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Lower Monoamine Oxidase-A Total Distribution Volume in Impulsive and Violent Male Offenders with Antisocial Personality Disorder and High Psychopathic Traits: An [^{11}C] Harmine Positron Emission Tomography Study

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Antisocial personality disorder (ASPD) often presents with highly impulsive, violent behavior, and pathological changes in the orbitofrontal cortex (OFC) and ventral striatum (VS) are implicated. Several compelling reasons support a relationship between low monoamine oxidase-A (MAO-A), an enzyme that regulates neurotransmitters, and ASPD. These include MAO-A knockout models in rodents evidencing impulsive aggression and positron emission tomography (PET) studies of healthy subjects reporting associations between low brain MAO-A levels and greater impulsivity or aggression. However, a fundamental gap in the literature is that it is unknown whether brain MAO-A levels are low in more severe, clinical disorders of impulsivity, such as ASPD. To address this issue, we applied [^{11}C] harmine PET to measure MAO-A total distribution volume (MAO-A V_T), an index of MAO-A density, in 18 male ASPD participants and 18 age- and sex-matched controls. OFC and VS MAO-A V_T were lower in ASPD compared with controls (multivariate analysis of variance (MANOVA): $F_{2,33} = 6.8$, $P = 0.003$; OFC and VS MAO-A V_T each lower by 19%). Similar effects were observed in other brain regions: prefrontal cortex, anterior cingulate cortex, dorsal putamen, thalamus, hippocampus, and midbrain (MANOVA: $F_{7,28} = 2.7$, $P = 0.029$). In ASPD, VS MAO-A V_T was consistently negatively correlated with self-report and behavioral measures of impulsivity ($r = -0.50$ to -0.52, all P-values < 0.05). This study is the first to demonstrate lower brain MAO-A levels in ASPD. Our results support an important extension of preclinical models of impulsive aggression into a human disorder marked by pathological aggression and impulsivity.
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INTRODUCTION

The vast majority of violent crime is perpetrated by a small group of males who exhibit conduct-disordered behavior from childhood onward and fulfill diagnostic criteria for antisocial personality disorder (ASPD) as adults (Moffitt *et al*, 2002). Pathological impulsivity is a core symptom of ASPD (Swann *et al*, 2009) that relates to the aversive behaviors and comorbidities associated with the disorder, including violent offending (Zhou *et al*, 2014) and alcohol dependence (AD) (Rubio *et al*, 2008). There are very few molecular imaging studies of ASPD and, to the best of our knowledge, no abnormalities are identified from postmortem investigations in clinically diagnosed individuals with the condition, although brain phenotypes such as low orbitofrontal cortex (OFC) 5-HT_{2A} receptor binding in impulsive males with ASPD (Meyer *et al*, 2008; Rylands *et al*, 2012) and increased amphetamine-induced nucleus accumbens dopamine release in humans with high impulsive-antisocial psychopathic traits (Buckholtz *et al*, 2010) have been reported. However, low brain monoamine oxidase-A (MAO-A), an enzyme localized to outer mitochondrial membranes that metabolizes amine neurotransmitters implicated in aggressive behavior (Bortolato *et al*, 2008), has emerged as a promising molecular target.

Multiple tiers of evidence from preclinical and clinical studies support a strong relationship between low or absent MAO-A and impulsive aggression. First, males with a rare point mutation in the eighth exon of the MAO-A gene leading to complete and selective deficiency of MAO-A exhibit severely impulsive and aggressive behavior (Brunner *et al*, 1993). Second, positron emission tomography (PET) studies of healthy humans that used MAO-A-selective

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radiotracers found inverse relationships between MAO-A binding in several brain regions and self-reported anger, aggression, and hostility (Alia-Klein *et al*, 2008; Soliman *et al*, 2011). Third, targeted knockout of MAO-A in mouse embryonic stem cells produces impulsively aggressive adult mice (Cases *et al*, 1995; Scott *et al*, 2008). Fourth, pharmacological inhibition of MAO-A during murine embryogenesis increases impulsive aggression on pharmacologic challenge in adult mice (Mejia *et al*, 2002). Fifth, MAO-A genetic polymorphisms that are associated with lower MAO-A transcription in cell lines have been found to interact with childhood adversity to increase the risk of adult violent convictions (Caspi *et al*, 2002). However, it has never been empirically determined whether brain MAO-A is lower in violent and clinically impulsive populations. To address this critical issue, the principal aim of the study was to measure MAO-A total distribution volume (MAO-A V_T), an index of MAO-A level, in the brains of highly impulsive, violent offenders with ASPD.

[^{11}C] Harmine is a PET radiotracer ideally suited to measure MAO-A level, because it is reversible, selective for the MAO-A isoenzyme, and binds with high affinity to the substrate cavity in the center of the MAO-A enzyme (Son *et al*, 2008). Lower MAO-A levels are associated with lower MAO-A activity in the brain (Saura *et al*, 1992).

We hypothesized that MAO-A V_T would be lower in the OFC and ventral striatum (VS) of ASPD with impulsive violence and that OFC and VS MAO-A V_T would vary inversely with measures of impulsivity. The OFC and VS were chosen as the main regions of interest (ROI), because they show consistent functional and/or biological abnormalities in ASPD and aggressive behavior (Blair, 2004; Buckholtz *et al*, 2010; Glenn and Yang, 2012; Meyer *et al*, 2008; Rylands *et al*, 2012) and are key structures in the neural circuitry mediating impulsivity (Dalley *et al*, 2011).

MATERIALS AND METHODS

Participants

Thirty-six males completed the study protocol: 18 participants with ASPD and 18 control participants without ASPD. Each participant provided written consent following explanation of study procedures. All study components were approved by the Research Ethics Board for Human Subjects at the Centre for Addiction and Mental Health, Toronto, Canada.

ASPD Subjects

ASPD participants were recruited from the community and probation services. ASPD participants were clinically assessed by a forensic psychiatrist (NJK) and diagnosed using the Structured Clinical Interview for DSM-IV Axis II, Personality Disorders (SCID II) (First *et al*, 1997), and the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID I) (First *et al*, 2002). Each ASPD participant had a history of impulsive violent offending that included assault, sexual assault, robbery, uttering threats, and manslaughter. Exclusion criteria included history of a psychotic, major depressive, or bipolar disorder and current drug abuse or dependence. Psychotropic medication use was also exclusionary. Sixty-seven percent of the ASPD sample had no lifetime exposure to psychotropic medication: four subjects had brief exposures to psychostimulants as children but had not taken psychotropic medication as adults. One subject received intermittent treatment with an atypical antipsychotic to manage acute aggression while previously incarcerated but had not been treated in over 5 years. Another subject was taking clonazepam intermittently until 2 months prior to study enrollment. Nine subjects additionally met criteria for current AD.

Control Subjects

Control subjects consisted of nine males with AD and nine subjects without AD. ASPD subjects were matched to controls based on the presence or absence of AD comorbidity, given the association of AD with global alterations of brain MAO-A V_T (Matthews *et al*, 2014). Therefore, we included controls with AD to optimize matching. Control subjects without AD were screened with the SCID I and SCID II by an experienced rater and verified by review with a psychiatrist (JHM). These subjects had no history of psychiatric illness and had not endorsed conduct disorder symptoms as children or youth. Control subjects with AD were also screened with the SCID I and SCID II, which was verified by a psychiatrist (JHM). This subset of controls had no lifetime history of additional psychiatric illness, including ASPD. One AD subject had been treated with diazepam for alcohol withdrawal 15 years prior to his involvement in the study. None of the other control participants had any previous psychotropic medication exposure. Control subjects were age-matched within 4 years to the ASPD participants.

Control subjects formed a subset of participants from previously published studies in our laboratory (Matthews *et al*, 2014; Soliman *et al*, 2011). None of the study subjects was a current smoker: 38.9% of the ASPD subjects and 33.3% of the control subjects were past smokers ($P = 1.0$, two-tailed Fisher's exact test). Non-smoking status was verified in the ASPD and AD control subjects by self-report and breathalyzer testing for carbon monoxide (MicroSmokerlyzer; Bedfont Scientific, Kent, United Kingdom) and by self-report in the healthy control subjects. All subjects provided negative urine drug screen tests on assessment and PET scanning days. Study subjects refrained from the use of tea, coffee, or caffeinated beverages on the day of PET scanning.

Image Acquisition

Participants underwent a single [^{11}C] harmine PET scan. 370 MBq of intravenous [^{11}C] harmine was administered as a bolus at the beginning of each PET scan. An automatic blood sampling system (Model PBS-101, Comecer Netherlands, Joure, the Netherlands) measured arterial blood radioactivity continuously for the first 22 min. Following bolus injection, manual samples were obtained at 2.5, 7.5, 15.0, 20.0, 30.0, 45.0, 60.0 and ~90.0 min. Whole-blood and plasma radioactivity was measured as previously reported (Ginovart *et al*, 2006). Plasma analysis of [^{11}C] harmine used column capture and switching methods (Hilton *et al*, 2000). Whole, unadulterated plasma was injected onto a small capture column insulated with OASIS resin (Waters, Milford, MA, USA). Highly polar metabolites and plasma proteins were

eluted through a coincidence flow detector (Bioscan Flow-Count). Less polar metabolites and [^{11}C] harmine were then back-flushed onto an HPLC (Phenomenex Luna C_{18}, 10 μ, 250 × 4.6 mm).

Frames were acquired as follows: fifteen frames lasting 1 min each were acquired, followed by 15 frames that were 5 min each. [^{11}C] Harmine was of very high radiochemical purity (98.9 ± 0.9%) and high specific activity (120.7 ± 72.9 GBq/μmol) 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, TN).

Image Analysis

MAO-A V_T represents the total tissue binding of [^{11}C] harmine at equilibrium and is highly correlated with MAO-A level, as would be expected since *in vivo* MAO-A affinity is similar across regions in primates (Bottlaender *et al*, 2010). Both the unconstrained two-tissue compartment model and Logan model with arterial sampling, for which the underestimate of V_T is negligible, measure V_T with high reliability and validity (Ginovart *et al*, 2006). In the original kinetic modeling of [^{11}C] harmine binding to MAO-A, the Pearson's correlation coefficient for MAO-A V_T values obtained using a two-tissue compartment model and the Logan graphical approach was 0.98 (Ginovart *et al*, 2006). In the present study, we applied the Logan model (Ginovart *et al*, 2006; Logan *et al*, 1990).

The OFC and VS were chosen as the primary ROI, because these regions show molecular abnormalities in ASPD and high psychopathic traits (Buckholtz *et al*, 2010; Meyer *et al*, 2008; Rylands *et al*, 2012) and comprise the neural circuitry underlying pathological impulsivity (Dalley *et al*, 2011). The boundary of the OFC was defined based on its cytoarchitectural differentiation from adjacent cortical tissue and was mapped onto the external morphology of the cortex (Uylings *et al*, 2010). The VS was based on the definition provided by Mawlawi *et al*, 2001. Other secondary ROI were structures previously shown to be abnormal in ASPD and/or those known to have moderate-to-high MAO-A density. These included the dorsal putamen, defined by Mawlawi *et al* (2001), and prefrontal cortex, anterior cingulate cortex, thalamus, midbrain, and hippocampus, which were derived from a neuroanatomy atlas of structural MRI and post-mortem tissue (Duvernoy, 1999), and were used for our previous investigations (Matthews *et al*, 2014; Soliman *et al*, 2011). Other subregions of the PFC (dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, and medial prefrontal cortex) were additionally sampled to assess whether the effects observed in the main analyses of the OFC were consistent within these subregions. The boundaries of these additional PFC subregions were defined similarly to the OFC (Rajkowska and Goldman-Rakic, 1995).

The ROI tested in the current investigation were determined by 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 grey matter voxels, as previously described (Rusjan *et al*, 2006). Participants received a high-resolution magnetic resonance imaging (MRI) scan to facilitate the ROI analysis (1.5-T GE scanner, fast spoiled gradient echo T_1-weighted image; x, y, z voxel dimensions, 0.78, 0.78, and 1.5 mm; GE Medical Systems, Milwaukee, WI; or 3.0-T GE scanner, fast spoiled gradient echo T_1-weighted image; x, y, z voxel dimensions, 0.37, 0.37, and 0.90 mm; GE Medical Systems). Previous within-subject cross-validation assessment found that regardless of MRI scanner type, regional MAO-A V_T values were virtually identical for the main ROIs ($n = 6$ subjects; ICC = 0.99–1.0).

Measures of Impulsivity in ASPD

Iowa gambling task. The Iowa Gambling Task (IGT) is a computerized, performance-based card game that indexes choice impulsivity. Participants were instructed to win as much virtual money as possible by selecting cards from any of four decks (A, B, C, or D) one at a time. Decks C and D yield high monetary gains but are accompanied by risk of high losses, whereas decks A and B consistently yield lower gains with the risk of smaller losses. Participants were advised that some decks are more disadvantageous than others and that they could win by avoiding these decks. Twenty trials were administered over five blocks for a total of 100 trials. Highly impulsive groups show the greatest impairment in performance during the latter trials of the IGT (Sweitzer *et al*, 2008). Accordingly, the net IGT was calculated by subtracting the number of cards selected from disadvantageous decks from the number of cards selected from advantageous decks over the last two blocks: ((C+D)-(A+B)).

NEO Personality inventory—Revised. The NEO Personality Inventory—Revised (NEO PI-R) (Costa, McCrae, 1992) is an extensively validated and reliable self-report measure of 'normal' and abnormal adult personality (Costa and McCrae, 1992) that provides norm-referenced test scores for broad-based dimensional personality domains and traits, including impulsivity. All participants completed the NEO PI-R.

Psychopathy Checklist—Revised. A trained forensic psychiatrist (NJK) administered the Psychopathy Checklist—Revised (PCL-R) (Hare, 2003) to the ASPD participants. The PCL-R evaluates 20 interpersonal, affective, and behavioral traits that relate to the personality disorder of psychopathy, including impulsivity. Items were scored from 0 to 2 based on the presence or absence of each trait (*0* = no; *1* = maybe; *2* = yes) using information obtained during the clinical interview and official criminal records.

Statistical Analysis

Multivariate analysis of variance (MANOVA) was used to test our hypothesis that OFC and VS MAO-A V_T would be lower in ASPD versus controls. To further characterize the comparison of ASPD and control subjects, MANOVA was applied to assess the group effect on MAO-A V_T in the PFC, VS, anterior cingulate cortex, dorsal putamen, thalamus, hippocampus, and midbrain. A separate MANOVA was conducted on the PFC subregions to test whether the anticipated effect of diagnosis was widespread

in the PFC. To test the hypothesis that OFC and VS MAO-A V_T would be inversely related to impulsivity, Pearson's correlation coefficients were calculated.

RESULTS

Subject Characteristics

Participants were aged 18–49 years. The ASPD group reported significantly greater impulsivity and more conduct disorder symptoms compared with the control group (see Table 1).

Difference in MAO-A V_T Between ASPD Group and Control Subjects

The main finding is that MAO-A V_T was significantly lower in ASPD versus controls, on average by 19.3% and 18.8% in the VS and OFC, respectively (MANOVA group effect: $F_{2,33} = 6.8$, $P = 0.003$). Significant univariate effects were also detected in the VS ($F_{1,34} = 12.9$, $P = 0.001$) and OFC ($F_{1,34} = 12.6$, $P = 0.001$; See Figure 1). Results did not change when the control participant with the highest MAO-A V_T values was removed from the analysis (MANOVA group effect: $F_{2,32} = 6.2$, $P = 0.005$; univariate effect of VS: $F_{1,33} = 11.3$, $P = 0.002$; univariate effect of OFC: $F_{1,33} = 11.7$, $P = 0.002$). A separate MANOVA that compared ASPD subjects ($n = 18$) with the controls lacking AD ($n = 9$) revealed lower OFC and VS MAO-A V_T in the ASPD group ($F_{2,24} = 3.8$, $P = 0.036$). Another MANOVA comparing the subgroup of ASPD subjects with AD ($n = 9$) with all control subjects ($n = 18$) additionally found that OFC and VS MAO-A V_T were lower in the ASPD subgroup (MANOVA group effect: $F_{2,24} = 6.0$, $P = 0.008$).

MAO-A V_T was also lower in all of the main brain regions analyzed for the ASPD participants ($n = 18$) compared with controls ($n = 18$) (MANOVA group effect: $F_{7,28} = 2.7$, $P = 0.029$), with significant univariate effects detected in all regions ($F_{1,34} = 4.2$ to 12.9, P-values $= 0.048$ to 0.001). In addition, subregions of the PFC were assessed with similar results (MANOVA group effect: $F_{4,31} = 3.2$, $P = 0.025$). *Post hoc* tests revealed that the group difference was significant for each prefrontal region (See Table 2).

In a subset of the entire sample that included 10 ASPD and 10 control participants, MAO-A V_T values for the PFC were compared using the Logan analysis and two-tissue compartment model. Results were highly correlated ($r = 0.996$, $P < 0.0001$) and similar, with an underestimate of 4% in MAO-A V_T using the Logan analysis.

Relationship Between VS and OFC MAO-A V_T and Measures of Impulsivity in ASPD Subjects

In the ASPD subjects, VS MAO-A V_T was negatively correlated with IGT performance ($r = -0.52$, $P = 0.034$). That is, lower VS MAO-A V_T was associated with more risky and impulsive decision making. VS MAO-A V_T also showed an inverse relationship with self-reported impulsivity on the NEO PI-R ($r = -0.50$, $P = 0.034$). ASPD subjects who were rated the most impulsive on the PCL-R had the lowest VS MAO-A V_T ($t_{16} = 2.8$, $P = 0.013$; see Figure 2). No significant relationships were detected in the ASPD sample between OFC MAO-A V_T and PCL-R impulsivity ($t_{16} = 1.7$, $P = 0.11$), OFC MAO-A V_T and IGT performance ($r = 0.07$, $P = 0.80$), or OFC MAO-A V_T and NEO PI-R impulsivity ($r = -0.02$, $P = 0.94$). No significant relationships were detected between MAO-A binding and impulsivity measures for any of the other regions tested, except that the dorsal putamen MAO-A V_T was lower in the ASPD subjects rated more impulsive on the PCL-R compared with those rated less impulsive (19.7 ± 1.9 *vs* 23.3 ± 1.3; $t_{16} = 2.9$, $P = 0.01$).

There was no relationship between MAO-A V_T, prior medication exposure, or class of prior medication exposure in the ASPD and control groups. When we excluded from the analyses the ASPD participant who had used benzodiazepines 2 months prior to his involvement in the study, all significant group and correlational findings persisted.

Table 1 Demographic and Clinical Characteristics

Characteristics[a]	ASPD ($n = 18$)	Controls ($n = 18$)
Age[b]	36.2 ± 9.4	36.4 ± 8.9
% Male	100	100
Comorbid substance use		
% Smoking	0	0
% Alcohol dependence	50	50
Medications		
% Taking psychotropic medications	0	0
Dysphoria		
17-item HDRS score[c]	3.6 ± 2.8	1.9 ± 2.0
Impulsivity (self-reported)		
NEO PI-R impulsivity subscale T-score[b]	59.2 ± 12.4*	50.4 ± 12.6
Conduct disordered behavior		
Number of conduct disorder symptoms[c]	7.9 ± 0.4**	0.4 ± 0.9
Psychopathy		
PCL-R total score	26.4 ± 6.8	NA[d]
PCL-R factor 1 score	9.4 ± 3.3	NA
PCL-R factor 2 score	14.8 ± 3.9	NA

Abbreviations: ASPD, antisocial personality disorder; HDRS, Hamilton Depression Rating Scale; NA, not available; NEO PI-R, NEO Personality Inventory—Revised; PCL-R, Psychopathy Checklist—Revised.
[a]Values are expressed as mean ± s.d., except where indicated.
[b]Independent samples *t*-test.
[c]Mann–Whitney *U*-test.
[d]For individuals with no history of ASPD or conduct disorder, the average total PCL-R score is <8 (Hare, 2003); *$P < 0.05$, two-tailed; **$P < 0.001$, two-tailed.

DISCUSSION

This study is the first investigation of MAO-A brain level in impulsive and violent offenders with a DSM-IV diagnosis of ASPD. Consistent with our main hypotheses, we found that OFC and VS MAO-A V_T were lower in ASPD and that

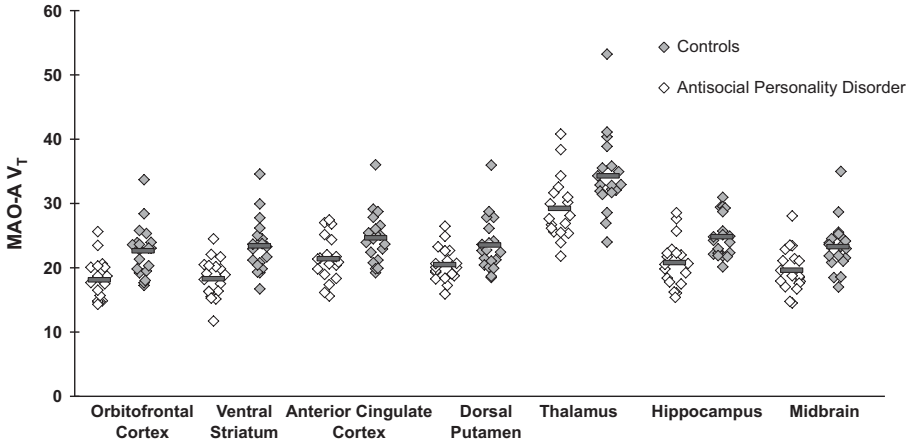

Figure 1 Lower MAO-A V_T in Antisocial Personality Disorder. Multivariate analysis of variance (MANOVA) indicates that antisocial personality disorder (ASPD) was associated with lower MAO-A V_T (monoamine oxidase-A total distribution volume) in orbitofrontal cortex and ventral striatum compared with controls (MANOVA group effect: F2,33 = 6.8, $P = 0.003$). Controls contained a mix of participants with no psychiatric comorbidity ($n = 9$) and participants with alcohol dependence and no other psychiatric comorbidity ($n = 9$) to optimally match with ASPD participants, nine of whom also had comorbid alcohol dependence. There was also an effect of diagnosis on MAO-A V_T across all brain regions indicated above (MANOVA group effect: $F_{7,28} = 2.8$, $P = 0.022$). Horizontal bars indicate mean MAO-A V_T values. Differences remained significant when the control subject with the highest MAO-A V_T values was removed from the analyses.

Table 2 Comparison of MAO-A V_T in ASPD Versus Controls for Prefrontal Cortex Subregions

	ASPD MAO-A V_T	Control MAO-A V_T	ANOVA	*P*-value
Region				
Orbitofrontal cortex	18.1 ± 3.2	22.3 ± 3.9	$F_{1,34} = 12.6$	0.001
Dorsolateral prefrontal cortex	20.1 ± 2.9	22.9 ± 3.9	$F_{1,34} = 6.0$	0.020
Ventrolateral prefrontal cortex	19.4 ± 3.2	23.3 ± 4.4	$F_{1,34} = 9.3$	0.004
Medial prefrontal cortex	21.6 ± 3.2	24.5 ± 3.7	$F_{1,34} = 6.6$	0.015

Abbreviations: ANOVA, analysis of variance; ASPD, antisocial personality disorder; MAO-A V_T, monoamine oxidase-A total distribution volume. Multivariate analysis of variance (MANOVA) indicates that antisocial personality disorder was associated with lower MAO-A V_T in all four subregions of the prefrontal cortex compared with controls (MANOVA group effect: $F_{4,31} = 3.2$, $P = 0.025$). Individual ANOVA results are also presented for each subregion.

behavioral, self-report, and clinically rated measures of impulsivity were all negatively associated with VS MAO-A V_T. In contrast to previous PET research examining brain MAO-A levels in healthy humans with relatively low trait aggression and impulsivity, the present investigation has the advantage of studying a clinical population with pathological aggression and impulsivity. The results of the present study have important implications for understanding the molecular underpinnings of ASPD and selecting preclinical models to represent ASPD. Our findings also suggest a neuromodulatory role of MAO-A on the impulsive and reward-seeking behavior that typifies ASPD.

Our main finding is that low OFC and VS MAO-A V_T was associated with a disorder characterized by pathological levels of impulsivity and aggression. There are two conceptual models relating lower MAO-A levels to impulsive-aggressive behavior in humans. One involves the very infrequent event of completely deficient MAO-A due to genetic disruption of the MAO-A gene that was identified in impulsively aggressive males from a single Dutch family (Brunner *et al*, 1993). However, subsequent efforts to isolate this mutation in targeted, antisocial populations have been unsuccessful (Schuback *et al*, 1999). To the best of our knowledge, there have been no additional human cases of the non-conservative cytosine to thymine mutation in exon 8 of the MAO-A gene documented in the literature. A second model implicates relative brain MAO-A deficiency as a more common event and potential neuropathological substrate of aberrant impulsivity and aggression. Although this study cannot exclude the possibility that other mutations of a similar magnitude effect occur in ASPD, it does suggest that low brain MAO-A levels are common in ASPD and that low brain MAO-A V_T is a viable target to pursue in therapeutic or preventative strategies.

Our results also have significant ramifications for the relevance of MAO-A knockout strategies to model ASPD and clinical level aggression and impulsivity in humans. For example, in addition to manifesting extreme impulsive aggression (Cases *et al*, 1995; Godar *et al*, 2011; Popova *et al*, 2001; Scott *et al*, 2008), MAO-A knockouts also exhibit cognitive and physiological responses characteristic of ASPD with high psychopathic traits, such as decreased startle reflex (Popova *et al*, 2001), reduced anxiety, impaired risk assessment (Godar *et al*, 2011), and attenuated stress reaction (Popova *et al*, 2006). Although there are several manipulations that can lead to impulsive-aggressive behavior in rodents, a critical issue is whether such models actually translate to the human clinical phenotype. In some cases, the

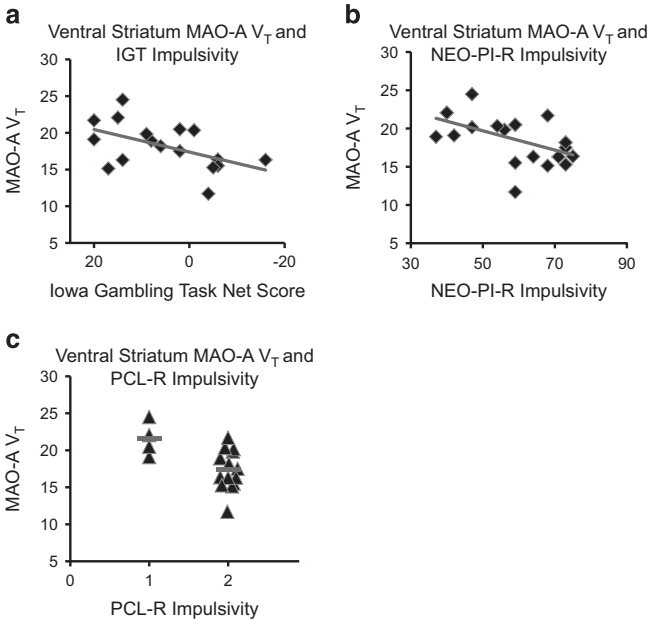

Figure 2 Ventral Striatum MAO-A V_T is Negatively Associated with Measures of Impulsivity in ASPD. (a) Ventral striatum MAO-A V_T is negatively correlated with risky performance during the latter half of the IGT Task (Pearson's $r = -0.52$, $P = 0.034$). (b) Ventral striatum MAO-A V_T is negatively correlated with self-reported impulsivity on the NEO PI-R (Pearson's $r = -0.50$, $P = 0.034$). Note that *x* axis depicts T-scores (a similar significant relationship was found with raw scores). (c) ASPD subjects rated the most impulsive on the PCL-R (PCL-R score = 2) had lower ventral striatum MAO-V_T than subjects rated less impulsive on the PCL-R (PCL-R score = 1) (means (horizontal bars): 17.4 *vs* 21.5; $t_{16} = 2.8$, $P = 0.013$). Note that columns in (c) are labeled according to PCL-R impulsivity score. MAO-A V_T, monoamine oxidase-A total distribution volume; IGT, Iowa Gambling Task; NEO PI-R, NEO Personality Inventory—Revised; ASPD, antisocial personality disorder; PCL-R, Psychopathy Checklist—Revised; ANOVA, analysis of variance.

phenotypes do not match. For instance, 5-HT_{1B} knockout conditions are associated with increased impulsive violence in mice (Saudou *et al*, 1994), but 5-HT_{1B} receptor binding in postmortem prefrontal cortex does not differ between pathologically aggressive and healthy individuals (Huang *et al*, 1999). Moreover, molecular imaging studies find a relationship between lower 5-HT_{1B} receptor expression and internalizing conditions, such as posttraumatic stress disorder and major depressive disorder, that are not, on average, associated with high aggression or impulsivity (Murrough *et al*, 2011a, b). By contrast, the consistency in phenotype between the MAO-A knockout and ASPD with high psychopathic traits (eg, increased aggression, high impulsivity, low anxiety, fearless dominance, and low stress hormones) suggests that the MAO-A knockout is an important model for understanding the pathophysiology of ASPD.

Although a previous investigation of healthy humans reported an association of impulsivity-related measures with OFC MAO-A level, this study differed from the present one in that it tested a non-pathological sample of subjects with normal personality measures (Soliman *et al*, 2011). We interpret our data to mean that MAO-A level in the VS may be more relevant to conditions of pathological impulsivity. It is possible that the neurobiological processes in the VS relating to extreme impulsivity are more affected by lower MAO-A level.

We actually found that VS MAO-A V_T in ASPD was negatively correlated with several measures of impulsivity, including a performance-based assessment and a validated self-report measure, and these results have implications for understanding the potential neuromodulatory influence of MAO-A on impulsive and reward-seeking behavior. Heightened behavioral sensitivity to reward versus punishment is a core feature of ASPD and psychopathy (Mitchell *et al*, 2002; Petry, 2002) underlying the reckless and impulsive behavior of these conditions (Blair, 2008). Mounting evidence suggests that exaggerated dopamine response to highly salient stimuli increases vulnerability to impulsive and reward-seeking behaviors (Leyton and Vezina, 2014). One model of impulsivity in individuals with high antisocial-impulsive psychopathic traits posits that neurochemical hypersensitivity of the mesolimbic dopamine system to rewarding stimuli underlies expression of impulsive and socially deviant behavior (Buckholtz *et al*, 2010). Consistent with this hypothesis, a recent molecular imaging study found that greater VS 6-[^{18}F] fluoro-L-DOPA influx constant, a measure of dopamine synthesis capacity and vesicular storage capacity, was associated with greater behavioral disinhibition (Lawrence and Brooks, 2014). Thus, it has been proposed that individuals at high risk for externalizing conditions have larger amounts of presynaptic dopamine (Lawrence and Brooks, 2014). As dopamine is a high-affinity substrate for MAO-A in humans (O'Carroll *et al*, 1983) and MAO-A inhibition potentiates striatal dopamine efflux (Finberg *et al*, 1995), we interpret the association between lower VS MAO-A V_T and increased impulsivity as supportive of the model linking greater VS presynaptic dopamine efflux and/or reward-based dopamine release to high impulsivity and externalizing behaviors.

Although the present study has the advantage of measuring an index of MAO-A density *in vivo*, it has disadvantages inherent to PET neuroimaging. The resolution of PET precludes investigation of the cellular specificity of changes in MAO-A, which does not allow differentiation of MAO-A between glia and neurons. Another limitation is that MAO-A V_T, while robustly measured with [^{11}C] harmine PET, reflects total MAO-A binding. However, as free and non-specific binding account for only 15% of MAO-A V_T, differences in the measure primarily reflect changes in specific MAO-A binding (Ginovart *et al*, 2006). Finally, similar to the overwhelming majority of studies of ASPD and violent offenders, our sample was limited to males, which may be justified on the basis that ASPD is 5–7 times more common in men than women (Hamdi and Iacono, 2014).

In summary, we found that highly impulsive, violent males with ASPD had lower MAO-A V_T in the OFC and VS. These results suggest that lower MAO-A in these regions is a common occurrence in ASPD and not limited to rare mutations. Our results also highlight the salience of preclinical models exhibiting low brain levels of MAO-A for understanding this clinical condition by demonstrating, to the best of our knowledge, the first clear link between a pathological marker in preclinical investigations of aggression with the same marker in human ASPD. Lower VS MAO-A levels were additionally associated with greater impulsivity, which, given the role of MAO-A in modulating dopamine efflux, suggests

greater complexity to the model linking elevated VS dopamine release to rewarding stimuli in externalizing disorders.

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