chosen as the primary regions of interest, because these regions participate in affective regulation (41), comprise the network of frontal control processes regulating emotional activity in subcortical limbic structures (19), and show hypoactivity during low mood states in BPD (25). In addition, several subregions of the PFC were sampled, including dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, medial prefrontal cortex, and orbitofrontal cortex (OFC). The borders of these subregions were defined based on their cytoarchitectural differences from adjacent cortex (42). Secondary ROIs included regions implicated in BPD and/or those known to have moderate to high MAO-A density and included hippocampus, dorsal putamen, thalamus, and midbrain.

MAO-A V_T represents the total tissue binding of [^{11}C] harmine at equilibrium and is highly correlated with MAO-A level (9,43), as would be expected since MAO-A affinity is similar across regions in primates in vivo (44). Both the unconstrained two-tissue compartment model and Logan model (45) with arterial sampling, for which the underestimate of V_T is negligible, measure V_T with high reliability and validity. We applied the latter technique, which has been described in detail previously (9).

Measures of Symptom Severity for BPD Subjects

BPD severity was defined as the number of DSM-IV BPD symptoms present in clinical assessment with the SCID-II. This method of defining BPD severity has been employed by other research groups (16–18,31). The severe BPD group was defined as having seven or more BPD symptoms and moderate BPD was defined as having five or six BPD symptoms; this cutoff was chosen based on the sample median. Measures of mood symptoms, suicidality, and cognition were administered on the day of the [^{11}C] harmine PET scan. Overall severity of mood symptoms was assessed with the 17-item Hamilton Depression Rating Scale (HDRS) (46) and suicidal ideation was assessed with the suicide subscale of the Overt Aggression Scale-Modified for Outpatients (OAS-M) (47). A set of cognitive tests were also administered with the prioritized measures being the Wechsler Test of Adult Reading-Revised (48) and Hopkins Verbal Learning Test-Revised (49). In addition, the Suicide Ideation Scale (50), Barratt Impulsiveness Scale Version 11 (51), Anger Questionnaire (52), and State-Trait Anger Expression Inventory-2 (53) were administered.

Statistical Analysis

To compare MAO-A V_T in the PFC and ACC across groups (severe BPD, moderate BPD, MDE, healthy), the primary analysis employed multivariate analysis of variance (MANOVA). To specifically assess whether regional MAO-A V_T was elevated in the severe BPD group compared with the moderate BPD group, MDE participants, and healthy subjects, additional comparisons were conducted using the protected least significant difference (LSD) procedure. To assess the relationship between PFC and ACC MAO-A V_T and severity of mood symptoms and suicidal ideation in BPD, Pearson's correlation coefficients were assessed. To assess the relationship between hippocampal MAO-A V_T and verbal memory,

the semi-partial correlation coefficient was calculated, which controlled for the effect of IQ on verbal memory ability. Tests of significance for correlational analyses were all two-tailed.

RESULTS

Subject Characteristics

Participants were aged 18 to 51 years. Groups did not differ in age. There was no significant group difference in HDRS scores between the three patient groups (Table 1).

The severe BPD group had significantly greater BPD symptoms, suicidal ideation, and trait anger compared with the moderate BPD group (Table 2).

Comparison of MAO-A V_T in Severe BPD, Moderate BPD, MDE, and Healthy Groups

As depicted in Figure 1, MAO-A V_T was substantially elevated in severe BPD, on average by 43% and 42% in the PFC and ACC, respectively, compared with the healthy group; by 16% and 13% in the PFC and ACC, respectively, compared with moderate BPD; and by 19% and 17% in the PFC and ACC, respectively, compared with MDE only (MANOVA group effect: $F_{6,102} = 5.6$, $p < .001$). Significant univariate effects were also detected in both PFC and ACC ($F_{3,52} = 9.4$ to 12.6 , p values all $< .001$). Comparisons based on the LSD test revealed that PFC and ACC MAO-A V_T were significantly elevated in severe BPD compared with moderate BPD (p values = .006 to .024), MDE only (p values = .002 to .007), and the healthy group (p values all $< .001$). In addition, moderate BPD showed greater PFC and ACC MAO-A V_T compared with the healthy group (p values = .002 to .005), as did the MDE group compared with the healthy group (p values = .005 to .017). No difference was observed in PFC and ACC MAO-A V_T between MDE and moderate BPD groups (p values = .62 to .73). When the analyses were repeated with only the unmedicated BPD subjects ($n = 20$), all significant relationships persisted. A post hoc analysis found that MAO-A V_T was increased in all BPD subjects versus MDE in the PFC ($t_{40} = 1.9$, $p = .035$, one-tailed) and ACC ($t_{40} = 1.8$, $p = .037$, one-tailed).

Multivariate analysis of covariance (MANCOVA) was used to test the group effect with HDRS score (HDRS ≥ 20 or HDRS < 20) as the covariate. Results indicated that the main group effect remained significant (MANCOVA group effect: $F_{6,100} = 3.4$, $p = .005$). All main contrasts were significant with inclusion of depressive symptoms as the covariate of interest (MANCOVA: severe BPD vs. moderate BPD: $F_{2,24} = 4.1$, $p = .029$; MANCOVA: severe BPD vs. healthy group: $F_{2,24} = 6.0$, $p = .008$; MANCOVA: severe BPD vs. MDE: $F_{2,24} = 3.6$, $p = .041$).

There was also a significant main group effect across all brain regions sampled (MANOVA group effect: $F_{30,127} = 2.8$, $p = .002$). In addition, comparisons using the LSD test revealed that besides the PFC and ACC, MAO-A V_T values for all other regions were significantly greater in severe BPD versus the healthy group (p values all $< .001$), severe BPD versus moderate BPD (p values = .001 to .012), and MDE versus the healthy group (p values = .001 to .027). MAO-A V_T values were significantly greater in severe BPD versus MDE for the additional regions, except the hippocampus and midbrain (p values = .002 to .21), and were significantly greater in moderate BPD versus the healthy group, save the hippocampus and

OFC (p values = .004 to .13). MAO-A V_T values did not differ between moderate BPD and MDE for any of the additional regions (p values = .11 to .99). Results were unchanged when only the unmedicated subjects were included in the analyses.

Relationship of MAO-A V_T With Severity of Mood Symptoms, Suicidality, and Cognition in BPD

In the 28 BPD subjects, PFC MAO-A V_T was correlated with both total HDRS score ($r = .52, p = .005$) (Figure 2) and suicidality, assessed using the OAS-M ($r = .40, p = .037$) (Figure 3), while ACC MAO-A V_T was similarly correlated with mood symptoms ($r = .53, p = .004$) (Figure 2) and suicidality ($r = .38, p = .046$) (Figure 3). Conversely, a negative correlation was observed between hippocampus MAO-A V_T in the BPD participants and total verbal recall, controlling for IQ on verbal recall (semi-partial correlation coefficient = $-.44, p = .023$) (Figure 4).

Relationship of MAO-A V_T With Severity of Mood Symptoms in Clinical Subjects

In a combined sample of the 42 clinical participants (28 BPD and 14 MDE), PFC MAO-A V_T and ACC MAO-A V_T were both strongly correlated with HDRS ($r = .47, p = .002$; and $r = .43, p = .005$, respectively).

DISCUSSION

This is the first imaging study of MAO-A in BPD, and its key findings are that PFC and ACC MAO-A V_T were significantly elevated in severe BPD compared with moderate BPD, MDE, and the healthy group. The difference in PFC and ACC MAO-A V_T between severe BPD and the healthy group was particularly robust: PFC and ACC MAO-A V_T were increased 43% and 42%, respectively, which is the largest magnitude reported for any psychiatric condition. Consistent with the relationship between overall severity of BPD and MAO-A V_T in these regions, greater MAO-A V_T in the PFC and ACC was also associated with severity of mood symptoms and suicidality. Additionally, an inverse relationship between verbal memory and MAO-A V_T in a region for which intact function is necessary for optimal cognitive performance (e.g., hippocampus) was detected. These findings have key implications for understanding the pathophysiology of BPD, especially when severe; for developing biomarkers of suicidality; and for identifying targets of cognitive impairment in BPD.

Since severe BPD is associated with greater functional impairment, suicidality, and consumption of health care resources (16,17), distinguishing and treating the underlying processes associated with illness severity is essential to reduce burden. Given that MAO-A increases production of hydrogen peroxide and ammonia through enhanced monoamine metabolism and heightens predisposition toward intrinsic apoptosis through mitochondrial membrane perturbation (3), it has been suggested that increased MAO-A protein and/or activity may contribute to neurodegeneration in Parkinson's disease (54), Huntington's disease (55), and Alzheimer's disease (56–58). Highly elevated MAO-A V_T in severe BPD may signal the involvement of similar patterns of ongoing neuronal and glial injury, since a high symptom burden typically persists in BPD for at least 5 to 10 years (59). Traditionally,

therapeutics with antioxidant or antiapoptotic properties have not been conceptualized as relevant for BPD, although evidence suggests that riluzole, a treatment indicated for amyotrophic lateral sclerosis that has antiapoptotic properties, can reduce suicidal behavior in BPD (60). Moreover, the newest MAO-A inhibitors that achieve a high brain-to-gut ratio to circumvent side effects have been studied in neurodegenerative conditions (3). Based on our finding of greater MAO-A expression in BPD, there is reason to consider such treatments for the illness, since classical MAO-A inhibitors are effective treatments for BPD, especially when severe (61,62).

The molecular abnormalities underlying severe BPD are largely unknown, since only a few studies have examined the relationship of symptom severity to neurochemical indices. In some illnesses, the severity of the pathology may relate to illness-specific expression of symptomatology that is common across disorders, such as dysphoria. However, it is also possible that biomarkers of severity relate to symptoms specific to the disorder. Because increased MAO-A V_T is associated with depressive symptoms in BPD and MDE, the relationship between MAO-A V_T and depressive symptoms in BPD could reflect a common biological mechanism operating in BPD and MDE. Alternatively, it may also relate to the influence of co-existing MDE on differential expression of BPD symptomatology. To date, the investigated markers of severity in BPD have mainly related to the domain of impulsivity. In a combined sample of healthy and BPD subjects, a correlation between an index related to total glutamate levels in the dorsal ACC and impulsivity, particularly cognitively oriented impulsivity, was found after controlling for group effects (63). Initial investigations of PFC serotonin 2A receptor binding in BPD reported no relationship to measures of severity (64,65), but a more recent sample found an association of lifetime aggression with reduced serotonin 2A receptor binding in the medial OFC of female subjects with BPD (66). Another study reported greater mu-opioid receptor binding in the OFC, caudate, and ventral striatum in BPD, which did not reach a statistically significant threshold when correlated with measures of impulsivity, neuroticism, or dissociation (67). Finally, reduced α [^{11}C]-methyl-L-tryptophan uptake in PFC and ACC was found to be correlated with measures of impulsivity and suicidal intent in samples of BPD patients (23,68). Interestingly, the findings of the present study are consistent with several reports of abnormal markers implicated in proapoptotic signaling from postmortem investigations that predominantly sampled the PFC of suicide victims with mood dysregulation: reduced phosphoinositide 3-kinase activity (69), reduced R1 levels (70), increased caspase-8 levels (71), and reduced Bcl-2 (72).

To the best of our knowledge, this is the first study of BPD to demonstrate a correlation between present suicidal ideation and an in vivo brain marker. There is a need for biomarkers associated with suicide risk, because 60% to 75% of people with BPD make suicide attempts and 8% to 10% commit suicide (73). Although empirically determined risk factors improve suicide risk assessment, these factors are mostly longstanding and cannot reliably predict when suicide is imminent. Biomarker development in psychiatric conditions involves creation of a panel of low-cost markers for which each marker specifically relates to an implicated pathology (74). We are unaware of any peripheral markers in development for the pathologies associated with apoptosis that have been identified in suicide victims with mood dysregulation. However, measurement of plasma MAO-A levels (75) and detection of

MAO-A activity using magnetic resonance spectroscopy (76) represent possibilities of low-cost surrogate markers for MAO-A levels in the brain.

The correlation between hippocampus MAO-A V_T and verbal memory in BPD is consistent with interpreting elevated MAO-A level as a pathological influence on this neural substrate of verbal memory function. Pathologies associated with apoptosis and/or oxidative stress in functionally critical regions are common in diseases presenting with memory impairment and are usually assumed to be etiological if correlated with severity of cognitive impairment (32). For example, decreased verbal memory performance is associated with microstructural alterations of hippocampal gray matter in Parkinson's disease (77) and increased hippocampal binding of radioligand selective for amyloid plaques and neurofibrillary tangles in Alzheimer's disease (78).

Our results indicated that group differences in MAO-A V_T were present beyond the hypothesized regions of PFC and ACC. In general, MAO-A V_T tends to be highly intercorrelated among brain regions. Although our results support the hypothesis that negative mood states in BPD are related to elevated PFC and ACC MAO-A V_T , the pathological mechanisms responsible for raising MAO-A levels may have a global effect. However, we suggest that the functional impact of increased MAO-A V_T may be most important in the PFC and ACC, given their role in affect regulation.

We note several limitations of the present investigation. We chose to assess BPD severity based on the number of DSM-IV symptoms present, an approach used in some laboratories (16–18,31). Although there is no universally accepted gold standard for measuring BPD severity (79), other options would have been the Zanarini Rating Scale for Borderline Personality Disorder (80) or the Borderline Personality Disorder Severity Index (81). These other scales are designed to capture DSM-IV BPD criteria (80,81) and are highly correlated with number of BPD criteria (81). Even so we found a consistent relationship between PFC and ACC MAO-A V_T and several additional measures of severity. Second, a small subset of our BPD participants had been taking psychotropic medication, mainly SSRIs, at the time of scanning, although our main findings did not change when we excluded these individuals from the analysis. Third, to decrease sample heterogeneity, we only sampled women; therefore, our findings may not be generalizable to men. Fourth, we applied MAO-A V_T as our primary measure, because it is the most stable and least variable measure of [^{11}C] harmine binding. However, the measure of MAO-A used in this study reflects total binding, and approximately 15% of MAO-A V_T represents free and nonspecific binding. Hence, our interpretations assumed that substantial changes in free and nonspecific binding (150% to 300%) were not occurring, an assumption consistent with previous evaluations observed in MAO-A occupancy studies (9).

In summary, we found that elevated MAO-A in PFC and ACC was related to several markers of severity in BPD, including more borderline and mood symptoms and greater suicidality. Increased hippocampal MAO-A levels were additionally associated with decreased verbal memory performance. Understanding severe BPD is paramount given its high morbidity and mortality and high healthcare burden. These results offer a novel perspective on the pathophysiological mechanisms of BPD and suggest that therapeutics that inhibit MAO-A,

reduce cellular oxidative stress levels, and/or oppose apoptotic processes should be tested in severe presentations of BPD.

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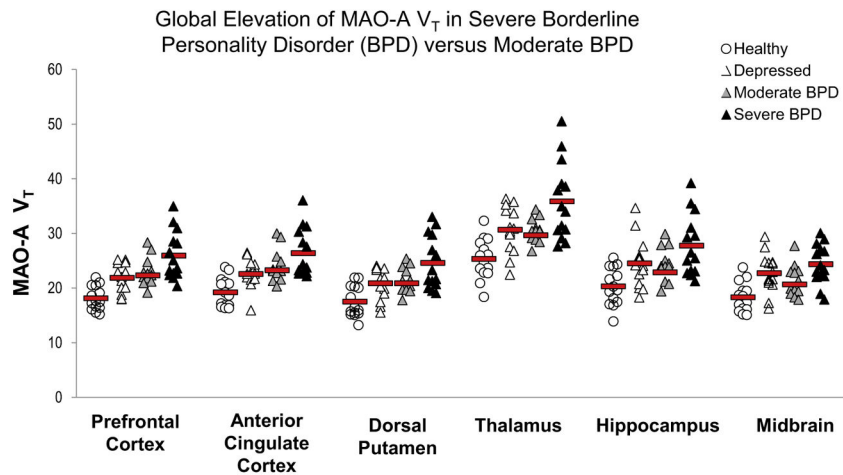


Figure 1.

Multivariate analysis of variance (MANOVA) indicates that severe BPD was associated with greater monoamine oxidase-A distribution volume (MAO-A V_T) in both prefrontal and anterior cingulate cortex compared with the moderate BPD, depressed, and healthy groups (MANOVA group effect: $F_{6,102} = 5.6$, $p < .001$; least significant difference for severe BPD vs. other groups, p value range: $<.001$ to $.024$). Mean MAO-A V_T was greater in severe vs. moderate BPD for each brain region sampled (p value range: $.003$ to $.024$). When the effect of group on MAO-A V_T was evaluated across all regions, similar results were found (MANOVA group effect: $F_{30,127} = 2.8$, $p = .002$). Red bars indicate mean MAO-A V_T values.

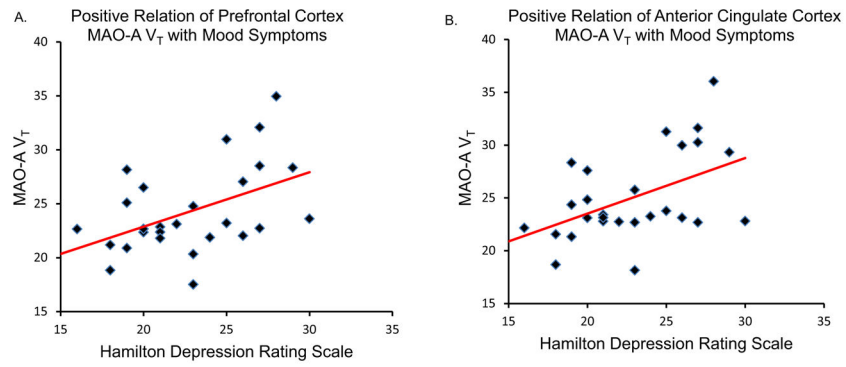


Figure 2.

(A) Prefrontal cortex monoamine oxidase-A total distribution volume (MAO-A V_T) is positively correlated with Hamilton Depression Rating Scale score (Pearson's $r = .52$, $p = .005$, two-tailed). (B) Anterior cingulate cortex MAO-A V_T is positively correlated with Hamilton Depression Rating Scale score (Pearson's $r = .53$, $p = .004$, two-tailed).

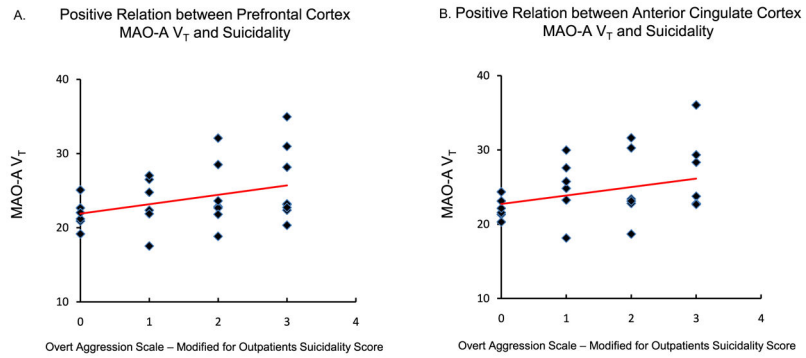


Figure 3.

(**A**) Prefrontal cortex monoamine oxidase-A total distribution volume (MAO-A V_T) is positively correlated with the Suicidality subscale score of the Overt Aggression Scale-Modified for Outpatients (Pearson's $r = .40$, $p = .037$, two-tailed). (**B**) Anterior cingulate cortex MAO-A V_T is positively correlated with the Suicidality subscale score of the Overt Aggression Scale-Modified for Outpatients (Pearson's $r = .38$, $p = .046$, two-tailed).

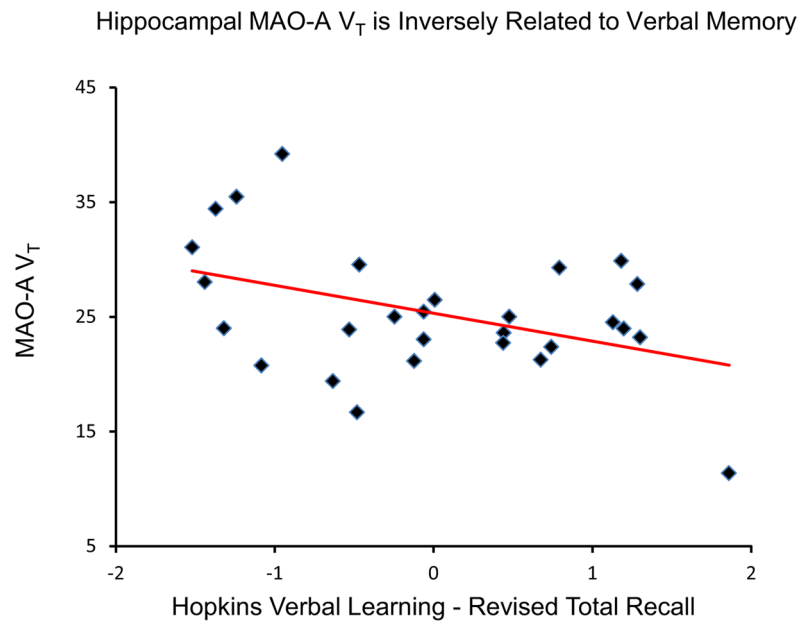


Figure 4. Hippocampal monoamine oxidase-A total distribution volume (MAO-A V_T) is negatively correlated with Total Recall score of the Hopkins Verbal Learning Test-Revised (HVLTR), controlling for IQ on HVLTR (semi-partial correlation coefficient = -0.41 , $p = .023$, two-tailed). Note: x axis depicts residuals of HVLTR total recall independent of IQ.

Table 1**Demographic and Clinical Characteristics of All Study Participants^a**

	Healthy (n = 14)	Major Depressive Episode (n = 14)	Moderate Severity BPD (n = 14)	High Severity BPD (n = 14)	p Value
Age, Years	32.9 (8.2)	30.9 (6.6)	32.9 (10.6)	34.2 (10.2)	.65 ^b
HDRS ^c	.9 (1.4)	20.1 (4.5)	21.3 (4.2)	23.6 (4.1)	.10 ^d

BPD, borderline personality disorder; HDRS, Hamilton Depression Rating Scale.

^aValues are expressed as mean (standard deviation).

^bAnalysis of variance of participant age for the four study groups (moderate BPD, severe BPD, major depressive episode only, and healthy).

^c17-item Hamilton Depression Rating Scale score on day of positron emission tomography scanning.

^dAnalysis of variance of Hamilton Depression Rating Scale scores for the three patient groups (moderate BPD, severe BPD, and major depressive episode only).

Table 2Clinical Characteristics of Borderline Personality Disorder Groups^a

Characteristics	Moderate BPD (n = 14)	Severe BPD (n = 14)
Education, Years ^b	14.9 (1.5)	14.5 (2.1)
Estimated Full-Scale IQ ^c	103.8 (9.2)	109.6 (8.9)
Diagnosis		
Number of BPD symptoms ^d	5.4 (.5)	7.8 (1.0) ^e
Comorbid conditions		
% with anxiety disorder ^d	64.3	71.4
% with eating disorder ^d	57.1	50.0
% with lifetime substance use disorder ^d	14.3	7.1
% with somatoform disorder ^d	7.1	7.1
% with other DSM-IV-TR personality disorder ^d	71.4	57.1
% Taking Psychotropic Medication ^d	28.6	28.6
Number of Psychiatric Hospitalizations ^b	2.3 (2.9)	3.2 (2.9)
Suicidality Measures		
Suicide Ideation Scale ^b	9.6 (9.5)	17.0 (9.0) ^f
OAS-M Suicidality Scale ^b	1.4 (1.2)	2.1 (1.1)
% endorsing moderate or severe suicidality on OAS-M Suicidality scale ^g	14.3	57.1 ^f
Anger/Aggression Measures		
STAXI-2 state anger (T-score) ^b	56.3 (11.6)	56.9 (15.0)
STAXI-2 trait anger (T-score) ^b	54.0 (11.9)	67.6 (14.5) ^f
Buss-Perry anger ^c	17.2 (6.9)	23.9 (7.4) ^f
Buss-Perry physical aggression ^c	18.4 (9.4)	24.4 (9.8)
Buss-Perry verbal aggression ^c	13.4 (5.3)	16.1 (5.4)
Barratt Impulsiveness Scale 11		
Attentional impulsiveness ^c	20.7 (4.8)	23.9 (3.5)
Motor impulsiveness ^c	27.2 (6.6)	28.5 (5.5)
Nonplanning impulsiveness ^c	30.5 (5.9)	31.3 (4.6)

BPD, borderline personality disorder; OAS-M, Overt Aggression Scale-Modified for Outpatients; STAXI-2, State Trait Anger Expression Inventory-2.

^aValues are expressed as mean (standard deviation), except where indicated.

^bMann-Whitney *U* test.

^cIndependent samples *t* test.

^dFisher's exact test.

^e $p < .001$, two-tailed.

^f $p < .05$, two-tailed.

^gChi-square test.