MONOAMINE OXIDASE-A IN BORDERLINE PERSONALITY DISORDER AND ANTISOCIAL PERSONALITY DISORDER

by

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ABSTRACT

Monoamine oxidase A (MAO-A) is a brain enzyme that serves several physiologic functions, including metabolism of monoamine neurotransmitters and induction of pro-apoptotic signaling pathways. Increased brain MAO-A level is present in clinical disorders characterized by low mood states, whereas decreased brain MAO-A level is associated with higher trait impulsivity and aggression in healthy volunteers. Borderline personality disorder (BPD) and antisocial personality disorder (ASPD) are common psychiatric conditions that exact a high healthcare and societal burden. BPD is associated with acute episodes of severe dysphoria, and ASPD presents high levels of impulsivity and aggression. The overall aim of the thesis was to investigate MAO-A brain level in BPD and ASPD. The first experiment used [^{11}C] harmine positron emission tomography (PET) to assess MAO-A total distribution volume (MAO-A V_T), an index of MAO-A density, in females with BPD. Our results showed that MAO-A V_T was elevated in the prefrontal cortex (PFC) and anterior cingulate cortex (ACC) of severe BPD compared to control groups. Greater PFC and ACC MAO-A V_T was additionally associated with more severe mood symptoms and suicidality in BPD. The second experiment applied [^{11}C] harmine PET to examine MAO-A V_T in

impulsive, violent male offenders with ASPD. We found that orbitofrontal cortex and ventral striatum (VS) MAO-A V_T were lower in ASPD compared to controls. Behavioral, self-report, and clinician-rated measures of impulsivity were also negatively correlated with VS MAO-A V_T. The third experiment employed functional magnetic resonance imaging to measure VS resting state functional connectivity (FC) in ASPD. Our results demonstrated functional coupling between superior VS and bilateral dorsomedial prefrontal cortex that was correlated with VS MAO-A V_T, and functional coupling between inferior VS and right hippocampus that was anti-correlated with VS MAO-A V_T. The observed FC patterns were additionally associated with measures of impulsivity. Taken together, this body of research implicates abnormal brain MAO-A level in the pathophysiology of two related yet distinct personality disorders and their symptom clusters. Novel interventions targeting abnormal brain MAO-A level could emerge as potential new therapeutics for these disorders.

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ABBREVIATIONS

A	Adenine
Å	Ångström
ACC	Anterior Cingulate Cortex
AD	Alcohol Dependence
AEA	Anandamide
ASPD	Antisocial Personality Disorder
BBB	Blood Brain Barrier
Bcl-2	B-cell Lymphoma 2
BET	Brain Extraction Tool
BP	Base Pair
BIS 11	Barratt Impulsiveness Scale 11
BOLD	Blood Oxygen-Level Dependent
BPD	Borderline Personality Disorder
C	Cytosine
CB1	Cannabinoid Subtype 1 Receptor
CNS	Central Nervous System
DA	Dopamine
DLPFC	Dorsolateral Prefrontal Cortex
DMPFC	Dorsomedial Prefrontal Cortex
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders Fourth Version, Text Revision
DSM-5	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
Δ9-THC	Delta 9-Tetrahydrocannabinol
ECS	Endocannabinoid System
FAAH	Fatty Acid Amide Hydrolase
FC	Functional Connectivity
FFM	Five-Factor Model

FLAME	Functional Magnetic Resonance Imaging of the Brain's Local Analysis of Mixed Effects
FLIRT	Functional Magnetic Resonance Imaging of the Brain's Linear Registration Tool
fMRI	Functional Magnetic Resonance Imaging
FMRIB	Functional Magnetic Resonance Imaging of the Brain
FOV	Field of View
FSL	Functional Magnetic Resonance Imaging of the Brain Software Library
FWHM	Full Width at Half Maximum
G	Guanine
GBq	Gigabecquerel
GE	General Electric
GLM	General Linear Model
Gly	Glycine
HDRS	Hamilton Depression Rating Scale
HRRT	High-Resolution Research Tomograph
5-HT	Serotonin
5-HT_{1B}	Serotonin Subtype 1B Receptor
5-HT_{2}	Serotonin Subtype 2 Receptor
5-HT_{2A}	Serotonin Subtype 2A Receptor
5-HT_{2C}	Serotonin Subtype 2C Receptor
HVLT – R	Hopkins Verbal Learning Test – Revised
ICC	Intraclass Correlation Coefficient
IGT	Iowa Gambling Task
Ile	Isoleucine
IST	Information Sampling Task
KB	Kilobase
Ki	Inhibition Constant
K_m	Michaelis-Menten Constant

KO	Knockout
LSD	Least Significant Difference
MANCOVA	Multivariate Analysis of Covariance
MANOVA	Multivariate Analysis of Variance
MAO	Monoamine Oxidase
MAO-A	Monoamine Oxidase-A
MAO-A D_S	Monoamine Oxidase-A Specific Distribution Volume
MAO-A V_T	Monoamine Oxidase-A Total Distribution Volume
MAO-B	Monoamine Oxidase-B
MAOI	Monoamine Oxidase Inhibitor
MATLAB	Matrix Laboratory
MBq	Megabecquerel
mCi	Millicurie
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
MNI	Montreal Neurological Institute
MPFC	Medial Prefrontal Cortex
MPQ	Multidimensional Personality Questionnaire
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
NA	Not Applicable
NAD	Nicotinamide Adenine Dinucleotide
NE	Norepinephrine
NEO PI-R	NEO Personality Inventory – Revised
NHLH2	Nescient Helix-Loop-Helix 2
NMDAR	N-methyl-D-aspartate Receptor
NR1	N-methyl-D-aspartate Receptor Subtype 1
NR2A	N-methyl-D-aspartate Receptor Subtype 2A
NR2B	N-methyl-D-aspartate Receptor Subtype 2B
OAS-M	Overt Aggression Scale – Modified for Outpatients

OFC	Orbitofrontal Cortex
PCC	Posterior Cingulate Cortex
PCL-R	Psychopathy Checklist – Revised
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
pmol	Picomole
PPD	Postpartum Depression
RCT	Randomized Controlled Trial
ROI	Region of Interest
ROS	Reactive Oxygen Species
SCID I	Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders Fourth Version Axis I Disorders
SCID II	Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders Fourth Version Axis II Personality Disorders
SIRT1	Sirtuin 1
SNP	Single Nucleotide Polymorphism
SP1	Specificity Protein 1
SRY	Sex-Determining Region Y
SSRT	Stop-Signal Reaction Time
SSRI	Selective Serotonin Reuptake Inhibitor
STAXI-2	State Trait Anger Expression Inventory – 2
T	Thymine
TCA	Tricyclic Antidepressant
TE	Echo Time
TN	Tennessee
TR	Repetition Time
TSPO	Translocator Protein
Tyr	Tyrosine
μmol	Micromole

VLPFC	Ventrolateral Prefrontal Cortex
V_{max}	Maximum Rate of Reaction
VMPFC	Ventromedial Prefrontal Cortex
VMAT2	Vesicular Monoamine Transporter 2
VNTR	Variable Nucleotide Tandem Repeat
VS	Ventral Striatum
VSi	Inferior Ventral Striatum
VSs	Superior Ventral Striatum
V_T	Total Distribution Volume
WI	Wisconsin

CHAPTER 1: Introduction

1.1 INTRODUCTION

The role of monoamine oxidase-A (MAO-A) in shaping human personality and increasing vulnerability for psychiatric illness has been the focus of intense scientific interest ever since Mary Hare's discovery in 1928 of an enzyme that could oxidatively metabolize biogenic amines (Hare, 1928). The overall aim of this thesis was to investigate MAO-A brain levels in borderline personality disorder (BPD) and antisocial personality disorder (ASPD) using [^{11}C] harmine positron emission tomography (PET). Following a comprehensive review of the literature that includes a discussion of the structure and function of MAO-A; the relationship of MAO-A to symptoms of depression/dysphoria, aggression, and impulsivity; and the importance of depression/dysphoria in BPD and impulsivity/aggression in ASPD, three studies are presented that describe [^{11}C] harmine PET neuroimaging findings in BPD and ASPD. The first study investigated MAO-A total distribution volume (MAO-A V_T), an index of MAO-A density, in highly dysphoric females with BPD. The second study assessed MAO-A V_T in impulsive, aggressive males ASPD with high psychopathic traits. The third study explored the relationship between MAO-A V_T and functional brain connectivity in ASPD using [^{11}C] harmine PET and resting state functional magnetic resonance imaging (fMRI).

1.2 GENERAL CHARACTERISTICS OF MONOAMINE OXIDASE-A

MAO-A is a mitochondrial-bound flavoprotein that catalyzes the oxidative deamination of biogenic and dietary amines; it, therefore, controls the availability and physiologic activity of amine neurotransmitters and xenobiotics (Fowler, Logan, Volkow, & Wang, 2005). Although MAO-A and the isoenzyme monoamine oxidase-B (MAO-B) derive from a common progenitor ancestral gene, map to the X-chromosome (Xp11.23-11.4), and share 72% sequence homology (Bach et al., 1988; Grimsby, Chen, Wang, Lan, & Shih, 1991; Lan et al., 1989), the MAO-A gene is under different transcriptional regulation than the MAO-B gene, and the two gene products are readily distinguished by their substrate preference, sensitivity to inhibitors, regional distribution, and biological function.

1.2.1 SUBSTRATE SELECTIVITY OF MONOAMINE OXIDASE-A

Several neurotransmitters implicated in mood and impulsivity are substrates for MAO-A in human brain: serotonin (5-HT), norepinephrine (NE), and dopamine (DA) (Youdim, Edmondson, & Tipton, 2006). MAO-A preferentially oxidizes 5-HT and to a lesser extent the catecholamines NE and DA (Shih, Chen, & Ridd, 1999; Tipton, Boyce, O'Sullivan, Davey, & Healy, 2004). Table 1-1 outlines the specificities of 5-HT, NE, and DA for human MAO-A (Youdim, Finberg, & Tipton, 1988).

[Insert Table 1-1]

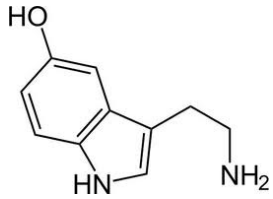
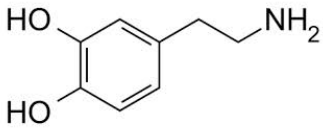
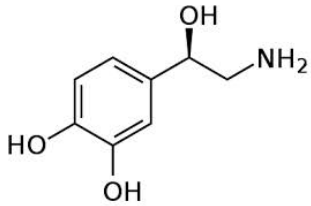
1.2.1.1 SEROTONIN

Several lines of evidence indicate that 5-HT is a high affinity substrate for MAO-A (Fowler & Oreland, 1979; Kinemuchi, 1984; Schoepp & Azzaro, 1981). MAO-A transcripts and protein are detected in rat raphe nuclei (Luque, Kwan, Abell, Da Prada, & Richards, 1995), MAO-A mRNA is found in monkey raphe nuclei (Luque, Bleuel, Hendrickson, & Richards, 1996), and MAO-A enzyme is located in serotonergic nerve terminals of human dorsal raphe nucleus (Konradi et al., 1988). MAO-A clearly influences extracellular levels of 5-HT, as evidenced by a 20-200% increase in extracellular 5-HT, depending on drug, dose, and region, following administration of pharmacologic MAO-A inhibitors (MAOI) (Adell, Biggs, & Myers, 1996; Curet et al., 1998; Fagervall & Ross, 1986; Haefely et al., 1992). Extracellular 5-HT is also highly elevated (100-200%) in prefrontal cortex (PFC), hippocampus, and superior raphe nuclei in the animal knockout (KO) model of MAO-A (Evrard et al, 2002; Cases et al, 1995; Lajard et al, 1999).

1.2.1.2 NOREPINEPHRINE

NE is a high affinity substrate for MAO-A (Houslay & Tipton, 1974), and MAO-A is easily detectable in cells that synthesize NE (Konradi et al., 1989; Konradi et al., 1988; Luque et al., 1995; Saura, Kettler, Da Prada, & Richards, 1992). Under

Table 1: Substrate Specificities of Monoamine Oxidase-A in Human Cerebral Cortex

	Serotonin	Norepinephrine	Dopamine
Chemical Structure			
K_m	137 +/- 24	284 +/- 17	212 +/- 33
V_{max}	228 +/- 31	561 +/- 42	680 +/- 123
V_{max}/K_m	1.66 +/- 0.37	1.98 +/- 0.19	3.21 +/- 0.77

K_m= Michaelis-Menten constant (units = μM); **V_{max}** = maximum rate (units = pmol/mg protein · minutes)
V_{max}/ K_m (units = μmol/ mg protein · M · minutes)
Reference: Youdim *et al*. (1988). *Handbook of Experimental Pharmacology.*

conditions of MAO-A inhibition, extracellular NE is increased in PFC as well as hypothalamus (Fagervall & Ross, 1986; Finberg, Pacak, Goldstein, & Kopin, 1994), which suggests that MAO-A modulates extracellular NE level in these brain regions.

1.2.1.3 DOPAMINE

DA is a high affinity substrate for MAO-A (Fowler & Oreland, 1979; Kinemuchi, 1984; Schoepp & Azzaro, 1981). Administration of MAOI increases extracellular DA in striatum under baseline conditions as well as during precursor loading paradigms (Adachi, Watanabe, Higuchi, Satoh, & Vizi, 2001; Brannan, Prikhojan, Martinez-Tica, & Yahr, 1995; Butcher, Fairbrother, Kelly, & Arbuthnott, 1990; Colzi, d'Agostini, Cesura, & Da Prada, 1992; Colzi, d'Agostini, Kettler, Borroni, & Da Prada, 1990; Finberg, Wang, Goldstein, Kopin, & Bankiewicz, 1995; Segal, Kuczenski, & Okuda, 1992). Immunohistochemical and ligand binding studies reveal a preferential localization of MAO-A to dopaminergic neurons in the substantia nigra in both rodent and primates (Moll et al., 1990; Westlund, Denney, Kochersperger, Rose, & Abell, 1985; Westlund, Krakower, Kwan, & Abell, 1993), although other studies have failed to detect the presence of MAO-A protein in these cells (Konradi et al., 1989; Konradi et al., 1988; Saura et al., 1996; Westlund, Denney, Rose, & Abell, 1988).

1.2.2 INHIBITION SENSITIVITY OF MONOAMINE OXIDASE-A

MAO-A was originally identified as a distinct isoenzyme of MAO based on its sensitivity to inhibition by clorgyline (Johnston, 1968). Clorgyline is an acetylenic inhibitor that, at low concentrations, irreversibly inactivates MAO-A (Johnston, 1968). MAO-A is composed of 527 amino acids and contains a flavin cofactor (Bach et al., 1988). Early work suggested that amino acid segments 161-375 in human MAO-A defined the substrate and inhibitor specificity of MAO-A (Grimsby, Zentner, & Shih, 1996). Site-directed mutagenesis later demonstrated that substitution of Ile-335 in human MAO-A with the corresponding residue in human MAO-B, Tyr-326, alters the substrate and inhibitor sensitivities of the MAO isoenzymes, such that mutant MAO-A is more sensitive to inhibition by deprenyl, a specific MAO-B inhibitor, than clorgyline (Geha, Rebrin, Chen, & Shih, 2001).

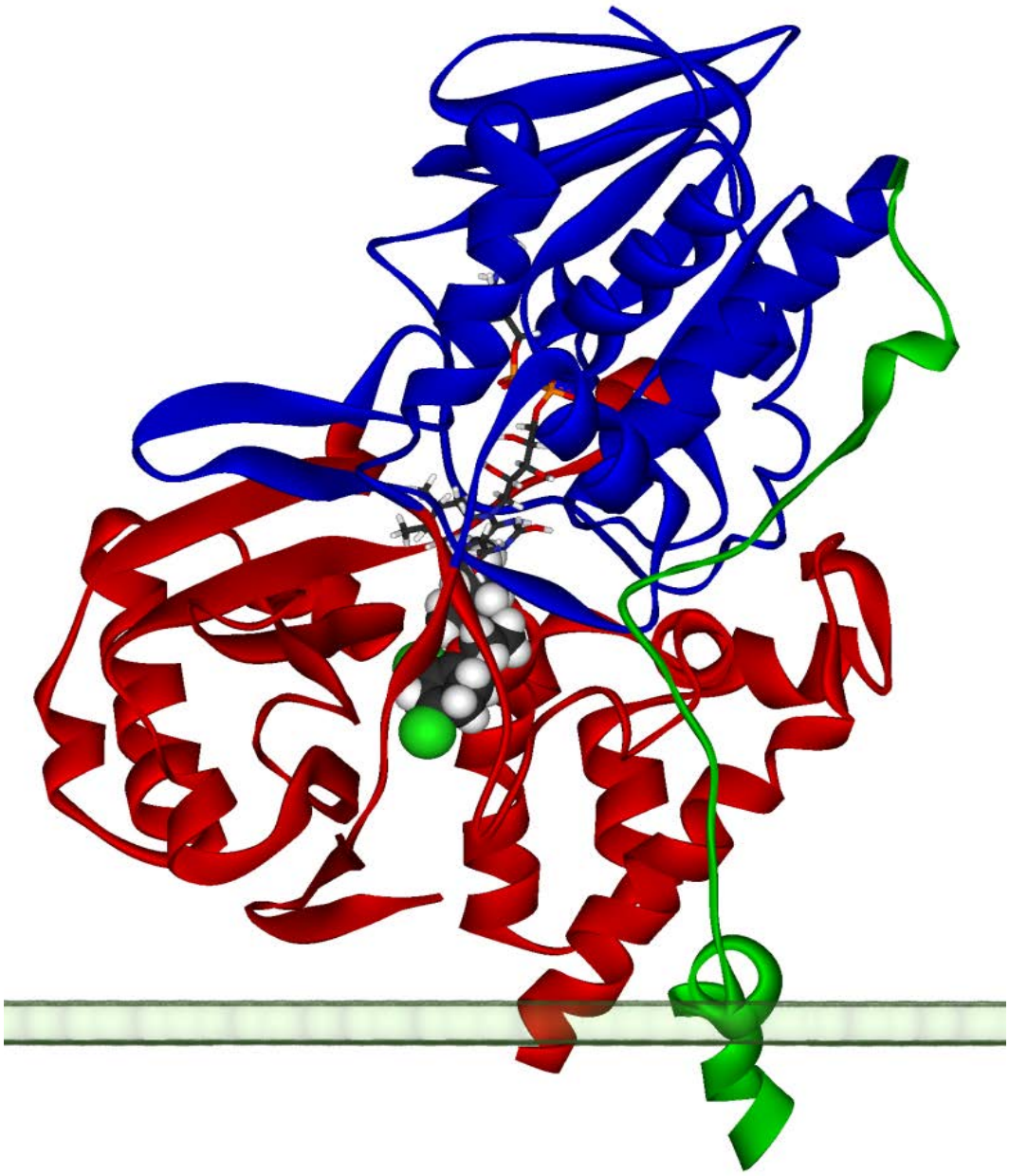
Protein crystallography, molecular modeling, and docking studies subsequently helped clarify observed differences in pharmacokinetics among various inhibitors of MAO-A. Both the crystal structures of MAO-A/clorgyline and MAO-A/harmine enzyme inhibitor complexes have been determined (De Colibus et al., 2005; Son et al., 2008). The inhibitor binding site of human MAO-A includes a monopartite substrate cavity of approximately 550 Å that extends from the flavin cofactor to a loop consisting of residues 210-216 situated at the entrance of the substrate cavity (De Colibus et al., 2005). This “cavity-shaping loop” is thought to influence the shape and volume of the substrate cavity and ultimately the specificity of MAO-A to

different inhibitors (Binda, Mattevi, & Edmondson, 2011; De Colibus et al., 2005). The substrate cavity is lined by 11 aliphatic and five aromatic amino acids (De Colibus et al., 2005). Figure 1-1 depicts a ribbon representation of the MAO-A monomer (De Colibus et al., 2005).

[Insert Figure 1-1]

X-ray crystallography of the inhibitor binding site in human MAO-A revealed that harmine, an irreversible MAO-A inhibitor, interacts with 12 of these amino acids, including Ile-335, as well as the flavin moiety when it is present in the MAO-A active site (Son et al., 2008). Results further demonstrated that human MAO-B is unable to accommodate harmine because of harmine's structural overlap with Tyr-326, the corresponding amino acid residue of Ile-335 in MAO-A. This finding suggests that Ile-335 confers inhibitor selectivity of MAO-A to harmine by restricting the size and shape of the substrate cavity (Son et al., 2008). This same study also showed that mutation of a residue (Gly-110) in loop 108-118, located near the MAO-A substrate cavity entrance, but far from the active site, reduced enzyme activity, which implies that physical integrity of this domain is critical for enabling access of substrate to the active site (Son et al., 2008).

Figure 1-1: Ribbon Representation of Human Monoamine Oxidase-A Monomer



Note: The blue region represents the FAD-binding domain and the N-terminus. The red region represents the substrate-binding domain. The green region represents the C-terminal membrane region. Clorgyline is depicted as the green/grey/white bulbous structure within the substrate-binding domain. FAD is depicted as the ladder-like structure continguous to clorgyline and located within the FAD-binding domain. Source: University of Michigan's Orientations of Proteins in Membranes database

1.2.3 DISTRIBUTION OF MONOAMINE OXIDASE-A IN HUMAN BRAIN

1.2.3.1 FETAL AND POSTNATAL LEVELS OF MONOAMINE OXIDASE-A

Location of MAO-A and its level of expression differ according to developmental stage. MAO-A is the dominant MAO isoenzyme in the developing human brain and is present before MAO-B appears (Lewinsohn, Glover, & Sandler, 1980). However, neither MAO-A nor MAO-B messenger ribonucleic acid (mRNA) expression is detected in striatum, thalamus, or hippocampus in human fetal tissue at 19 weeks gestation (Grimsby, Lan, Neve, Chen, & Shih, 1990). Whereas MAO-B rapidly increases after birth to become the most abundant isoenzyme in adult brain, MAO-A transcripts dramatically decline in the PFC during the first two years of life and remain at constant levels thereafter (Kornhuber et al., 1989; Nicotra, Pierucci, Parvez, & Senatori, 2004), although one recent report found that MAO-A mRNA levels declined across human development, while MAO-A protein levels increased (Rothmond, Weickert, & Webster, 2012). The authors of the study suggested that their results could reflect inefficient translation of mRNA into protein and/or unstable protein levels early in development.

1.2.3.2 ADULT LEVELS OF MONOAMINE OXIDASE-A

In adult brain, MAO-A is principally found in catecholaminergic neurons and to a much lesser extent in glial cells. Enzyme radioautography employing radiolabeled

inhibitors of MAO-A provided initial information on the distribution and amount of MAO-A. Results determined that MAO-A protein is most abundant in the interpeduncular nucleus, periaqueductal grey, pars compacta of the substantia nigra, locus coeruleus, superior cervical ganglion, and ventromedial hypothalamus in human brain (Saura et al., 1996; Saura et al., 1992). *In situ* hybridization histochemistry subsequently identified cells expressing the highest level of MAO-A mRNA in the locus coeruleus, subcoeruleus, and superior cervical ganglion (Saura et al., 1996). PET studies using the radiotracer [^{11}C] clorgyline have also confirmed that *in vivo* levels of MAO-A protein align with MAO-A protein distribution in cadaveric human central nervous system (CNS) (Fowler et al., 1987). Some studies have additionally reported expression of MAO-A transcripts in astrocytes (Konradi et al., 1989; Konradi et al., 1988; Westlund et al., 1988), although MAO-B transcripts are much more commonly found in glial cells (Konradi et al., 1989).

1.2.4 PHYSIOLOGICAL FUNCTIONS OF MONOAMINE OXIDASE-A IN HUMAN BRAIN

1.2.4.1 AMINE DEGRADATION AND PRODUCTION OF HYDROGEN PEROXIDE

Early studies suggested that the primary functions of MAO were to protect neurons from xenobiotics, abort neurotransmitter signaling, and control intracellular stores of amines (Youdim et al., 2006). It was later determined, however, that the by-products

of MAO activity also play key roles in human physiologic and pathologic processes. The oxidation of amines by MAO requires molecular dioxygen and produces aldehyde, ammonia, and hydrogen peroxide, a reactive oxygen species (ROS) (Scrutton, 2004). ROS erode biological macromolecules, such as proteins, nucleic acids, and lipids, through oxidative alterations that result in impaired cellular functioning and cell death (Magder, 2006). In human neuroblastoma cell lines, MAO activity has been shown to increase oxidative stress and induce cell death (Fitzgerald, Ufer, De Girolamo, Kuhn, & Billett, 2007). However, tonic levels of cellular peroxide are necessary to maintain cellular redox homeostasis by regulating intracellular signaling pathways and gene expression in mammals (Ufer, Wang, Borchert, Heydeck, & Kuhn, 2010). The importance of precise peroxide tone regulation during critical developmental periods is exemplified during mammalian embryogenesis, where the hydrogen peroxide generated by MAO-A activity initiates critical cellular signaling pathways and modulates myriad downstream events of these signaling cascades (Ufer et al., 2010). While these data stem from murine models, they may also be applicable to humans. Thus, regulation of hydrogen peroxide production, in part through monoamine metabolism, is critical to cell survival under various conditions. Factors that determine whether generation of hydrogen peroxide is beneficial or deleterious include developmental stage of the organism, baseline cellular concentration of hydrogen peroxide, and activation of signaling pathways capable of countering increased hydrogen peroxide levels (Tang, Liu, et al., 2013).

1.2.4.2 INDUCTION OF APOPTOTIC PATHWAYS

Multiple lines of evidence implicate MAO-A as a pro-apoptotic gene. Apoptosis refers to an energy-driven and highly regulated process of programmed cell death that occurs under both physiologic and pathologic conditions (Elmore, 2007). In neuronal pheochromocytoma cells of rat origin, MAO-A expression increases following withdrawal of nerve growth factor and subsequent induction of apoptosis. From this study, it was determined that inhibition of the pro-apoptotic p38 mitogen-activated protein kinase prevented the increase in MAO-A expression as a result of nerve growth factor withdrawal-induced apoptosis (De Zutter & Davis, 2001). In human melanoma cells of neural crest origin, clorgyline was shown to protect the cell culture from apoptosis secondary to serum starvation, whereas deprenyl pre-treatment did not rescue cells from apoptosis (Malorni et al., 1998), suggesting that the MAO-A isoenzyme is principally involved in apoptotic signaling pathways. In a human neuroblastoma cell line (B-cell lymphoma 2 – Bcl-2) that expresses MAO-A but not MAO-B, binding of a dopaminergic neurotoxin to MAO-A activated mitochondrial apoptotic signaling (Yi et al., 2006), while, in another study, MAO-A mRNA was increased in human neuroblastoma SK-N-BE(2)-C cells subjected to serum starvation-induced apoptosis (Ou, Chen, & Shih, 2006b). Furthermore, reduced levels of apoptosis were demonstrated in cortical cells from MAO-A KO mice but not MAO-A KOs after primary cultures were serum-starved (Ou et al., 2006b). Finally, the reversible, selective MAOI, moclobemide, was shown to up-regulate levels of the anti-apoptotic protein Bcl-2 in neural stem cells from rat

hippocampal tissue (Chiou et al., 2006). Results of these *in vitro* investigations in neuronal cell lines suggest that MAO-A may participate in the regulation of apoptotic mechanisms.

1.2.5 TRANSCRIPTION REGULATION OF THE MONOAMINE OXIDASE-A GENE

1.2.5.1 SPECIFICITY PROTEIN 1 AND R1

The MAO-A gene consists of 15 exons and resides on band Xp11.23 and possibly band Xp22.1 of the short arm of the X-chromosome (Lan et al., 1989). MAO-A promoter activity has been localized to a 0.14-kb region (-303/-64); the MAO-A core promoter region lacks a TATA box, contains four specificity protein 1 (Sp1) binding sites, and displays bi-directional promoter activity (Zhu, Chen, & Shih, 1994). Sp1 is a transcriptional factor that exerts strong control over MAO-A expression through its interaction with Sp1 binding sites (Zhu et al., 1994). Cellular concentration of Sp1 is positively associated with both MAO-A promoter activity and MAO-A mRNA level (Zhu et al., 1994). By contrast, R1 is a transcriptional repressor protein that competes with Sp1 for Sp1 binding sites and represses activation of the MAO-A promoter *in vitro* and *in vivo* (Chen, Ou, Chen, Choi, & Shih, 2005). R1 is widespread in the human brain and located in the cell nucleus and cytosol. In addition to repressing MAO-A promoter activity, R1 has also been shown to down-regulate MAO-A enzyme activity when overexpressed in neuronal

cell lines (Chen et al., 2005), suggesting that it plays an important role in the negative regulation of MAO-A gene expression.

1.2.5.2 SEX-DETERMINING REGION Y

A transcription factor encoded by the sex-determining region Y (SRY) gene, which is located on the Y-chromosome and regulates initiation of testis development during embryogenesis (Wilhelm, Palmer, & Koopman, 2007), stimulates MAO-A promoter and enzyme activity by interacting with SRY-binding sites in the MAO-A promoter region. In a human male neuroblastoma cell line, Sp1 was shown to potentiate SRY activation of the MAO-A promoter in dose-dependent fashion and, together with SRY, form a transcriptional regulatory complex within the MAO-A core promoter region that facilitated SRY binding to the promoter (Wu, Chen, Li, Lau, & Shih, 2009). It has been proposed that regulation of an X-encoded gene (MAO-A) by a Y-encoded transcription factor (SRY) provides a mechanism for sexual dimorphism in CNS development and manifestation of neuropsychiatric illness associated with abnormal MAO-A (Wu et al., 2009).

1.2.5.3 GLUCOCORTICOIDS

Glucocorticoids up-regulate MAO-A gene expression by mobilizing their receptors to bind to the glucocorticoid response element in the MAO-A promoter region (Ou, Chen, & Shih, 2006a). Prolonged exposure to glucocorticoids has been linked to

elevated MAO-A protein level, expression, and enzyme activity in animal and cell models. Adult male Sprague Dawley rats administered dexamethasone, a synthetic glucocorticoid, for 26 days showed a 300% elevation of frontal and parietal cortex MAO-A activity (Slotkin, Zhang, McCook, & Seidler, 1998). Human skin fibroblasts treated with dexamethasone or hydrocortisone for five days resulted in a 6- to 14-fold increase in MAO-A activity (Edelstein & Breakefield, 1986), while human myocytes exposed to dexamethasone for seven days displayed increased MAO-A mRNA and protein levels (Manoli et al., 2005). Finally, human neuronal and glial cell lines treated with dexamethasone for 24 but not 12 hours yielded increased MAO-A gene expression (Ou et al., 2006a). These results coincided with the observation that R1 translated into the cell nucleus after 12 hours of treatment but returned to the cytosol following 24 hours of treatment.

1.2.6 MONOAMINE OXIDASE-A GENETIC POLYMORPHISMS

A 30-bp variable nucleotide tandem repeat (VNTR) polymorphism located 1.2 kb upstream of the transcription start site in the human MAO-A promoter region (Sabol, Hu, & Hamer, 1998) has attracted considerable attention in psychiatric genetics research. A VNTR is a sequence of nucleotides in the genome composed of tandem repeats that represent a single locus (Nakamura et al., 1987). The 30-bp MAO-A VNTR is present in multiple copies: 2, 3, 3.5, 4, 5, or 6 (Huang et al., 2004). The number of 30-bp copies has been shown to influence MAO-A promoter activity and transcriptional efficiency in an allele-specific manner. For example,

alleles with 3.5 or 4 copies are transcribed 2-10 times more efficiently *in vitro* than alleles containing 3 or 5 copies of the 30-bp sequence (Sabol et al., 1998). Other repeated nucleotide sequences in the promoter region of the human MAO-A gene have been identified (Zhu & Shih, 1997; Zhu, Grimsby, Chen, & Shih, 1992), but none was found to be variable.

Several other polymorphisms in the human MAO-A gene have been described in the literature, including a $(AC)_{18}CG(AC)_3$ dinucleotide sequence in the second intron (Black, Chen, Craig, & Powell, 1991); a 23-bp VNTR motif and dinucleotide repeat near exon 1 (Hinds, Hendriks, Craig, & Chen, 1992); and a single dinucleotide substitution in the coding sequences of MAO-A cDNA (T → G substitution at position 941), where the G allele is associated with a 30-fold increase in MAO-A activity compared to the T allele (Hotamisligil & Breakefield, 1991).

1.3. MONOAMINE OXIDASE-A AND PSYCHIATRIC SYMPTOMS

Converging evidence from *in vitro* and *in vivo* investigations highlights an association of MAO-A genetic variants and enzyme levels with common psychiatric symptoms, such as depressed mood, dysphoria, impulsivity, and aggression. These symptom clusters are frequently observed in individuals with BPD and ASPD. This section considers neuroimaging and genetic results from animal and human research that link symptom expression to specific MAO-A genotypes and phenotypes.

1.3.1 MONOAMINE OXIDASE-A IN DEPRESSION AND DYSPHORIA

1.3.1.1 HUMAN STUDIES OF MONOAMINE OXIDASE-A, DEPRESSION, AND DYSPHORIA

1.3.1.1.1 CLINICAL STUDIES LINKING ELEVATED MONOAMINE OXIDASE-A TO DEPRESSION

The identification of MAO-A as a key enzyme in the pathophysiology of depressive disorders came about as a result of serendipity. In the early 1950s, physicians observed that the anti-tubercular agent iproniazid, a derivative of the hydrazine compound isocarboxazid, produced elevated mood in their tuberculosis patients with comorbid depression (Lopez-Munoz & Alamo, 2009). Contemporaneous with this unexpected observation, a team of basic scientists at Northwestern University Medical School reported on iproniazid's mechanism of action that involved inhibition of MAO (Zeller, 1952). These findings spurred Nathan S. Kline and colleagues to conduct the first clinical trial of iproniazid, whose results demonstrated that iproniazid improved depressive symptomatology in 70% of the depressed subjects enrolled in their study (Loomer, 1958). One year later, over 400,000 depressed individuals had been treated with iproniazid (Sneader, 1985). The development of novel compounds that offered greater inhibition of MAO soon followed and included the MAOIs tranylcypromine, phenelzine, and isocarboxazid. Once it was discovered that inhibition of the MAO-A isoenzyme was primarily

responsible for the antidepressant effects of these MAOIs, molecules that selectively inhibited MAO-A, displayed reversibility, and/or allowed for competitive inhibition of MAO-A were actively pursued, in the hope of obviating unwanted side effects and potentially lethal interactions with tyramine-containing foodstuffs characteristic of the classical MAOIs (Youdim, 1972). Moclobemide and brofaromine were two such reversible and selective inhibitors of MAO-A that were developed (Lecrubier & Guelfi, 1990; Volz, Gleiter, Waldmeier, Struck, & Moller, 1996).

Clinical trials have consistently shown that tranylcypromine, phenelzine, and isocarboxazid are as effective as tricyclic antidepressants (TCAs) in treating major depressive disorder (MDD) (Thase, Trivedi, & Rush, 1995). Furthermore, approximately half of all patients resistant to TCAs ultimately respond to MAOIs (McGrath et al., 1993; Thase, Frank, Mallinger, Hamer, & Kupfer, 1992). Together, these and other studies advanced the monoamine hypothesis of major depression (Schildkraut, 1965) by highlighting the influence of elevated MAO-A as a likely pathology in depressive illness. MAOIs may be particularly efficacious for atypical depression (e.g., symptoms of hyperphagia, hypersomnia, hypersensitivity to rejection, and leaden paralysis) and appear to offer higher remission rates than TCAs for this subtype of depression (Henkel et al., 2006; Stewart, 2007). A meta-analysis of 66 trials that tested moclobemide for the treatment of various subtypes of depression similarly confirmed the efficacy of this agent (Lotufo-Neto, Trivedi, & Thase, 1999), providing additional support for the involvement of MAO-A in the pathophysiology of depressive disorders.

1.3.1.1.2 POSTMORTEM STUDIES OF MONOAMINE OXIDASE-A

Although one postmortem study found an increase in hypothalamus MAO-A activity in suicide victims (Sherif, Marcusson, & Oreland, 1991), other investigations have reported contrary results. One study found reduced MAO-A activity in suicides, particularly those with alcoholism (Gottfries, Oreland, Wiberg, & Winblad, 1975), while another investigation found no difference between suicide victims and healthy controls (Grote, Moses, Robins, Hudgens, & Croninger, 1974). As the latter two studies included many individuals who had died from drug overdose or carbon monoxide poisoning, these exposures may have affected measurement of MAO-A (Mann & Stanley, 1984). The literature includes another postmortem investigation of suicide victims that reported no alteration in frontal lobe MAO-A enzyme kinetics between suicides and controls (Mann & Stanley, 1984). However, it is unclear what proportion of suicide victims suffered from mood disorders, as the authors acknowledged that they did not have sufficient information to make retrospective psychiatric diagnoses.

1.3.1.1.3 MOLECULAR IMAGING STUDIES OF MONOAMINE OXIDASE-A IN DEPRESSION

A substantial body of PET neuroimaging evidence has accumulated in recent years that highlights the importance of increased brain MAO-A level in the pathophysiology of MDD, major disorder episodes (MDEs), conditions with sad or

dysphoric mood states, and physiologic states in females predisposing to depressive illness (Bacher et al., 2011; Chiuccariello et al., 2014; Matthews et al., 2013; Meyer et al., 2006; Meyer et al., 2009; Rekkas et al., 2014; Sacher et al., 2014; Sacher et al., 2010). These studies have in common the careful selection of clinical participants who were rigorously evaluated for the condition under investigation and who were all non-smoking, non-substance using, free of comorbid psychiatric illness, and largely medication-free. Specific study details are outlined in Table 1-2.

[Insert Table 1-2]

1.3.1.1.3.1 [^{11}C] HARMINE POSITRON EMISSION TOMOGRAPHY

As [^{11}C] harmine demonstrates the properties of an excellent PET radiotracer for MAO-A, it was the radiotracer used in the above-mentioned studies. The properties of [^{11}C] harmine that make it appealing as a PET radiotracer for MAO-A include its significant uptake in human brain (Bergstrom, Westerberg, Nemeth, et al., 1997; Ginovart et al., 2006), polar metabolites (Tweedie & Burke, 1987), and high affinity (K_i = 2nM) for the MAO-A enzyme (Bergstrom, Westerberg, & Langstrom, 1997). [^{11}C] Harmine is also highly selective for MAO-A. For example, the affinity of [^{11}C] harmine for MAO-A is three orders of magnitude higher than its affinity for MAO-B (Bergstrom, Westerberg, & Langstrom, 1997). Its uptake is highest in brain regions with high MAO-A density and lowest in regions with low MAO-A density, such as white matter (Bergstrom, Westerberg, Nemeth, et al., 1997). Furthermore,

Table 1-2: [^{11}C] Harmine Positron Emission Tomography Studies of Monoamine Oxidase-A and Depression/Dysphoria

Study	Participants	Participant Criteria	Outcome Measure	Main Results
Meyer *et al* (2006)	17 subjects with MDD; 17 healthy controls	**Common:** non-smoking; no drug use or history of neurotoxin exposure; not in menopause or perimenopause (for women); no BPD or ASPD; **MDD**: current MDE with no comorbid axis I condition; **Healthy**: no axis I condition	MAO-A DV_S in PFC, ACC, PCC, caudate, putamen, thalamus, anterior temporal cortex, midbrain, hippocampus, and parahippocampus	• Significant elevation of MAO-A DV_S in all regions sampled in MDD versus controls • Average 34% elevation of MAO-A DV_S across entire brain in MDD versus controls
Meyer *et al* (2009)	16 subjects with MDE (scanned twice: before and after SSRI treatment); 18 subjects with MDD in recovery; 28 healthy subjects	**Common:** non-smoking; no drug use or history of neurotoxin or antipsychotic exposure; not in menopause or perimenopause (for women); no BPD or ASPD; **MDE**: current MDE; score $\geq$ 20 on 17-item HDRS; no antidepressant treatment in 6 months prior to scan; no comorbid axis I condition; **Recovered MDD**: no MDE or antidepressant use in past year; HDRS $\leq$ 7; no history of psychosis, bipolar disorder, drug or alcohol abuse; no history of self-harm behavior outside of MDE; **Healthy**: no axis I condition	MAO-A V_T in PFC, ACC, PCC, dorsal putamen, VS, thalamus, anterior temporal cortex, midbrain, and hippocampus	• Significant elevation of MAO-A V_T in all brain regions during MDE and after 6 weeks of SSRI treatment versus healthy subjects • Significant elevation of MAO-A V_T in all brain regions in recovered MDD versus healthy controls • Higher PFC and ACC MAO-A V_T in recovered MDD who went on to have subsequent MDE versus those who did not

Table 1-2 (Continued): [^{11}C] Harmine Positron Emission Tomography Studies of Monoamine Oxidase-A and Depression/Dysphoria

Study	Participants	Participant Criteria	Outcome Measure	Main Results
Sacher *et al* (2010)	15 females who were 4-6 days postpartum; 15 females who were not postpartum	**Common:** non-smoking; no drug use; no history of neurotoxin exposure; no history of axis I psychiatric illness	MAO-A V_T was measured in PFC, ACC, anterior temporal cortex, dorsal putamen, thalamus, hippocampus, and midbrain	• Significant elevation of MAO-A V_T in all regions sampled in postpartum women versus non-postpartum women • Average 43% elevation of MAO-A V_T across entire brain in postpartum state versus non- postpartum
Bacher *et al* (2011)	24 healthy non-smokers; 24 otherwise healthy cigarette smokers	**Common:** no history of neurotoxin exposure; not in perimenopause or menopause (for women); no axis I psychiatric disorder other than nicotine dependence in smokers; no ASPD or BPD; no history of psychotropic medication use	MAO-A V_T was measured in PFC and ACC	• In heavy smokers, PFC and ACC MAO-A V_T was greater during cigarette smoking withdrawal versus during active, heavy smoking • PFC and ACC MAO-A V_T was greater in heavy smokers during withdrawal than PFC and ACC MAO-A V_T in non-smokers • The change in MAO-A V_T between withdrawal and active, heavy smoking covaried with severity of depression

Table 1-2 (Continued): [^{11}C] Harmine Positron Emission Tomography Studies of Monoamine Oxidase-A and Depression/Dysphoria

Study	Participants	Participant Criteria	Outcome Measure	Main Results
Matthews *et al* (2013)	16 participants with AD; 16 healthy controls	**Common:** non-smoking; no drug use; not in perimenopause or menopause or postpartum (for women) **AD:** 5 drinks/day for men or 4 drinks/day for women for 5 days of the week; no alcohol-induced neurological disease; **Healthy:** no axis I psychiatric disorder; no significant alcohol use	MAO-A V_T in PFC	• Significant elevation of PFC MAO-A V_T in AD versus healthy controls • Greater duration of drinking correlated with PFC MAO-A • Greater MAO-A V_T in PFC and ACC associated with greater depressed mood and anger/hostility in AD
Chiuccariello *et al* (2014)	42 individuals with MDE secondary to MDD; 37 healthy controls	**Common:** age 18-50 years; non-smoking; no drug use; no ASPD or BPD; not in perimenopause or postmenopause (for women) **MDE:** onset of MDE prior to age 45; 14 ≥ on the 17-item HDRS; no comorbid axis I psychiatric illness; no psychotropic medication use in past 8 weeks, except for SSRIs (use in past 2 weeks permitted); **Healthy:** no axis I psychiatric disorder	MAO-A V_T in PFC and ACC	• Greater depression severity (HDRS ≥ 20) was associated with elevated MAO-A V_T in PFC and ACC compared with less severe depression (HDRS < 20) • MDE with reversed neurovegetative symptoms of MDE (e.g., hypersomnia, hyperphagia, weight again) was associated with greater MAO-A V_T in PFC and ACC than MDE without atypical symptoms

Table 1-2 (Continued): [^{11}C] Harmine Positron Emission Tomography Studies of Monoamine Oxidase-A and Depression/Dysphoria

Study	Participants	Participant Criteria	Outcome Measure	Main Results
Rekkas *et al* (2014)	19 young reproductive age women; 27 women in perimenopause; 12 women in menopause	**Common:** no past or current psychiatric illness; no medication use in past 8 weeks; no smoking or drug use; no history of suicide attempt; no pregnancy or abortion in past 6 months; no oral contraceptive use in past 2 months or history of hormone replacement therapy, treatment with bioidentical hormones, or hysterectomy	MAO-A V_T in PFC, ACC, dorsal striatum, VS, thalamus, hippocampus, midbrain	• Significant elevation of MAO-A V_T in all sampled regions in perimenopause versus menopause or reproductive age • Within perimenopause group, tendency to cry was positively associated with PFC MAO-A V_T
Sacher *et al* (2014)	15 females with first-onset PPD; 12 postpartum females who cry due to sad mood; 15 asymptomatic postpartum women; 15 healthy women not recently pregnant	**Common:** age 18-50 years; non-smoking; no drug use; no ASPD or BPD; not in perimenopause or postmenopause (for women) **MDE:** onset of MDE prior to age 45; 14 ≥ on the 17-item HDRS; no comorbid axis I psychiatric illness; no psychotropic medication use in past 8 weeks, except for SSRIs (use in past 2 weeks permitted); **Healthy:** no axis I psychiatric disorder	MAO-A V_T in PFC, ACC, dorsal striatum, VS, thalamus, hippocampus, and midbrain, with a focus on the first two regions	• Greater PFC and ACC MAO-A V_T in PPD and crying groups compared with asymptomatic postpartum group

displacement studies in baboons using MAO-A selective inhibitors show complete displacement of [^{11}C] harmine in regions with high MAO-A density (Bergstrom, Westerberg, Kihlberg, & Langstrom, 1997), and [^{11}C] harmine binding is also inhibited by other MAOIs, including clorgyline, esuprone, brofaromine, and Ro 41-1049 (Bergstrom, Westerberg, Kihlberg, et al., 1997). In humans, one week of treatment with moclobemide at a daily dose of 600 mg reduces MAO-A specific binding by 75% (Ginovart et al., 2006).

1.3.1.1.3.2 MONOAMINE OXIDASE-A TOTAL DISTRIBUTION VOLUME

MAO-A V_T is measured using [^{11}C] harmine PET. MAO-A V_T is equivalent to the ratio of tissue-to-plasma concentration of [^{11}C] harmine at equilibrium. Approximately 85% of [^{11}C] harmine radioligand is specifically bound to MAO-A at equilibrium (Ginovart et al., 2006); thus, fluctuations in MAO-A V_T can be interpreted as signifying changes in harmine binding to MAO-A. MAO-A V_T can also be described using the following rate parameters: $(K_1/k_2) \times (k_3/k_4) + (K_1/k_2)$, where K_1 and k_2 represent influx and efflux rate parameters, respectively, for passage of harmine across the blood brain barrier (BBB), and k_3 and k_4 denote transfer of harmine between the free and/or nonspecific compartment and the specific binding compartment (Ginovart et al., 2006). MAO-A V_T is measured reliably and validly using the Logan model with arterial sampling or an unconstrained two-tissue compartment model. The Logan model (Logan et al., 1990) was the technique applied in the [^{11}C] harmine PET studies to investigate

brain MAO-A V_T in MDD, MDE, dysphoric mood states, and high risk physiological conditions (Bacher et al., 2011; Chiuccariello et al., 2014; Matthews et al., 2013; Meyer et al., 2009; Rekkas et al., 2014; Sacher et al., 2014; Sacher et al., 2010).

Increased MAO-A V_T in PFC and anterior cingulate cortex (ACC) is a common finding not only in the studies that specifically investigated MDE/MDE (Chiuccariello et al., 2014; Meyer et al., 2009; Sacher et al., 2014) but also those that examined dysphoric states associated with substance misuse (Bacher et al., 2011; Matthews et al., 2013) and physiological states at high risk for MDE in females (Rekkas et al., 2014; Sacher et al., 2010). Several explanations for the increase in PFC and ACC MAO-A V_T observed in these conditions have been proffered. First, MAO-A density is correlated with monoamine metabolism (Youdim et al., 2006), and monoamine loss as a result of acute monoamine depletion or protracted removal with reserpine induces depressed mood (Freis, 1954; Laruelle et al., 1997; Leyton et al., 1997; Neumeister et al., 2004; Verhoeff et al., 2002; Young, Smith, Pihl, & Ervin, 1985). Second, MAO-A plays a role in pro-apoptotic pathways (Youdim et al., 2006), and abnormal expression of pro-apoptotic genes has been reported in the PFC of depressed individuals (Shelton et al., 2011).

1.3.1.1.4 GENETIC STUDIES OF MONOAMINE OXIDASE-A AND DEPRESSIVE ILLNESS

The association between several functional variants of the MAO-A gene (CA-repeat microsatellite in intron 2 and 23-bp VNTR polymorphisms) and bipolar disorder is supported by meta-analysis (Furlong et al., 1999). Additionally, an association study reported increased frequency of the G/T silent polymorphism at position 941 and the high activity allele of the 30-bp MAO-A VNTR in BPD, an illness that is highly comorbid with MDD (Zanarini, Frankenburg, Dubo, et al., 1998) and features acute episodes of intense dysphoria (Ni et al., 2007).

More recent studies have examined the relationship between psychiatric illnesses characterized by depressive symptoms and genes controlling MAO-A transcription. Over 3,200 Swiss adults were randomly selected in one study, genotyped for 14 single nucleotide polymorphisms (SNPs) of the sirtuin 1 (SIRT1) gene, and screened for anxiety disorders (Libert et al., 2011). SIRT1 is an NAD-dependent protein that influences brain metabolism and stimulates transcription of the MAO-A gene by deacetylating a transcription factor bound to the MAO-A promoter (Chen et al., 2008; Libert et al., 2011). Anxiety disorders were found to be associated with several of the SIRT1 SNPs. Additionally, a trend association was observed between one SIRT1 SNP and history of MDD; an independent sample of Japanese subjects provided confirmatory evidence of a positive association between SIRT1 and MDD (Kishi et al., 2010). Results of these epidemiologic and case-control studies indicate

that genes activating MAO-A transcription may be associated with internalizing disorders.

1.3.1.2 ANIMAL STUDIES OF MONOAMINE OXIDASE-A AND DEPRESSIVE SYMPTOMS

1.3.1.2.1 PRECLINICAL STUDIES OF MONOAMINE OXIDASE-A AND DEPRESSIVE SYMPTOMS

MAO-A KO models exploited to investigate the relationship of MAO-A to impulsive, aggressive behavior (reviewed in detail below) have also found associations between deficient MAO-A expression and/or activity and the absence of depressive symptomatology, suggesting, perhaps, that MAO-A deficiency could be protective against low mood states. For example, Tg8 MAO-A KO mice exhibit low levels of depressive symptoms during the forced swim test (Cases et al., 1995).

Additional preclinical studies report elevated MAO-A mRNA levels in raphe nuclei (Filipenko, Beilina, Alekseyenko, Dolgov, & Kudryavtseva, 2002) and increased MAO-A expression and catalytic activity in the thalamus and PFC of rats subjected to chronic social defeat stress (Grunewald et al., 2012). A transgenic mouse strain engineered to over-express SIRT1 exhibited greater anxiety behaviors compared to wild-type and showed more depressive-like behaviors during the forced swim test (Libert et al., 2011). These behaviors were accompanied by increased brain MAO-A

mRNA and protein that could be reduced by administration of phenelzine. Further experimentation revealed that SIRT1 activates MAO-A transcription by deacetylating a transcription factor, nescient helix-loop-helix 2 (NHLH2), in the MAO-A promoter region (Grunewald et al., 2012).

Another investigation reported that Rines, a member of ubiquitin proteasomal system that regulates synaptic plasticity through ubiquination, also influences MAO-A protein level and anxiety-like behaviors (Kabayama et al., 2013). Compared with non-mutants, Rines KO mice were reported to display increased anxiety-like behaviors upon exposure to novel, unpainful sensory stimuli and altered stress reactivity during the forced swim test. Increased levels of MAO-A mRNA and protein were detected in the locus coeruleus of the mutant mouse strain but not in the other brain regions assayed, which included the raphe nuclei, substantia nigra, PFC, and amygdala. Treatment of the Rines KOs with MAOIs ameliorated anxiety-like behaviors in the KOs, suggesting that enhanced anxiety and emotional reactivity in the mutant model may have been mediated by increased brain MAO-A (Kabayama et al., 2013).

1.3.2 MONOAMINE OXIDASE-A IN IMPULSIVITY AND AGGRESSION

1.3.2.1 HUMAN STUDIES OF MONOAMINE OXIDASE-A, IMPULSIVITY, AND AGGRESSION

1.3.2.1.1 MONOAMINE OXIDASE-A GENETIC MUTATION

A rare, non-conservative point mutation of cytosine (C) to T that converts a glutamine amino acid to a stop codon at position 936 of the eighth exon of the human MAO-A gene has been identified (Brunner, Nelen, Breakefield, Ropers, & van Oost, 1993; Brunner, Nelen, van Zandvoort, et al., 1993). Males from a large Dutch family with this lesion displayed a common phenotype of mild intellectual disability and impulsive, aggressive behavior that subsequently became known as "Brunner syndrome." Cultured fibroblasts from affected individuals showed "negligible amounts of apparent MAO-A activity" (Brunner, Nelen, Breakefield, et al., 1993, pg. 579) compared with normal baseline MAO-A activity observed in two, healthy unrelated controls and the low-moderate levels of MAO-A activity seen in two carrier females and one non-carrier female from the same pedigree. The study investigators ultimately concluded that this mutation results in complete and selective deficiency of MAO-A among male carriers (Brunner, Nelen, Breakefield, et al., 1993).

Affected males in the Dutch kindred were described as exhibiting a "tendency toward aggressive outbursts, often in response to anger, fear, or frustration" (Brunner, Nelen, Breakefield, et al., 1993, pg. 579). Examples of aggressive-impulsive behaviors exhibited by men with the mutation included arson, voyeurism, exhibitionism, and rape. Several investigators have commented on the inadequate clinical assessment of the cognitive and behavioral phenotype of the affected males in this study (Hebebrand & Klug, 1995). It is also worth noting that subsequent investigations have failed to detect the same MAO-A gene mutation in targeted samples of men with intellectual disabilities or those receiving treatment at sexual disorders clinics (Schuback et al., 1999).

1.3.2.1.2 MONOAMINE OXIDASE-A GENETIC POLYMORPHISMS

Since publication of a population cohort study reporting that risk of violence was increased in males exposed to childhood maltreatment who also carried MAO-A VNTR polymorphisms associated with low transcription activity (Caspi et al., 2002), several meta-analyses have replicated this gene-by-environment interaction in antisocial and conduct-disordered populations (Byrd & Manuck, 2014; Kim-Cohen et al., 2006; Taylor & Kim-Cohen, 2007). These studies indicate that in general population samples, the combination of lower MAO-A gene expression in non-neuronal human cell lines and a history of early adverse experiences is related to increased risk of conduct-disordered and antisocial behaviors in males. Important to note, however, is that the MAO-A genotype conferring high or low transcriptional

efficiency has not been found to correlate with *in vivo* brain levels of MAO-A assessed using PET (Fowler et al., 2007) or *in vitro* levels of MAO-A measured in human postmortem samples (Balciuniene, Emilsson, Oreland, Pettersson, & Jazin, 2002), leading to the conclusion that variability of MAO-A protein in human brain is not likely regulated to a significant degree by the MAO-A 30-bp VNTR. More recent evidence suggests that the methylation status of the MAO-A core promoter region may influence brain MAO-A levels (Shumay, Logan, Volkow, & Fowler, 2012).

1.3.2.1.3 MONOAMINE OXIDASE-A NEUROIMAGING STUDIES

1.3.2.1.3.1 POSITRON EMISSION TOMOGRAPHY STUDIES

Two PET studies have reported findings on the relationship between MAO-A brain levels and impulsive/aggressive traits in healthy humans. The first study (Alia-Klein et al., 2008) used the radiopharmaceutical [^{11}C] clorgyline to estimate MAO-A activity using a three-compartment model that yields λk_3, an index of catalytically active MAO-A. Regions of interest (ROI) were manually drawn for each participant on a composite image of the summed time frames and then projected onto the dynamic scan to acquire time-activity curves. Twenty-seven, non-smoking males were scanned and completed the Multidimensional Personality Questionnaire (MPQ) (Tellegen, 1997), a self-report instrument pinpointing clusters of personality traits related to longstanding behavioral patterns.

Personality data indicated that subjects generally reported low levels of aggression (mean ± standard deviation = 5.52 ± 3.4; range = 0-12), where the range for the aggression subscale score is 0 to 20. Study investigators reported significant negative correlations between MAO-A enzymatic activity in several cortical (frontal cortex, medial prefrontal cortex [MPFC], precuneus, occipital cortex, and temporal cortex) and subcortical (putamen and thalamus) regions and aggression subscale scores after correction for multiple comparisons. None of the other MPQ subscales were significantly correlated with MAO-A level in any region. Uncorrected independent samples *t*-tests found significant differences in MPFC MAO-A λk_3 between the four most aggressive subjects in the sample (one standard deviation about the mean) and the five least aggressive (one standard deviation below the mean). Neither trait aggression nor MAO-A λk_3 differed as a function of MAO-A genotype (high versus low activity alleles based on 30-bp sequences of the MAO-A VNTR). Despite the relatively small number of participants with moderate or high levels of aggression, this study was the first to identify brain MAO-A enzymatic activity as a potential intermediate phenotype of aggressive behavior (Alia-Klein et al., 2008).

The second PET study to examine MAO-A binding in relation to personality traits (Soliman et al., 2011) used [^{11}C] harmine to quantify MAO-A V_T in 37 healthy males and females. In contrast to [^{11}C] clorgyline, which is irreversible and whose blood flow (e.g., ligand delivery) cannot be separated from MAO-A measurement (Fowler et al., 2001), [^{11}C] harmine, as noted above, is reversible and insensitive to

artifacts of blood flow (Ginovart et al., 2006). Participants completed the NEO Personality Inventory-Revised (NEO PI-R), a well-validated personality measure based on the five-factor model (FFM) of personality that indexes normal to pathological personality traits (Costa Jr., 1992). It was hypothesized that PFC MAO-A V_T would correlate with the facet measuring anger/hostility.

NEO PI-R results confirmed that all personality measures were in the normal range. Consistent with the study hypothesis, anger/hostility was found to be highly negatively correlated with PFC MAO-A V_T. Regression analyses subsequently determined that a two-factor model consisting of the personality facets anger/hostility and deliberation best described MAO-A binding in the PFC. Together, anger/hostility and deliberation accounted for 38% of the variance in PFC MAO-A V_T. In contrast to anger/hostility, deliberation was strongly positively correlated with MAO-A V_T in the PFC. In fact, a similar relationship between these two facets and MAO-A binding was detected in ACC, hippocampus, putamen, midbrain, and thalamus. Moreover, other personality facets, including impulsivity, were similarly negatively correlated with PFC MAO-A binding. In summary, this study built upon previous findings of an inverse relationship between MAO-A enzyme activity and aggression (Alia-Klein et al., 2008) and also identified impulsivity and deliberation as personality facets related to MAO-A brain level.

1.3.2.1.3.2 GENETIC – FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDIES

Several fMRI studies have studied the effect of MAO-A genotype on neural activation patterns elicited during experimental paradigms targeting aggressive or impulsive behavior. Unlike PET investigations that provide a quantitative estimate of *in vivo* brain MAO-A level, fMRI-genetics studies cannot determine the amount or location of gene product in the brain. This study design is, therefore, unable to directly attribute observed differences in neural activity to brain MAO-A level. In one fMRI-genetics investigation, male carriers of the low-activity allele of the MAO-A 30-bp VNTR showed hyper-arousal of the amygdala and decreased responsiveness of prefrontal regulatory regions, compared to males with the high-activity MAO-A allele, during perceptual matching of fearful and angry faces (Meyer-Lindenberg et al., 2006). Decreased activation of the ACC and prefrontal regions during tasks of response inhibition was also demonstrated in this (Meyer-Lindenberg et al., 2006) and other studies (Fan, Fossella, Sommer, Wu, & Posner, 2003; Passamonti et al., 2006) of males with the low transcription variant of the MAO-A gene.

Imaging-genetic studies testing other MAO-A genetic polymorphisms in relation to aggressive/impulsive behavior have also been reported in the literature. A SNP, (rs6609257), located on Xp11.23 approximately 6.6 kb downstream of the MAO-A gene was found to modulate the activation of fronto-parieto-occipital brain regions

underlying visuospatial working memory; moreover, working memory load was found to correlate with externalizing behaviors in typically developing children (Ziermans et al., 2012). A haplotype consisting of three other MAO-A polymorphisms (rs12843268, rs3027400, and rs1137070) (Brookes et al., 2006) was similarly associated with visuospatial working memory in another study sampling participants with attention deficit hyperactivity disorder (Rommelse et al., 2008).

1.3.2.2 ANIMAL STUDIES OF MONOAMINE OXIDASE-A, IMPULSIVITY, AND AGGRESSION

Several animal models have been employed to investigate the phenotypical manifestations that emerge following complete or partial loss of MAO-A function. These strategies include targeted KO of MAO-A in embryonic stem cells and pharmacological inhibition of MAO-A.

1.3.2.2.1 MONOAMINE OXIDASE-A KNOCKOUT STRATEGIES

Although two different MAO-A KO mice strains have been exploited to investigate the behavioral effects of MAO-A deficiency, neither originated as a result of a targeted genetic KO strategy. Rather, naturally occurring MAO-A gene mutations led to MAO-A deficiency in these mouse strains (Tang, Liu, et al., 2013).

1.3.2.2.1.1 Tg8 STRAIN

The first mutant mouse strain (Tg8) was generated following the accidental insertion of an interferon-β minigene into the MAO-A gene of wildtype (C3H) mice, resulting in displacement of exons 2 and 3 and truncated mRNA that could not be translated into functional MAO-A enzyme (Cases et al., 1995). Abnormal behaviors in Tg8 mice were noted across the lifespan that varied according to development stage. For example, newborn Tg8 pups exhibited intense head bobbing that progressed to hyperlocomotion, violent shaking during sleep, tendency to bite the experimenter, abnormal posturing, and hypersensitivity to stimuli from postnatal days 11-16. These same behaviors could be induced in C3H pups receiving a daily injection of clorgyline, the irreversible MAO-A inhibitor, albeit to a lesser degree. Among the Tg8 pups, administration of parachlorophenylalanine, a 5-HT synthesis inhibitor, but not alpha-methylparatyrosine, a catecholamine synthesis inhibitor, restored behavior back to normal, suggesting that elevated 5-HT levels had played a role in the observed behavioral abnormalities.

In contrast to newborn Tg8 pups, adult Tg8 mice reared as littermates displayed signs of overt aggressive behavior, including biting attacks on the genitals and backends of other Tg8 mice. Results from two different resident-intruder tests revealed that Tg8 males were quicker to attack intruders than C3H males. Anomalous mating behaviors of the Tg8 adult males were also noted, such as increased grasping and oppressive behaviors toward sexually naïve, resistant C3H

females. In an open field test (Chen, Rainnie, Greene, & Tonegawa, 1994), designed to assess whether rodents avoid exposure in the center of an open field out of fear and instead seek refuge at the perimeter (e.g., thigmotaxis), Tg8 adults spent a longer time in the center. Study investigators commented that they could not conclude whether this behavior reflected reduced fear or sensory/cognitive deficits.

High-performance liquid chromatographic assay of 5-HT, NE, and DA uncovered higher levels of all three amines in Tg8 versus C3H whole brain. Notably, 5-HT was elevated nine-fold at postnatal day 1 and six-fold at postnatal 12 in Tg8 pups, which reverted back to a normal level as the mice aged. 5-HT immunohistochemistry staining in 7-day-old Tg8 brains showed increased density of serotonergic fibers in the cerebral cortex, striatum, and hippocampus, whereas 5-HT staining was anomalously present in the locus coeruleus, substantia nigra, and ventral tegmental area. During chronic treatment with parachlorophenylalanine, these neurons were no longer immunoreactive to the 5-HT antibody, suggesting that the abnormal 5-HT immunoreactivity was related to increased 5-HT uptake into the cell bodies. Conversely, the density and regional distribution of 5-HT immunoreactive cell bodies in 10-week-old Tg8 mice did not differ from age-matched C3H mice.

In typically developing pups, serotonergic afferents coalesce with cylindrical aggregates or barrels of granule cells in layer IV of the somatosensory cortex (Osterheld-Haas et al, 1994), supporting a neurotrophic role for 5-HT in developing mammalian somatosensory systems (Persico et al, 2000). Accordingly, in C3H

mice, 5-HT immunoreactive fibers delineated the presence of barrels in layer IV of somatosensory cortex. However, in Tg8 pups, 5-HT immunostaining revealed the absence of barrelfields in the somatosensory cortex and anomalous presence of barrelettes in trigeminal and thalamic nuclei contiguous with the sensory cortex. Administering parachlorophenylalanine to the neonates offered only partial restoration of the cortical barrels.

Although the translational approach of the Tg8 line has been criticized given the active insertion of the interferon-β cassette in the MAO-A gene and its possible control over epigenetic modulation of MAO-A-dependent behaviors (Scott, Bortolato, Chen, & Shih, 2008), the results of this animal KO study demonstrate several important consequences relating to MAO-A deficiency. First, an absence of MAO-A at birth is associated with higher levels of amine neurotransmitters postnatally, especially 5-HT, which spontaneously revert to normal levels over time. Second, MAO-A deficiency from birth onwards is linked to structural abnormalities of brain regions (e.g., somatosensory cortex) that are highly reliant on serotonergic input during neurodevelopment. Treatment with 5-HT synthesis inhibitors during the postnatal period only partially ameliorates these defects, suggesting that some abnormalities persist as a result of excessive 5-HT levels *in utero*. Third, aggressive behavior and possibly reduced fearfulness only emerges during adulthood in the MAO-A deficient model when neurotransmitter levels are normal, suggesting, perhaps, that the observed aberrant adult behaviors relate to a neurodevelopmental insult sustained *in utero* and/or shortly after birth.

In subsequent studies of the Tg8 mutant mouse line involving resident-intruder and other behavioral paradigms, Tg8 mice exhibited increased ferocity and quickness to attack resident intruder mice, increased propensity to attack docile resident intruder mice, and shorter latency to attack crickets (Popova et al., 2001; Vishnivetskaya, Skrinskaya, Seif, & Popova, 2007).

Both ketanserin, a highly selective 5-HT_{2A} receptor antagonist and moderately selective 5-HT_{2C} receptor antagonist, and tetrabenazine, a reversible high affinity inhibitor of the vesicular monoamine transporter 2 (VMAT2), were shown to abolish aggressive behaviors in Tg8 mice in a dose-dependent fashion without affecting investigative, defensive, social, or locomotive behaviors (Shih, Ridd, et al., 1999). Radioligand binding and autoradiography determined that the number of 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors in the frontal cortex was decreased in the mutant mice, which the authors interpreted as receptor down-regulation in response to excessive 5-HT levels. VMAT2 binding sites in striatum were also reduced. The authors concluded that ketanserin mediated its anti-aggressive effect through inhibition of 5-HT_{2A} and VMAT2 binding sites, and tetrabenazine through inhibition of VMAT2 (Shih, Ridd, et al., 1999). Gingko biloba was similarly shown to decrease aggressive behavior in the Tg8 line and reduce [^{3}H] ketanserin binding to frontal 5-HT_{2A} receptors, thus indicating that its anti-aggressive effects may have been mediated by reduced serotonergic signaling (Shih, Chen, Ridd, & Seif, 2000).

Additional studies have illuminated further phenotypical abnormalities of adult Tg8 mice that could relate to enactment of aggressive behavior. These include enhanced fear learning (Kim et al., 1997); decreased startle response, anxiety, and investigative activity (Popova et al., 2001); and attenuated adrenocortical response to acute stressors and chronic stress reported in some but not all experiments (Popova, Maslova, Morosova, Bulygina, & Seif, 2006; Shih, 2004; Shih, Chen, et al., 1999).

1.3.2.1.1.2 MONOAMINE OXIDASE-A^{A863T} KNOCKOUT STRAIN

A second MAO-A-deficient murine line harboring a spontaneous nonsense point mutation in the eighth exon of the MAO-A gene was similarly discovered serendipitously via genotyping in a colony of 129/SvEvTac mice (Scott et al., 2008). The mutation corresponds to the genetic defect identified in Brunner syndrome (Brunner, Nelen, Breakefield, et al., 1993; Brunner, Nelen, van Zandvoort, et al., 1993) and results in nonsense-mediated mRNA degeneration of the mutated MAO-A mRNA. Adult MAOA^{A863T} KO resident mice, similar to the adult Tg8 strain, displayed increased impulsivity and aggression that was manifested by a reduced latency to attack in addition to increased fighting behaviors and tail rattling of intruders in a resident-intruder paradigm. In contrast to Tg8 mice, MAOA^{A863T} KO mice did not exhibit observable behavioral anomalies at birth and were less mobile as adults.

A subsequent study reported on biochemical analyses of the MAOA^{A863T} KO strain, including CNS glutamate concentration and N-methyl-D-aspartate receptor (NMDAR) binding (Bortolato et al., 2012). Although glutamate content was no different in mutant mice versus controls and quantitative autoradiographic analyses revealed no difference in [^{3}H] dizocilpine (NMDAR antagonist) binding, increased expression of NMDAR subunits (NR2A and NR2B) and decreased glycosylation of NR1 were detected in the PFC of MAOA^{A863T} KO mice.

Whole-cell patch-clamp recordings from postmortem PFC showed reduced decay time and excitability of NMDAR-mediated excitatory post-synaptic currents that were further decreased by application of NMDAR subunit antagonists. Administration of these same agents to live mutant mice produced marked anti-aggressive effects during the resident-intruder paradigm, including increased latency to attack and decreased number and duration of fights. Based on these findings, the authors surmised that MAO-A moderates aggressive behaviors in MAOA^{A863T} KO mice by manipulating the structure and function of NMDARs in the PFC (Bortolato et al., 2012).

Behavioral experiments employing the emergence test (Holmes, Yang, Lesch, Crawley, & Murphy, 2003) have found that MAOA^{A863T} KO mice display reduced defensive or fearful behaviors in response to predator cues (Godar et al., 2011). For example, mutant mice exhibited reduced latency to escape from their starting chamber when confronted with either inanimate objects impregnated with predator

urine or an anesthetized rat in their immediate environment. Since behavioral deficits in the $MAOA^{A863T}$ KO mice strain were not accompanied by sensorimotor deficits, the authors concluded that MAO-A deficiency was responsible for the impaired risk assessment and defensive reactivity observed in the mutant mice.

1.3.2.2.2 MONOAMINE OXIDASE-A PHARMACOLOGICAL INHIBITION

Pharmacological inhibition of MAO-A throughout gestation and/or postnatally has also been applied to rodent models to investigate the phenotype that emerges following partial loss of MAO-A enzyme activity. An early study that exposed developing rats to clorgyline and deprenyl during embryogeny reported hyperlocomotion on postnatal days16 and 30 (the two days on which testing occurred) and impaired passive avoidance learning on postnatal day 24 (the sole testing day) among treated rats compared to rats that were not exposed to MAOIs *in utero* (Whitaker-Azmitia, Zhang, & Clarke, 1994). Results were interpreted as indicative of increased impulsivity and hyperactivity in the MAOI-treated rats.

Direct binding assays of the radiolabeled uptake inhibitors ^{3}H-paroxetine and ^{3}H-GBR 12935 were conducted to measure 5-HT terminal density and DA terminal density, respectively, in hippocampus, cortex, and caudate. MAO enzyme activity in brain tissue was also assessed at postnatal day 5 using tryptamine, a substrate of both MAO-A and MAO-B. Rat pups treated with MAOIs during gestation but not postnatally evidenced greater 5-HT terminal density in the hippocampus and

caudate. Increased 5-HT terminal density was also increased in the cortex at postnatal days 5 and 30 but not postnatal day 15. Similar results were obtained in rat pups treated with MAOIs during gestation and postnatally until sacrifice. No difference in DA terminal density was detected in the two treated rat groups versus control rats. MAO-A enzyme activity was significantly reduced in rats treated with MAOIs during gestation and from birth onward compared with rats treated only during gestation. No difference in MAO-A enzyme activity was observed in the latter group compared to control rats (Whitaker-Azmitia et al., 1994). Although the neurochemical and behavioral findings from this study support findings from MAO-A KO models, it must be noted that combined inhibition of MAO-A and MAO-B may have led to these results.

A subsequent study in CD1 mice investigated the behavioral phenotypes that emerged following selective or combined inhibition of MAO-A and MAO-B during murine embryogenesis and early postnatal life (Mejia, Ervin, Baker, & Palmour, 2002). In this study, mice were assessed before and after an acute pharmacological challenge consisting of clorgyline and deprenyl. An additional study aim was to investigate the effectiveness of prenatal MAO inhibition by assessing enzymatic activity in the brains of mice treated with clorgyline, deprenyl, or both from embryogeny to sacrifice at postnatal day 21.

Results revealed that prior to pharmacologic challenge, mice that had been treated with both clorgyline and deprenyl *in utero* were quickest to attack and launched the

most attacks during the resident-intruder paradigm. Conversely, prenatal treatment with clorgyline alone produced offspring that had similar attack rates as control mice and attacked less often than combined clorgyline- and deprenyl-treated mice. However, following acute challenge with clorgyline and deprenyl, the number of attacks increased significantly in mice treated prenatally with MAOIs and to a lesser extent in mice treated prenatally with MAO-B inhibitors. The attack number did not change in mice whose MAO-A and MAO-B had both been pharmacologically inhibited *in utero,* which the authors suggested was the result of a ceiling effect. Because neither selective nor extensive MAO-A inhibition had been achieved in the clorgyline-treated mice (MAO-A and MAO-B had both been inhibited by approximately 25%, as determined by radiochemical procedures), the authors duly noted that the observed behavioral effects in this group could not be specifically linked to alteration in MAO-A level. They ultimately concluded that the developing CNS responds to MAO inhibition much differently than the mature brain, since MAOI treatment in adulthood does not yield the same behavioral effects as those observed in mice treated prenatally with MAOIs (Mejia et al., 2002).

1.4 BORDERLINE PERSONALITY DISORDER

1.4.1 CLINICAL CHARACTERISTICS

BPD is a serious psychiatric illness that limits healthy adult functioning due to instability in affect regulation, interpersonal relationships, and identity. The point

prevalence of BPD was measured as 0.7% in a representative sample of Norwegian adults (Torgersen, Kringlen, & Cramer, 2001). As discussed below, suicide and self-harming behaviors account for the high morbidity and mortality of BPD. Psychiatric comorbidity in BPD is the rule rather than exception. BPD is most frequently associated with mood, anxiety, and substance use disorders (Grant et al., 2008; Lenzenweger, Lane, Loranger, & Kessler, 2007). Among one sample of BPD inpatients, 82.8% were diagnosed with comorbid MDD (Zanarini, Frankenburg, Dubo, et al., 1998). Given such high rates of suicidal behavior and psychiatric comorbidity, it is unsurprising that BPD patients are large consumers of mental health resources. In fact, two studies reported that BPD was associated with more treatment utilization than any other psychiatric condition (Bender et al., 2001; Zanarini, Frankenburg, Khera, & Bleichmar, 2001).

1.4.2 SYMPTOMATOLOGY

Heterogeneity of symptomatology in BPD and the observation that 151 permutations of the condition are possible based on fulfillment of any five of nine DSM-5 (American Psychiatric Association, 2013) criteria (Oldham, 2006; Skodol et al., 2002) has lent support to a polythetic model of BPD that may include illness subtypes. Factor analyses provide evidence for both one-factor and three-factor models (affective dysregulation, behavioral dysregulation, and disturbed relatedness) of BPD (Sanislow, Grilo, & McGlashan, 2000; Sanislow et al., 2002), while latent class analysis has identified classes of individuals that generally endorse

low, moderate, or high BPD symptoms (Trull, Distel, & Carpenter, 2011). Finally, dimensional research employing the FFM has revealed a moderate positive correlation between neuroticism scores and BPD and negative associations of BPD with conscientiousness and agreeableness scores (Ball, Tennen, Poling, Kranzler, & Rounsaville, 1997; Samuel & Widiger, 2008; Saulsman & Page, 2004; Wright, Hopwood, & Zanarini, 2014).

1.4.2.1 DYSPHORIA

One theory of BPD posits that it is a disorder of affect dysregulation encompassing episodes of intense dysphoria (Linehan, 1993). Other research groups have proposed that chronic, intense, inner pain is a key feature of BPD (Zanarini & Frankenburg, 2007). According to this model, the pain experienced by BPD sufferers is characterized by a dysphoric affect and cognitive style that is distinguished from other types of psychic pain by its breadth and intensity (Zanarini, Frankenburg, DeLuca, et al., 1998). Empirical evidence indicates that experienced clinicians who treat BPD largely agree with this conceptualization (Conklin & Westen, 2005). A growing body of neurobiological research on the experience of negative emotional states in BPD has recently begun to emerge (Ruocco, Amirthavasagam, Choi-Kain, & McMain, 2013).

1.4.2.2 DEPRESSIVE ILLNESS IN BORDERLINE PERSONALITY DISORDER

The observation that comorbid MDD in BPD is qualitatively different from MDD without comorbid BPD has been aptly described (Silk, 2010). Some research suggests that the depression of BPD is highly interconnected with feelings of anger and hostility (Wilson et al., 2007) and closely tied to self-critical attitudes (Southwick, Yehuda, & Giller, 1995). One study that compared depressive experiences in BPD with comorbid MDD, BPD without MDD, and MDD without BPD found that BPD subjects, irrespective of MDD comorbidity, reported greater loneliness, emptiness, negative affect, and dysregulation of self-concept than the MDD subjects without BPD (Westen et al., 1992). Other studies have reached similar conclusions and report greater self-reported depressive symptomatology in BPD with comorbid MDD than in MDD without BPD (Abela, Payne, & Moussaly, 2003; Corbitt, Malone, Haas, & Mann, 1996). Consistent with this line of research, additional reports have revealed that individuals with BPD and comorbid MDD typically rate themselves higher on self-report questionnaires measuring depressive symptoms than what would be expected from scores derived from clinician-rated instruments (Comtois, Cowley, Dunner, & Roy-Byrne, 1999; Stanley & Wilson, 2006). Given that the depression of BPD manifests important qualitative differences from depressive illness seen in individuals without BPD, it has been suggested that instruments traditionally used to measure depressive symptoms in MDE or MDD, such as the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960), may not

adequately capture the nature of depressive symptoms experienced by patients with BPD (Southwick et al., 1995).

There has been an ongoing debate in the literature surrounding the issue of whether BPD is a separate disorder from MDD, given the high comorbidity of the two conditions (Zanarini, Frankenburg, Dubo, et al., 1998). Several reviews (Gunderson & Elliott, 1985; Gunderson & Phillips, 1991) have considered the merits of the following perspectives: 1) BPD represents an atypical manifestation of MDD; 2) BPD is distinct from MDD and places individuals with the disorder at risk of MDD; 3) BPD and MDD share overlapping, non-specific risk factors; and 4) BPD and MDD are distinct and unrelated diagnostic entities. The overarching conclusion of these reviews was that BPD and MDD frequently co-exist because of the high prevalence of the two conditions but that otherwise BPD and MDD are discrete, unrelated disorders (Goodman, New, Triebwasser, Collins, & Siever, 2010).

More recent reviews have considered the possibility that each disorder influences the development of the other and that the high co-occurrence of BPD and MDD is a reflection of common biological underpinnings (Goodman et al., 2010; Koenigsberg et al., 1999). Several biological processes common to MDD and BPD have been identified. These include amygdala hyperreactivity, volumetric abnormalities of the subgenual ACC, and diminished serotonergic functioning (Goodman et al., 2010). On the other hand, differences in sleep architecture (De la Fuente, Bobes, Vizuete, & Mendlewicz, 2001), cortisol reactivity to dexamethasone administration (Carrasco

et al., 2007; Koenigsberg et al., 1999), and thyrotropin-releasing hormone stimulation test blunting (De la Fuente, Bobes, Vizuete, & Mendlewicz, 2002) have been reported in BPD and MDD, suggesting that the neurobiology of BPD and MDD may be shared but not identical.

1.4.2.3 SUICIDALITY IN BORDERLINE PERSONALITY DISORDER

A core feature of BPD is recurrent suicidal and self-harming behavior. The seriousness of suicidality in BPD is reflected by several troubling statistics: 60-70% of patients with BPD attempt suicide at some point during their lives, the average patient makes 3.3 attempts over the lifespan, and between 8-10% of BPD patients successfully commit suicide (American Psychiatric Association, 2001; Gunderson & Ridolfi, 2001). In short, the extremely high rate of completed suicide in BPD makes it one of the most lethal psychiatric conditions. Extreme dysphoric episodes, as noted above, are common in BPD and often precede suicidal ideation, intent, and behavior (Nisenbaum, Links, Eynan, & Heisel, 2010). BPD with comorbid depression is associated with a greater number of lifetime suicide attempts and higher objective planning (Soloff, Lynch, Kelly, Malone, & Mann, 2000). Longitudinal studies of BPD cohorts have found that worsening of dysphoric symptoms increases risk of attempted suicide in the following month (Yen et al., 2003) and that MDD is the strongest predictor of suicide attempts within a year of follow-up (Soloff & Fabio, 2008). Yet, despite accumulating clinical data on the suicidality of BPD, very little is known about its underlying neurobiology.

1.5 ANTISOCIAL PERSONALITY DISORDER

1.5.1 CLINICAL CHARACTERISTICS

ASPD is a common yet relatively understudied psychiatric illness that is characterized by a lifelong pattern of impulsive, irresponsible, and reckless behavior. ASPD is one of the most reliable and valid diagnostic categories in males (Hare, 1983; Jackson et al., 1991; Lorenz & Newman, 2002). Epidemiologic studies have found that the lifetime prevalence of ASPD ranges from 3-4% (Compton, Conway, Stinson, Colliver, & Grant, 2005; Goodwin & Hamilton, 2003; Robins et al., 1984; Swanson, Bland, & Newman, 1994), while the prevalence of ASPD among incarcerated males approaches 50% (Fazel & Danesh, 2002). ASPD is highly comorbid with substance use disorders. Results from the National Institute of Mental Health Epidemiological Catchment Area Study determined that 83.6% of respondents with ASPD had co-occurring substance abuse (Regier et al., 1990). Interestingly, anxiety disorders may be more prevalent in ASPD than previously recognized. In a representative, adult community sample, 54.3% of adults with ASPD had a comorbid lifetime anxiety disorder (Goodwin & Hamilton, 2003). Most individuals with ASPD do not exhibit comorbid psychopathy, while virtually all with psychopathy meet diagnostic criteria for ASPD (Hare, 2003). ASPD and psychopathy both present high levels of externalizing and antisocial behavior; however, individuals with high psychopathy scores also feature personality traits of narcissism, callousness, and remorselessness not necessarily present in ASPD.

Males with ASPD are more likely to suffer from premature expiration as a result of suicide, homicide, and accidental death (Repo-Tiihonen, Virkkunen, & Tiihonen, 2001).

1.5.2 CRIMINALITY AND VIOLENCE

Epidemiologic studies confirm that approximately half of all individuals with ASPD possess a record of criminal offending and that 85% have engaged in violence towards others (Robins & Regier, 1991; Samuels et al., 2004). A cross-sectional survey of British households determined that the odds ratio of having engaged in five or more violent incidents or having victimized three or more victim types (e.g., spouse, child, and stranger) over the past five years was 2.67 and 3.59, respectively, in ASPD individuals compared to persons with no psychiatric illness (Coid et al., 2006). Although some experts contend that ASPD without comorbid psychopathy is associated with the exclusive use of reactive/impulsive aggression (Blair, Mitchell, & Blair, 2005), there is research indicating that ASPD individuals with relatively low psychopathic traits also employ proactive (e.g., premeditated) aggression (Nouvion, Cherek, Lane, Tcheremissine, & Lieving, 2007).

1.5.3 IMPULSIVITY

Impulsivity is a multi-faceted construct that in the broadest terms refers to the propensity to engage in maladaptive or problematic behaviors (de Wit, 2009).

Several forms of impulsivity have been described that likely reflect distinct underlying neural processes. Comprehensive reviews have been written on the topic (Dalley, Everitt, & Robbins, 2011; Fineberg et al., 2014) and pertinent findings for each impulsivity subtype are discussed below.

1.5.3.1 MOTOR IMPULSIVITY

Motor impulsivity describes impairment in the ability to discontinue motoric responses following change of environmental circumstances. Laboratory tests that have been employed to index motor impulsivity include go/no-go and stop-signal reaction time (SSRT) tasks (Aron & Poldrack, 2005; Logan, Cowan, & Davis, 1984). Lesion studies, animal research, and fMRI investigations of humans converge in their findings that a neural network encompassing the right inferior frontal gyrus and subcortical/sub-thalamic connections mediates response inhibition (Potenza & de Wit, 2010; Rubia, Smith, Brammer, & Taylor, 2003), whereas pharmacological studies in humans and animals indicate that inhibitory control, as measured using SSRT tasks, is likely modulated by NE (Chamberlain et al., 2007; Chamberlain et al., 2006; Chamberlain & Robbins, 2013). By contrast, the central serotonergic system has not been heavily implicated in regulating this type of impulsivity (Clarke et al., 2005).

1.5.3.2 CHOICE IMPULSIVITY

Excessive discounting of delayed reinforcement is an example of choice impulsivity (Evenden & Ryan, 1999). In other words, choice impulsivity reflects the preference for small, immediate rewards over larger, delayed rewards. Choice impulsivity can be indexed using temporal discounting tasks. For example, participants can be taught to choose between small rewards given immediately and larger rewards that are obtained after a relative delay. Greater temporal discounting, or a steeper decrease in a reward's subjective value as the delay to its receipt increases, provides a measure of choice impulsivity (Cardinal, 2006; Fineberg et al., 2014). Research points to the involvement of three discrete neural systems in temporal discounting: 1) regions involved in valuation of rewards (ventromedial prefrontal cortex [VMPFC], substantia nigra, and ventral striatum [VS]); 2) structures associated with cognitive control (ACC and VMPFC), and regions implicated in representation of mental imagery (medial temporal lobe) (Peters & Buchel, 2011). One study that measured 5-HT, DA, and their metabolites in rat MPFC and orbitofrontal cortex (OFC) using *in vivo* micro-dialysis techniques during a delay discounting task reported increased 5-hydroxytryptamine efflux in MPFC, but not OFC, and greater levels of the DA metabolite 3,4-dihydroxyphenylacetic acid in OFC, but not MPFC, during task performance (Winstanley, Theobald, Dalley, Cardinal, & Robbins, 2006). The authors interpreted their findings as evidence of a dissociation between the neuromodulatory and regional effects of 5-HT and DA systems regulating impulsive behavior. Preclinical investigations have additionally implicated the

glutamatergic and endocannabinoid neurotransmitter systems in choice impulsivity (Cottone et al., 2013; Floresco, Tse, & Ghods-Sharifi, 2008; Navarrete, Perez-Ortiz, & Manzanares, 2012; Wischhof, Hollensteiner, & Koch, 2011; Wiskerke, Stoop, Schetters, Schoffelmeer, & Pattij, 2011).

1.5.3.4 REFLECTION IMPULSIVITY

Reflection impulsivity denotes the disinclination towards obtaining salient information from the environment before acting or the tendency to make rapid choices rather than gathering further information that could guide effective decision making (Fineberg et al., 2014; Kagan, 1966). The Information Sampling Task (IST) (Clark, Robbins, Ersche, & Sahakian, 2006) is a behavioral paradigm that has been used to provide a measure of reflection impulsivity (Clark et al., 2006). The IST assesses information sampling as opposed to visual processing or working memory by requiring participants to consider which of two underlying colors are in the majority when presented with squares of either color arranged in a 5×5 matrix. Current and former substance users of opiates and amphetamines were found to sample less information on the IST than non-users (Clark et al., 2006). Acute tryptophan depletion, which leads to lower central serotonergic functioning (Young, 2013), was associated with over-sampling of information in healthy subjects that was detrimental to overall performance on the IST (Crockett, Clark, Smillie, & Robbins, 2012). Animal models further link the 5-HT system to reflection impulsivity. For example, 5-HT_2 receptor antagonism was found to increase

reflection impulsivity in rats, while 5-HT_2 agonism produced the opposite effect (Evenden, 1999).

1.5.3.4 IMPULSIVITY OF ANTISOCIAL PERSONALITY DISORDER

Although impulsivity has been a longstanding criterion for the diagnosis of ASPD according to classification systems outlined in successive iterations of the Diagnostic and Statistical Manual of Mental Disorders (DSM), there is surprisingly little empirical research on impulsivity in ASPD. Total score and subscale scores on the Barratt Impulsiveness Scale 11 (BIS 11), a self-report measure indexing nonplanning, motor, and attentional components of impulsivity (Patton, Stanford, & Barratt, 1995), were found to be elevated in several studies of ASPD compared to healthy controls (Lijffijt et al., 2009; Swann, Lijffijt, Lane, Steinberg, & Moeller, 2009), although behavioral results from one of these studies found that neither attention nor reward-delay measures of impulsivity were impaired in ASPD (Swann et al., 2009). Some studies have examined how delayed rewards are processed in both ASPD and substance use disorders give their frequent co-occurrence. One investigation reported that substance abusers with comorbid ASPD discounted delayed rewards on a behavioral task using fictitious rewards at higher rates than substance abusers without ASPD (Petry, 2002), while another study found that alcoholics with ASPD showed greater inability to delay gratification than alcoholics with BPD on a delay task (Rubio et al., 2007). To the best of our knowledge, only one molecular imaging study has investigated the neurochemical correlates of

impulsivity in ASPD (Meyer et al., 2008), thus pointing to a need for further investigation of this understudied area.

CHAPTER 2: Elevated Monoamine Oxidase-A Distribution Volume in Borderline Personality Disorder is Associated with Severity across Mood Symptoms, Suicidality, and Cognition

This chapter is modified from the following:

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2.1 ABSTRACT

Background: MAO-A is a treatment target in neurodegenerative illness and mood disorders that increases oxidative stress and predisposition towards apoptosis. Increased MAO-A levels in PFC and ACC occur in rodent models of depressive behavior and human studies of depressed moods. Extreme dysphoria is common in 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}C] Harmine PET measured MAO-A V_T, an index of MAO-A density, in severe BPD (*n*=14), moderate BPD (*n*=14), subjects with a MDE only (*n*=14), and health (*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 health (multivariate analysis of various [MANOVA] group effect: $F_{6,102} = 5.6$, $p < 0.001$; PFC and ACC MAO-A V_T increased 43% and 42%, respectively, in severe BPD versus health). In BPD, PFC and ACC MAO-A V_T were positively correlated with mood symptoms (PFC: $r = 0.52$, $p = 0.005$; ACC: $r = 0.53$, $p = 0.004$) and suicidality (PFC: $r = 0.40$, $p = 0.037$; ACC: $r = 0.38$, $p = 0.046$), while hippocampus MAO-A V_T was negatively correlated with verbal memory ($r = -0.44$, $p = 0.023$).

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.

2.2 INTRODUCTION

Psychiatric illnesses are often conceptualized as comprising multiple clusters of target pathologies that co-segregate across different disorders (Cuthbert & Insel, 2013). Consistent with this perspective, MAO-A is an important target in neurodegenerative illness, due to its role in apoptosis (Ou et al., 2006b; Youdim et al., 2006), and in affect dysregulation, due to the association of elevated MAO-A levels in the PFC and ACC with depressive symptoms (Bacher et al., 2011; Meyer et al., 2006; Meyer et al., 2009; Sacher et al., 2010). MAO-A is an enzyme located on outer mitochondrial membranes in glia and monoamine-releasing neurons that increases oxidative stress, affects predisposition toward intrinsic apoptosis, and metabolizes monoamines (Youdim et al., 2006). In brain tissue, greater MAO-A levels are correlated with elevated MAO-A activity (Saura et al., 1992), and an index of MAO-A density, MAO-A V_T, can be measured with [^{11}C] harmine PET (Ginovart et al., 2006). [^{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 (Son et al., 2008).

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 (Torgersen et al., 2001). 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 (Koenigsberg et al., 2001; Tragesser, Solhan, Schwartz-Mette, & Trull, 2007). Severe dysphoria in BPD is highly clinically relevant, because it is associated with need for inpatient care (Zanarini, Frankenburg, DeLuca, et al., 1998), although other dimensions of the illness, such as neurocognitive impairment, also contribute to BPD severity (Bazanis et al., 2002). Severe BPD is associated with greater functional impairment (Black et al., 2006; Gunderson et al., 2006), dysregulated emotional responses to negative stimuli (Hazlett et al., 2007), and increased suicidality (Black et al., 2006), 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 dysfunctional regulatory control system in PFC and ACC (New, Triebwasser, & Charney, 2008) that is based on PET studies showing reduced engagement of these regions (Goyer et al., 1994; Leyton et al., 2001; New et al., 2002; Siever et al., 1999; Soloff, Meltzer, Greer, Constantine, & Kelly, 2000). 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 (Ruocco et al., 2013). Depressive behaviors in rodents, such as those observed in chronic social defeat or chronic restraint stress paradigms, are associated with greater MAO-A mRNA and activity in the PFC (Filipenko et al., 2002; Grunewald et al., 2012). 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 (Kabayama et al., 2013; Libert et al., 2011). Since affect dysregulation emerges from impaired social interaction and is core to worsened presentations of BPD (Sadikaj, Russell, Moskowitz, & Paris, 2010; Yen, Zlotnick, & Costello, 2002), 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 (Yuan & Yankner, 2000), 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.

2.3 METHOD AND MATERIALS

2.3.1 PARTICIPANTS

Fifty-six female subjects completed the study protocol: 14 with severe BPD, 14 with moderate BPD, 14 with a MDE and no BPD, and 14 healthy controls. In clinical settings, females comprise up to 74% of BPD cases (Korzekwa, Dell, Links, Thabane, & Webb, 2008). 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 controls were selected based on matching age and sex to the BPD samples. All subjects in the study were female and age-matching between controls and BPD samples was within three years. Samples had a similar proportion of women aged 41-51 years in each group to control for the effect of perimenopause on MAO-A V_T ($\chi^2(3)= 0.6$, $p = 0.63$) (Rekkas et al., 2014). 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.

2.3.1.1 BORDERLINE PERSONALITY DISORDER SUBJECTS

BPD participants were recruited from outpatient 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) (First, Gibbon, Spitzer, Williams, & Benjamin, 1997) by a psychiatrist experienced in the assessment and treatment of personality disorders (NJK), who also administered the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First, Spitzer, Gibbon, & Williams, 2002). The BPD diagnosis was consistent with the diagnosis given to subjects by their treatment providers from tertiary care centers. 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 MDD (Zanarini, Frankenburg, Dubo, et al., 1998). To rule out potential 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 three months that are known or hypothesized to interfere with MAO-A levels, such as MAOIs, mood stabilizers (e.g., lithium, valproic acid, carbamazepine), and psychostimulants (Arai et al., 1990). 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 (Meyer et al., 2009). 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 prior to PET scanning, which included SSRIs (8 subjects), selective serotonin/norepinephrine reuptake inhibitors (1 subject), atypical antipsychotics (3 subjects), and benzodiazepines (3 subjects).

2.3.1.2 MAJOR DEPRESSIVE EPISODE 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 two years to the BPD participants. MDE subjects had no lifetime history of additional psychiatric illness and had not taken antidepressant

medication within the previous two weeks. Forty-three percent had never taken antidepressant treatment.

2.3.1.3 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 three 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 (Chiuccariello et al., 2014; Meyer et al., 2009). All study participants were non-smoking 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.

2.3.2 IMAGE ACQUISITION

Each participant underwent a single [^{11}C] harmine PET scan. 370 MBq (10 mCi) of intravenous [^{11}C] harmine 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 min. Manual samples were obtained at 2.5, 7.5, 15.0,

20.0, 30.0, 45.0, 60.0 and approximately 90.0 min after injection. Whole blood and plasma radioactivity was measured as previously described (Ginovart et al., 2006). Fifteen frames lasting 1 min each were acquired, followed by 15 frames of 5 min each. [^{11}C] Harmine was of very high radiochemical purity (99.0 ± 0.9%) and high specific activity (109.5 ± 67.0 GBq [2958.6 ± 1811.1 mCi]/μmol) at the time of injection. PET images were obtained using a high-resolution research tomograph (HRRT) PET camera (in-plane resolution; FWHM, 3.1 mm; 207 axial sections of 1.2 mm; Siemens Molecular Imaging, Knoxville, TN) as described elsewhere (Meyer et al., 2009).

2.3.3 IMAGE ANALYSIS

Each participant also underwent magnetic resonance imaging (MRI) on a 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) for the 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 grey matter voxels, as previously reported (Meyer et al., 2009; Rusjan et al., 2006).

The PFC and ACC were chosen as the primary ROIs, because these regions and their subregions participate in affective regulation (Ressler & Mayberg, 2007), comprise the network of frontal control processes regulating emotional activity in subcortical limbic structures (New et al., 2008), and show hypoactivity during low mood states in BPD (Ruocco et al., 2013). In addition, several subregions of the PFC were sampled, including dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), MPFC, and OFC. The borders of these subregions were defined based on their cytoarchitectural differences from adjacent cortex (Uylings et al., 2010). 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 (Ginovart et al., 2006; Tong et al., 2013), as would be expected since MAO-A affinity is similar across regions in primates *in vivo* (Bottlaender et al., 2010). Both the unconstrained two-tissue compartment model and Logan model (Logan et al., 1990) with arterial sampling, for which the underestimate of MAO-A V_T is negligible, measure MAO-A V_T with high reliability and validity. We applied the latter technique, which has been described in detail previously (Ginovart et al., 2006).

2.3.4 MEASURES OF SYMPTOM SEVERITY FOR BORDERLINE PERSONALITY DISORDER SUBJECTS

BPD severity was defined as the number of DSM-IV-TR (American Psychiatric Association, 2000) BPD symptoms present in clinical assessment with the SCID-II. This method of defining BPD severity has been employed by other research groups (Black et al., 2006; Gunderson et al., 2006; Hazlett et al., 2007; Yen et al., 2002). 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 HDRS (Hamilton, 1960) and suicidal ideation was assessed with the suicide subscale of the Overt Aggression Scale – Modified for Outpatients (OAS-M) (Coccaro, Harvey, Kupsaw-Lawrence, Herbert, & Bernstein, 1991). A set of cognitive tests were also administered with the prioritized measures being the Wechsler Test of Adult Reading – Revised (Wechsler, 1981) and Hopkins Verbal Learning Test – Revised (Benedict, 1998). In addition, the Suicide Ideation Scale (Beck, Kovacs, & Weissman, 1979), BIS 11 (Patton et al., 1995), Anger Questionnaire (Buss & Perry, 1992), and State Trait Anger Expression Inventory-2 (Spielberger, 1999) were administered.

2.3.5 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 a 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.

2.4 RESULTS

2.4.1 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.

[Insert Table 2-1]

Table 2-1. Demographic and Clinical Characteristics of All Study Participants[a]

	Healthy (n=14)	**Major Depressive Episode (n=14)**	**Moderate Severity BPD[c] (n=14)**	**High Severity BPD (n=14)**	***p*-values**
Age, years	32.9 (8.2)	30.9 (6.6)	32.9 (10.6)	34.2 (10.2)	0.65[c]
HDRS[b]	0.9 (1.4)	20.1 (4.5)	21.3 (4.2)	23.6 (4.1)	0.10[d]

[a] values are expressed as mean (standard deviation)
[b] 17-item Hamilton Depression Rating Scale score on day of positron emission tomography scanning
[c] analysis of variance indicates no significant difference in age between the four groups
[d] analysis of variance indicates no significant difference in Hamilton Depression Rating Scale scores for the three patient groups

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

[Insert Table 2-2]

2.4.2 COMPARISON OF MONOAMINE OXIDASE-A TOTAL DISTRIBUTION VOLUME IN SEVERE BORDERLINE PERSONALITY DISORDER, MODERATE BORDERLINE PERSONALITY DISORDER, MAJOR DEPRESSIVE EPISODE, AND HEALTH

As depicted in Figure 2-1, MAO-A V_T was substantially elevated in severe BPD, on average by 43% and 42% in the PFC and ACC, respectively, compared with health; 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: $F_{6,102} = 5.6$, $p < 0.001$). Significant univariate effects were also detected in both PFC and ACC ($F_{3,52} = 9.4$ to 12.6, p-values all < 0.001). 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 = 0.006 to 0.024), MDE only (p-values = 0.002 to 0.007), and health (p-values all $\leq$ 0.001). In addition, moderate BPD showed greater PFC and ACC MAO-A V_T compared with health (p-values = 0.002 to 0.005), as did the MDE group compared with health (p-values = 0.005 to 0.017). No difference was observed in PFC and ACC MAO-A V_T between MDE and moderate BPD groups (p-values = 0.62 to

Table 2-2. Clinical Characteristics of Borderline Personality Disorder Groups[1]

Characteristics	Moderate BPD (n=14)	Severe BPD (n=14)
Education, years[2]	14.9 (1.5)	14.5 (2.1)
Estimated Full-scale IQ[3]	103.8 (9.2)	109.6 (8.9)
Diagnosis		
- Number of BPD Symptoms[4]	5.4 (0.5)	7.8 (1.0)**
- Comorbid Conditions		
- % with anxiety disorder[4]	64.3	71.4
- % with eating disorder[4]	57.1	50.0
- % with lifetime substance use disorder[4]	14.3	7.1
- % with somatoform disorder[4]	7.1	7.1
- % with other DSM-IV-TR personality disorder[4]	71.4	57.1
% taking psychotropic medication[4]	28.6	28.6
Number of psychiatric hospitalizations[2]	2.3 (2.9)	3.2 (2.9)
Suicidality Measures		
- Suicide Ideation Scale[2]	9.6 (9.5)	17.0 (9.0)*
- Overt Aggression Scale – Modified for Outpatients (OAS-M) Suicidality scale[2]	1.4 (1.2)	2.1 (1.1)
- % endorsing moderate or severe suicidality on OAS-M Suicidality scale[5]	14.3	57.1*
Anger/Aggression Measures		
- STAXI-2 state anger (*T*-score)[2]	56.3 (11.6)	56.9 (15.0)
- STAXI-2 trait anger (*T*-score)[2]	54.0 (11.9)	67.6 (14.5)*
- Buss-Perry anger[3]	17.2 (6.9)	23.9 (7.4)*
- Buss-Perry physical aggression[3]	18.4 (9.4)	24.4 (9.8)
- Buss-Perry verbal aggression[3]	13.4 (5.3)	16.1 (5.4)
Barratt Impulsiveness Scale 11		
- Attentional Impulsiveness[3]	20.7 (4.8)	23.9 (3.5)
- Motor Impulsiveness[3]	27.2 (6.6)	28.5 (5.5)
- Nonplanning Impulsiveness[3]	30.5 (5.9)	31.3 (4.6)

[1] values are expressed as mean (standard deviation), except where indicated; [2] Mann-Whitney U test; [3] independent samples *t*-test; [4] Fisher's exact test; [5] Chi-square test; * $p < 0.05$, two-tailed; ** $p < 0.001$, two-tailed

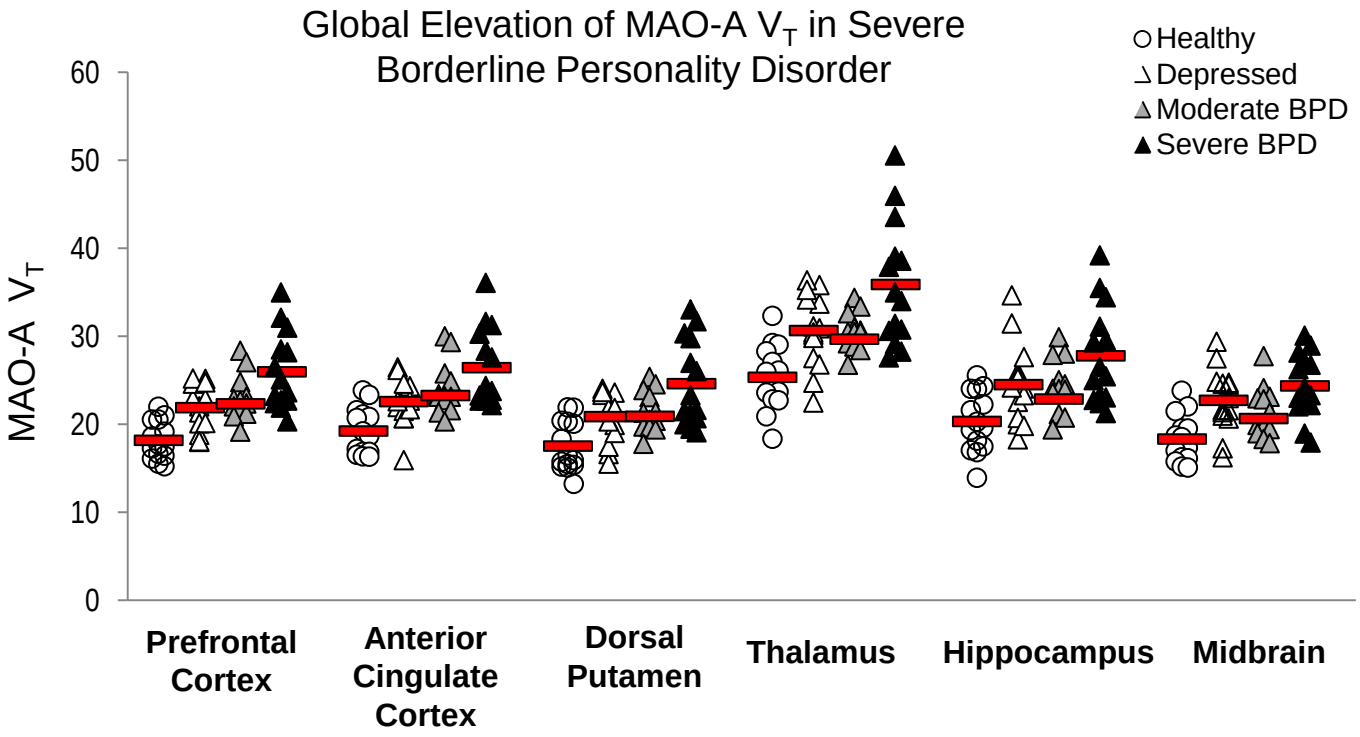
0.73). When the analyses were repeated with only the unmedicated BPD subjects (n = 20), all significant relationships persisted. A post-hoc analysis found that MAO-A V_T was increased in all BPD subjects versus MDE in the PFC (t_{40} = 1.9, p = 0.035, one-tailed) and ACC (t_{40} = 1.8, p = 0.037, one-tailed).

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 = 0.005). All main contrasts were significant with inclusion of depressive symptoms as the covariate of interest (MANCOVA: severe BPD versus moderate BPD: $F_{2,24}$ = 4.1, p = 0.029; MANCOVA: severe BPD versus health: $F_{2,24}$ = 6.0, p = 0.008; MANCOVA: severe BPD versus MDE: $F_{2,24}$ = 3.6, p = 0.041).

[Insert Figure 2-1]

There was also a significant main group effect across all brain regions sampled (MANOVA group effect: $F_{30,127}$ = 2.8, p = 0.002). 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 health (p-values all < 0.001), severe BPD versus moderate BPD (p-values = 0.001 to 0.012), and MDE versus health (p-values ≤ 0.001 to 0.027). MAO-A V_T values were significantly greater in severe BPD versus MDE for the additional regions, except the hippocampus and midbrain (p-values = 0.002 to 0.21), and were significantly greater

Figure 2-1



Severe BPD was associated with greater MAO-A V_T in both PFC and ACC compared with the moderate BPD, depressed, and healthy groups (MANOVA group effect: $F_{6,102} = 5.6$, $p < 0.001$; least significant difference for severe BPD vs. other groups, p-value range: < 0.001 to 0.024). Mean MAO-A V_T was greater in severe versus moderate BPD for each brain region sampled (p-value range: 0.003 to 0.024). When the effect of group on MAO-A V_T was evaluated across all regions, similar results were found (MANOVA group effect: $F_{30,127} = 2.8$, $p = 0.002$). Red bars indicate mean MAO-A V_T values.

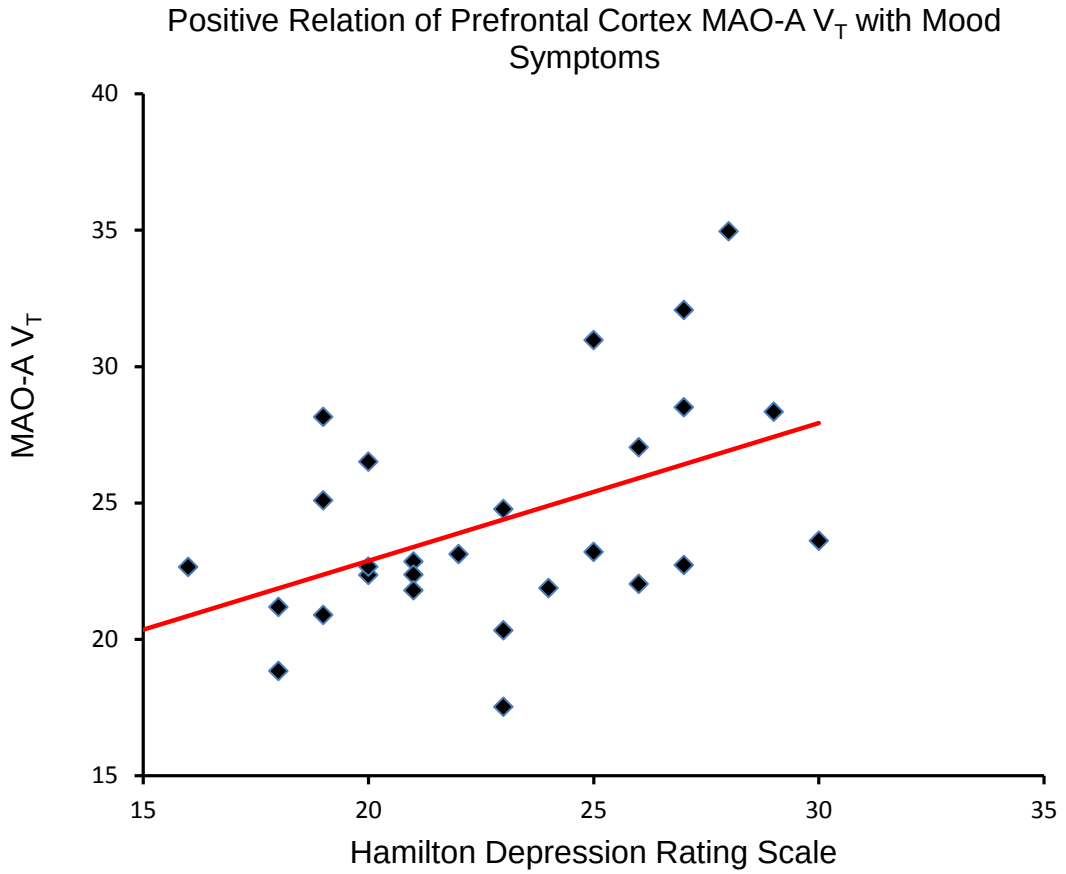
in moderate BPD versus health, save the hippocampus and OFC (*p*-values = 0.004 to 0.13). MAO-A V_T values did not differ between moderate BPD and MDE for any of the additional regions (*p*-values = 0.11 to 0.99). Results were unchanged when only the unmedicated subjects were included in the analyses.

2.4.3 RELATIONSHIP OF MONOAMINE OXIDASE-A TOTAL DISTRIBUTION VOLUME WITH SEVERITY OF MOOD SYMPTOMS, SUICIDALITY, AND COGNITION IN BORDERLINE PERSONALITY DISORDER

In the 28 BPD subjects, PFC MAO-A V_T was correlated with both total HDRS score ($r = 0.52$, $p = 0.005$) and suicidality, assessed using the OAS-M ($r = 0.40$, $p = 0.037$), while ACC MAO-A V_T was similarly correlated with mood symptoms ($r = 0.53$, $p = 0.004$) and suicidality ($r = 0.38$, $p = 0.046$). 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 = -0.44, $p = 0.023$).

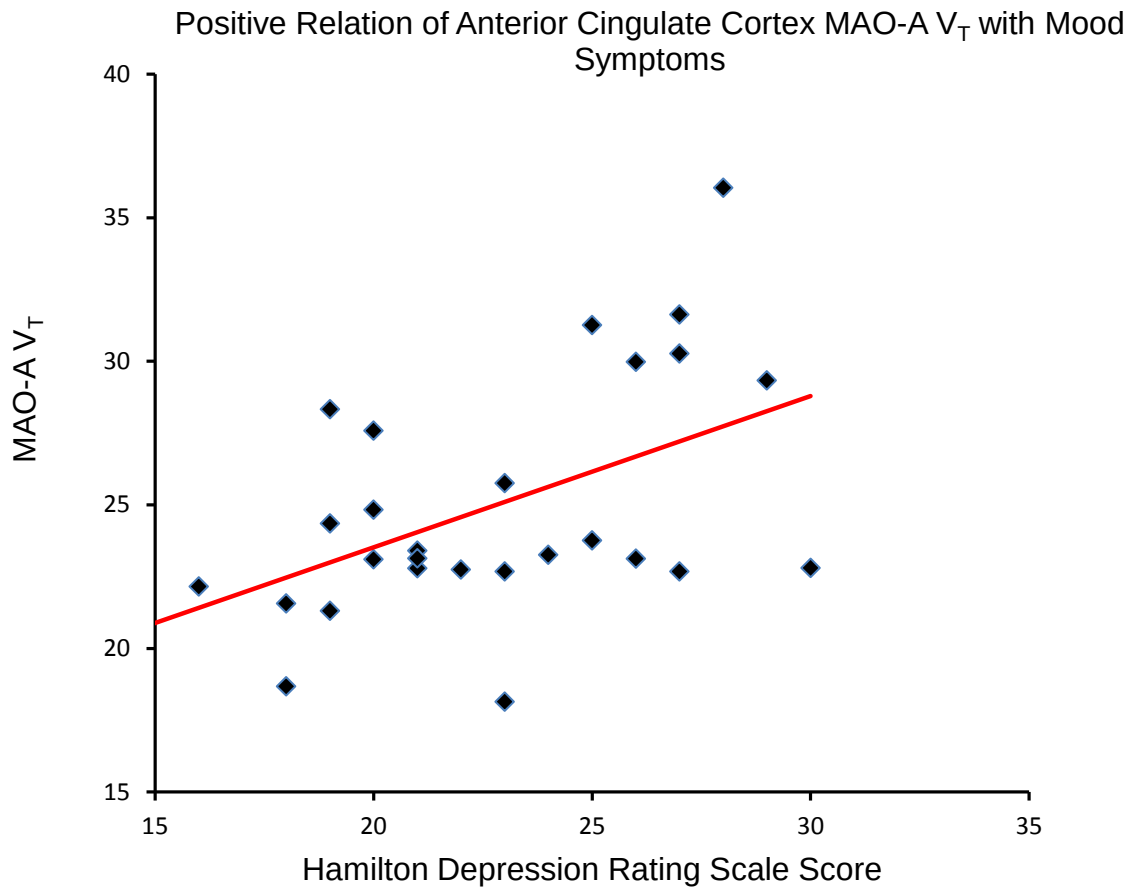
[Insert Figures 2-2, 2-3, 2-4, 2-5, 2-6]

Figure 2-2



Prefrontal cortex MAO-A V_T is positively correlated with HDRS score (Pearson's *r* = 0.52, *p* = 0.005, two-tailed).

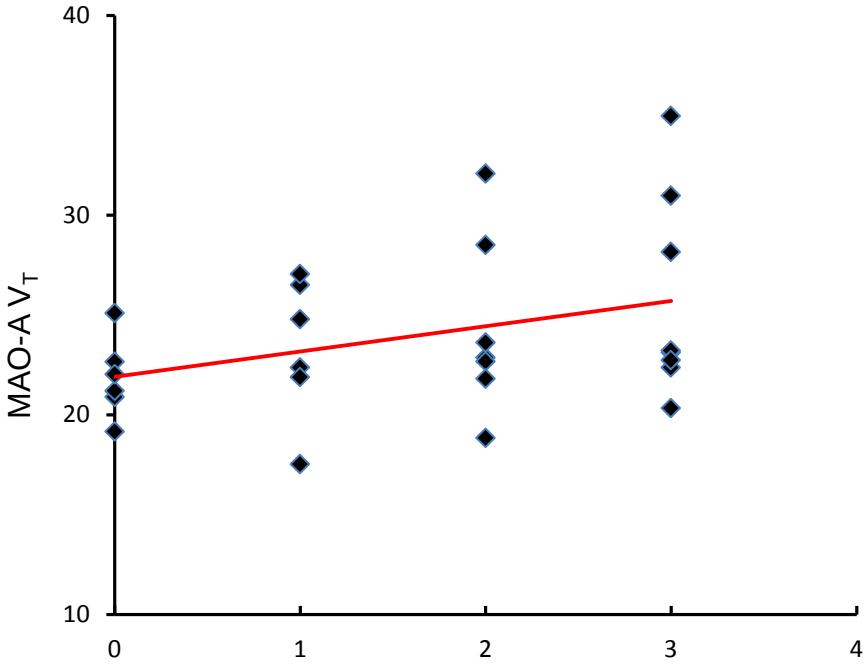
Figure 2-3



Anterior cingulate cortex MAO-A V_T is positively correlated with HDRS score (Pearson's $r = 0.53$, $p = 0.004$, two-tailed).

Figure 2-4

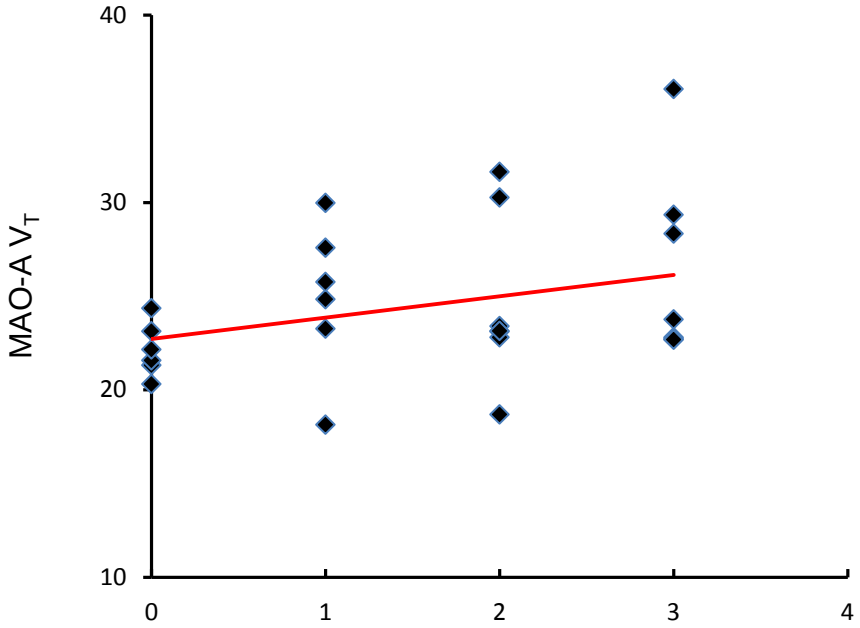
Positive Relation between Prefrontal Cortex MAO-A V_T and Suicidality



PFC MAO-A V_T is positively correlated with the Suicidality subscale score of the OAS-M (Pearson's r = 0.40, p = 0.037, two-tailed).

Figure 2-5

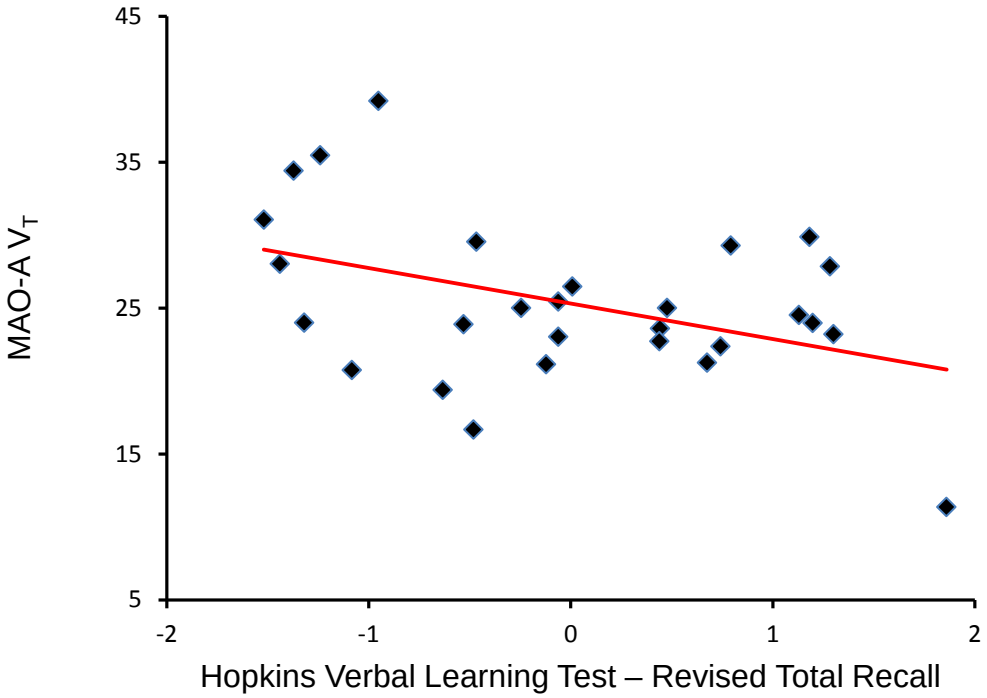
Positive Relation between Anterior Cingulate Cortex MAO-A V_T and Suicidality



ACC MAO-A V_T is positively correlated with the Suicidality subscale score of the OAS-M (Pearson's r = 0.38, p = 0.046, two-tailed).

Figure 2-6

Hippocampal MAO-A V_T is Inversely Related to Verbal Memory



Hippocampal MAO-A V_T is negatively correlated with Total Recall score of the Hopkins Verbal Learning Test – Revised (HVLT-R), controlling for IQ on HVLT-R (semi-partial correlation coefficient = -0.41, p = 0.023, two-tailed). Note: x-axis depicts residuals of HVLT-R total recall independent of IQ.

2.4.4 RELATIONSHIP OF MONOAMINE OXIDASE-A TOTAL DISTRIBUTION VOLUME 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 = 0.47, p = 0.002; and r = 0.43, p = 0.005, respectively).

2.5 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 to moderate BPD, MDE, and health. The difference in PFC and ACC MAO-A V_T between severe BPD and health 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 (Black et al., 2006; Gunderson et al., 2006), 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 (Youdim et al., 2006), it has been suggested that increased MAO-A protein and/or activity may contribute to neurodegeneration in Parkinson's disease (Jiang, Jiang, Liu, & Feng, 2006), Huntington's disease (Richards et al., 2011), and Alzheimer's disease (Emilsson et al., 2002; Sherif, Gottfries, Alafuzoff, & Oreland, 1992; Sparks, Woeltz, & Markesbery, 1991). 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 5-10 years (Gunderson et al., 2011). Traditionally, therapeutics with anti-oxidant or anti-apoptotic properties have not been conceptualized as relevant for BPD, although evidence suggests that riluzole, a treatment indicated for amyotrophic lateral sclerosis that has anti-apoptotic properties, can reduce suicidal behavior in BPD (Pittenger, Krystal, & Coric, 2005). Moreover, the newest MAOIs that achieve a high brain-to-gut ratio to circumvent side effects have been studied in neurodegenerative conditions (Youdim et al., 2006). Based on our finding of greater

MAO-A level in BPD, there is reason to consider such treatments for the illness, since classical MAOIs are effective treatments for BPD, especially when severe (Cowdry & Gardner, 1988; Soloff et al., 1993).

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 (Hoerst et al., 2010). Initial investigations of PFC 5-HT_{2A} receptor binding in BPD reported no relationship to measures of severity (Meyer et al., 2003; Soloff et al., 2007), but a more recent sample found an association of lifetime aggression with reduced 5-HT_{2A} receptor binding in the medial OFC of females with BPD (Soloff, Chiappetta, Mason, Becker, & Price,

2014). Another study reported greater mu-opioid receptor binding in the OFC, caudate, and VS in BPD, which did not reach a statistically significant threshold when correlated with measures of impulsivity, neuroticism, or dissociation (Prossin, Love, Koeppe, Zubieta, & Silk, 2010). Finally, in samples of BPD patients and high-lethality suicide attempters with cluster B personality disorders, reduced α-[^{11}C]-methyl-L-tryptophan uptake in PFC and ACC was found to be correlated with measures of impulsivity and suicidal intent (Leyton et al., 2001; Leyton et al., 2006). Interestingly, the findings of the present study are consistent with several reports of abnormal markers implicated in pro-apoptotic signaling from postmortem investigations that predominantly sampled the PFC of suicide victims with mood dysregulation: reduced phosphoinositide 3-kinase activity (Dwivedi et al., 2008), reduced R1 levels (Johnson et al., 2011), increased caspase 8 levels (Miguel-Hidalgo et al., 2014), and reduced Bcl-2 (Kim, Rapoport, & Rao, 2010).

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 60-75% of people with BPD make suicide attempts and 8-10% commit suicide (Oldham, 2006). 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 (Schmidt, Shelton, & Duman, 2011). 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 (Meyer, 2012) and detection of MAO-A activity using magnetic resonance spectroscopy (Yamaguchi et al., 2011) 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 (Yuan & Yankner, 2000). For example, decreased verbal memory performance is associated with microstructural alterations of hippocampal gray matter in Parkinson's disease (Carlesimo et al., 2012) and increased hippocampal binding of radioligand selective for amyloid plaques and neurofibrillary tangles in Alzheimer's disease (Shin, Lee, Kim, Kim, & Cho, 2008).

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 inter-correlated 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 level 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.

2.6 STUDY LIMITATIONS

We note several limitations of the present investigation. We chose to assess BPD severity based on the number of DSM-IV-TR symptoms present, an approach used in some laboratories (Black et al., 2006; Gunderson et al., 2006; Hazlett et al., 2007; Yen et al., 2002). Although there is no universally accepted gold standard for measuring BPD severity (Zanarini et al., 2010), other options would have been the Zanarini Rating Scale for Borderline Personality Disorder (Zanarini et al., 2003) or the Borderline Personality Disorder Severity Index (Arntz et al., 2003). These other scales are designed to capture DSM-IV BPD criteria (Arntz et al., 2003; Zanarini et al., 2003) and are highly correlated with number of BPD criteria (Arntz et al., 2003). Further, 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 non-specific binding. Hence, our interpretations assumed that substantial changes in free and non-specific binding (150-300%) were not occurring, an assumption consistent with previous evaluations observed in MAO-A occupancy studies (Ginovart et al., 2006).

2.7 CONCLUSION

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 level was 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 which inhibit MAO-A, reduce cellular oxidative stress levels, and/or oppose apoptotic processes should be tested in severe presentations of BPD.

CHAPTER 3: Lower Monoamine Oxidase-A Distribution Volume in Impulsive and Violent Male Offenders with Antisocial Personality Disorder and High Psychopathic Traits: An [^{11}C] Harmine Positron Emission Tomography Study

This chapter is modified from the following:

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3.1 ABSTRACT

Background: ASPD often presents with highly impulsive, violent behavior, and pathological changes in the OFC and VS are implicated. Several compelling reasons support a relationship between low MAO-A, an enzyme that regulates neurotransmitters, and ASPD. These include MAO-A KO models in rodents evidencing impulsive aggression and PET studies of healthy subjects reporting associations between low brain MAO-A level 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.

Methods: To address this issue, we applied [^{11}C] harmine PET to measure MAO-A V_T, an index of MAO-A density, in 18 male ASPD participants and 18 age- and sex-matched controls.

Results: OFC and VS MAO-A V_T were lower in ASPD compared to controls (MANOVA: $F_{2,33} = 6.8$, $p = 0.003$; OFC and VS MAO-A V_T each reduced 19%). Similar effects were seen in other brain regions: ACC, dorsal putamen, thalamus, hippocampus, and midbrain (MANOVA: $F_{7,28} = 2.9$, $p = 0.022$). In ASPD, VS MAO-A V_T was consistently negatively correlated with self-reported, clinician-rated, and behavioral measures of impulsivity ($r = -0.50$ to -0.52, all p-values < 0.05).

Conclusions: This study is the first to demonstrate a reduction of brain MAO-A level in ASPD. Our results support an important extension of preclinical models of

impulsive aggression into a human disorder marked by pathological aggression and impulsivity.

3.2 INTRODUCTION

The vast majority of violent crime is perpetrated by a small group of males who exhibit conduct-disordered behavior from childhood onwards and fulfill diagnostic criteria for ASPD as adults (Moffitt, Caspi, Harrington, & Milne, 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 identified from postmortem investigations in clinically diagnosed individuals with the condition, although brain phenotypes such as decreased 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 DA release in humans with high impulsive-antisocial psychopathic traits (Buckholtz et al., 2010) have been reported. However, low brain MAO-A, an enzyme localized to outer mitochondrial membranes that metabolizes amine neurotransmitters implicated in aggressive behavior (Bortolato, Chen, & Shih, 2008), has emerged as a promising molecular target.

Multiple tiers of evidence from preclinical and clinical studies support a strong relationship between decreased 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, Nelen, Breakefield, et al., 1993). Second, PET studies of healthy humans that used MAO-A-selective radiotracers found inverse relationships between MAO-A binding in several brain regions and self-reported impulsivity and aggression (Alia-Klein et al., 2008; Soliman et al., 2011). Third, targeted KO 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 upon 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 risk of adult violent convictions (Caspi et al., 2002). However, it has never been empirically determined whether brain MAO-A is decreased in violent and clinically impulsive populations. To address this critical issue, the principal aim of the study was to measure MAO-A V_T in the brains of highly impulsive, violent offenders with ASPD.

[^{11}C] Harmine is a PET radiotracer ideally suited to measure MAO-A levels, 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). Reduced MAO-A levels are associated with reduced MAO-A activity in brain (Saura et al., 1992).

We hypothesized that MAO-A V_T would be reduced in the OFC and 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 ROIs, because they show consistent functional and/or biological abnormalities in ASPD and aggressive behavior (Blair, 2004; Buckholtz et al., 2010; Glenn & Yang, 2012; Meyer et al., 2008; Rylands et al., 2012) and are key structures in the neural circuitry mediating impulsivity (Dalley et al., 2011).

3.3 METHOD AND MATERIALS

3.3.1 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.

3.3.1.1 ANTISOCIAL PERSONALITY DISORDER 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 SCID-II (First et al., 1997) and 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. Nine subjects met criteria for AD.

3.3.1.2 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., 2013). 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. All controls were free of medication use and age-matched within four years to the ASPD participants. Control subjects formed a subset of participants from previously published studies in our laboratory (Matthews et al., 2013; Soliman et al., 2011). All study participants were non-smoking and 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.

3.3.2 IMAGE ACQUISITION

Participants underwent a single [^{11}C] harmine PET scan. 370 MBq (10 mCi) of intravenous [^{11}C] harmine was administered as a bolus at the beginning of each PET scan. An automatic blood sampling system 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 approximately 90.0 min. Whole blood and plasma radioactivity was measured as previously reported. Fifteen frames lasting 1 min each were acquired, followed by 15 frames that were each 5 min. [^{11}C] Harmine was of very high radiochemical purity (98.9 ± 0.9%) and high specific activity (120.7 ± 72.9 GBq [3262.2 ± 1970.3 mCi]/μmol) at the time of injection. PET images were obtained using a HRRT PET camera (in-plane resolution; FWHM, 3.1 mm; 207 axial sections of 1.2 mm; Siemens Molecular Imaging, Knoxville, TN) as described elsewhere (Ginovart et al., 2006).

3.3.3 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 (Logan et al., 1990). We applied the Logan model, which is described in detail elsewhere (Ginovart et al., 2006; Logan et al., 1990).

The OFC and VS were chosen as the primary ROIs, 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 and colleagues (Mawlawi et al., 2001). Other secondary ROIs 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 ACC, thalamus, midbrain, and hippocampus, which were derived from a neuroanatomy atlas of structural MRI and postmortem tissue (Duvernoy, 1999) used for our previous investigations (Matthews et al., 2013; Soliman et al., 2011). Other

subregions of the PFC (DLPFC, VLPFC, and MPFC) were 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 & Goldman-Rakic, 1995).

The ROIs tested in the current investigation 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 grey matter voxels, as previously described (Rusjan et al., 2006). Participants received a high resolution 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, Milwaukee, WI). 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 to 1.0).

3.3.4 MEASURES OF IMPULSIVITY IN ANTISOCIAL PERSONALITY DISORDER

3.3.4.1 IOWA GAMBLING TASK

The Iowa Gambling Task (IGT) (Bechara, Damasio, Damasio, & Anderson, 1994) 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, while decks A and B consistently yield lower gains with 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, Allen, & Kaut, 2008). Accordingly, the net IGT score 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)].

3.3.4.2 NEO PERSONALITY INVENTORY – REVISED

The NEO PI-R (Costa Jr., 1992) is an extensively validated and reliable self-report measure of “normal” and abnormal adult personality that provides norm-referenced

test scores for broad-based dimensional personality domains and traits, including impulsivity. All participants completed the NEO PI-R.

3.3.4.3 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.

3.3.5 STATISTICAL ANALYSIS

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 all regions sampled (OFC, VS, ACC, dorsal putamen, thalamus, hippocampus, and midbrain). A separate MANOVA was conducted on the PFC subregions. To test the hypothesis that OFC and VS MAO-A V_T would be inversely related to impulsivity, Pearson's correlation coefficients were calculated.

3.4 RESULTS

3.4.1 SUBJECT CHARACTERISTICS

Participants were aged 18 to 49 years. The ASPD group reported significantly greater impulsivity and more conduct disorder symptoms compared to the control group.

[Insert Table 3-1]

3.4.2 DIFFERENCE IN MONOAMINE OXIDASE-A TOTAL DISTRIBUTION VOLUME BETWEEN ANTISOCIAL PERSONALITY DISORDER AND CONTROL SUBJECTS

The main finding is that MAO-A V_T was significantly reduced 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 ($F_{2,33} = 12.9$, $p = 0.001$) and OFC ($F_{2,33} = 12.6$, $p = 0.001$). Results did not change when the control participant with the highest MAO-A V_T values was removed from the analysis (MANOVA group effect: $F_{2,32} = 7.1$, $p = 0.003$; univariate effect of VS: $F_{2,32} = 12.8$, $p = 0.001$; univariate effect of OFC: $F_{2,32} = 12.4$, $p = 0.001$). A separate MANOVA that compared the controls without AD ($n = 9$) with the ASPD subjects ($n = 18$) showed a similar reduction of OFC and VS

Table 3-1. Demographic and Clinical Characteristics

Characteristics[1]	**ASPD (n=18)**	**Controls (n=18)**
Age[2]	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[3]	3.6 ± 2.8	1.9 ± 2.0
Impulsivity (Self-reported)		
- NEO-PI-R Impulsivity subscale score (*T*-score)[2]	59.2 ± 12.4*	50.4 ± 12.6
Conduct Disordered Behavior		
- Number of conduct disorder symptoms[3]	7.9 ± 0.4**	0.4 ± 0.9
Psychopathy		
- PCL-R total score	26.4 ± 6.8	NA[4]
- PCL-R factor 1 score	9.4 ± 3.3	NA
- PCL-R factor 2 score	14.8 ± 3.9	NA

[1]values are expressed as mean ± standard deviation, except where indicated; [2]independent samples *t*-test; [3]Mann-Whitney U test; [4]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; NA = not available

MAO-A V_T in the ASPD group ($F_{2,24}$ = 3.8, p = 0.036). There was also a significant reduction of MAO-A V_T in all of the main brain regions analyzed for the ASPD participants (n = 18) compared to controls (n = 18) (MANOVA group effect: $F_{7,28}$ = 2.9, p = 0.022), with significant univariate effects detected in all regions ($F_{2,33}$ = 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.

[Insert Table 3-2 and Figure 3-1]

3.4.3 RELATIONSHIP BETWEEN VENTRAL STRIATUM AND ORBITOFRONTAL CORTEX MONOAMINE OXIDASE-A TOTAL DISTRIBUTION VOLUME AND MEASURES OF IMPULSIVITY IN ANTISOCIAL PERSONALITY DISORDER

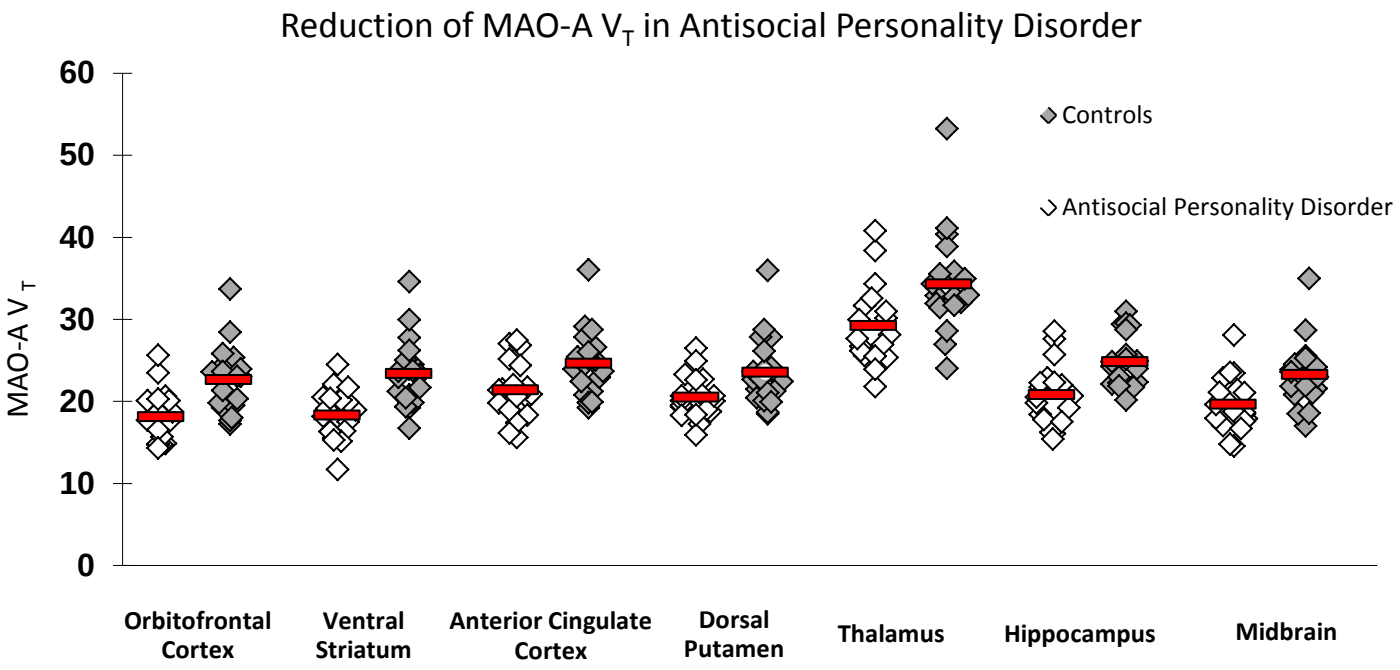
In the ASPD subjects, VS MAO-A V_T was negatively correlated with IGT performance (r = -0.52, p = 0.034). That is, lower VS MAO-A V_T was associated with more risky and impulsive decision making. VS MAO-A V_T also showed an inverse relationship with self-reported impulsivity on the NEO PI-R (r = -0.50, p = 0.034). ASPD subjects rated the most impulsive on the PCL-R had the lowest VS MAO-A V_T (t_{16} = 2.8, p = 0.013). No significant relationships were detected in the ASPD sample between OFC MAO-A V_T and PCL-R impulsivity (t_{16}= 1.7, p =

Table 3-2. Comparison of MAO-A V_T in Antisocial Personality Disorder 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

Antisocial personality disorder was associated with decreased 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.

Figure 3-1



ASPD was associated with decreased MAO-A V_T in OFC and VS compared with controls (MANOVA group effect: $F_{2,33}$ = 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, 9 of whom also had comorbid alcohol dependence. There was also an effect of diagnosis on MAO-A V_T across all brain regions (MANOVA group effect: $F_{7,28}$ = 2.8, p = 0.022). Red 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.

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).

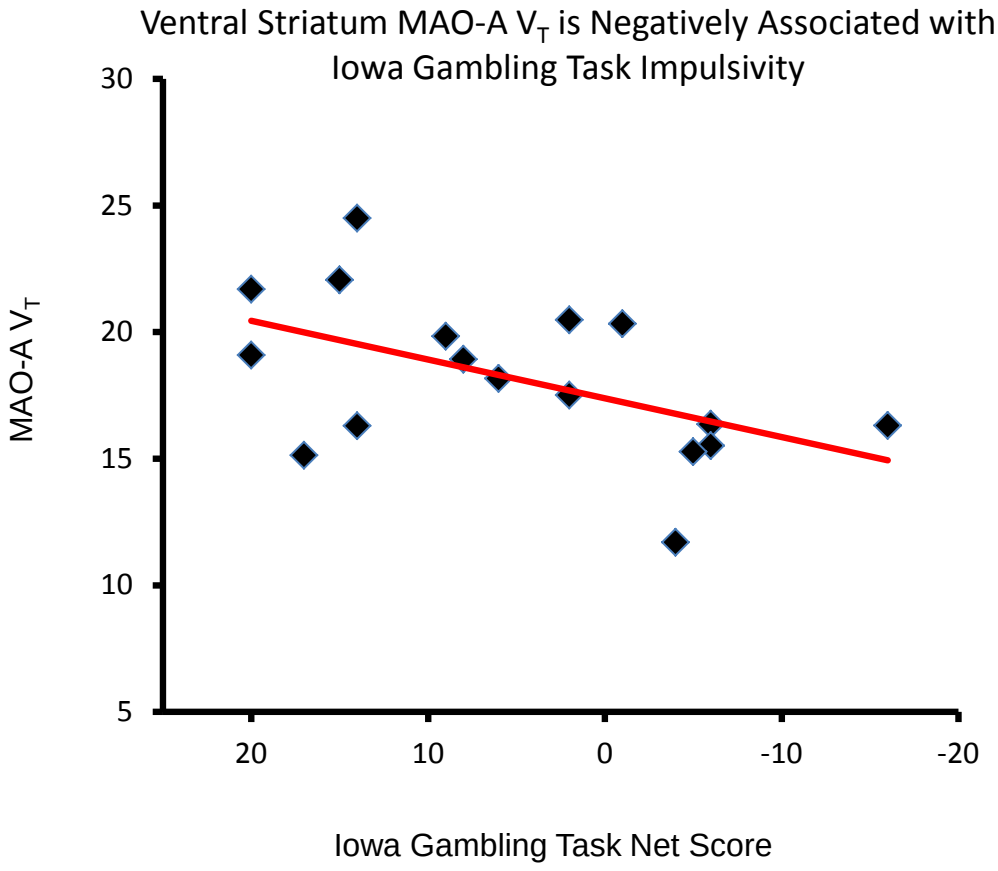
[Insert Figures 3-2, 3-3, 3-4]

3.5 DISCUSSION

This study is the first investigation of MAO-A brain levels in impulsive and violent offenders with a DSM-IV-TR diagnosis of ASPD. Consistent with our main hypotheses, we found that OFC and VS MAO-A V_T were significantly decreased in ASPD and that behavioral, self-report, and clinically-rated measures of impulsivity were all negatively correlated 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.

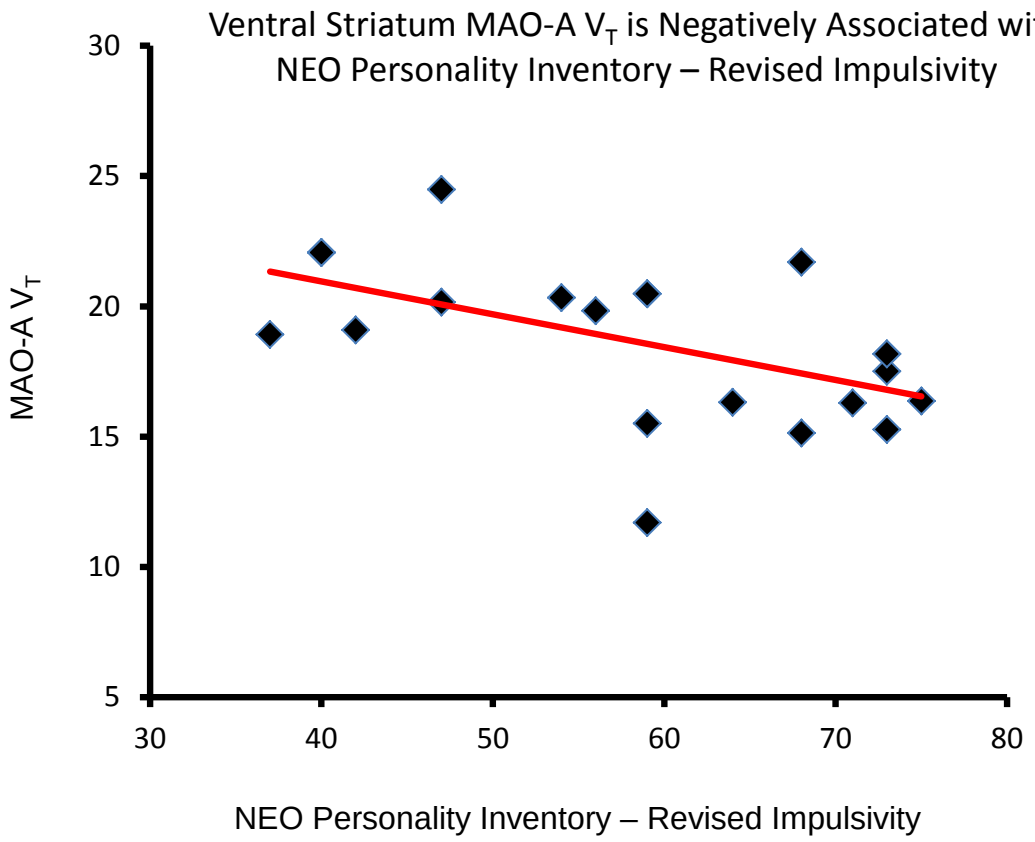
Our main finding is that low OFC and VS MAO-A V_T were associated with a disorder characterized by pathological levels of impulsivity and aggression. There are two conceptual models relating reduced MAO-A levels to impulsive-aggressive

Figure 3-2



VS 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).

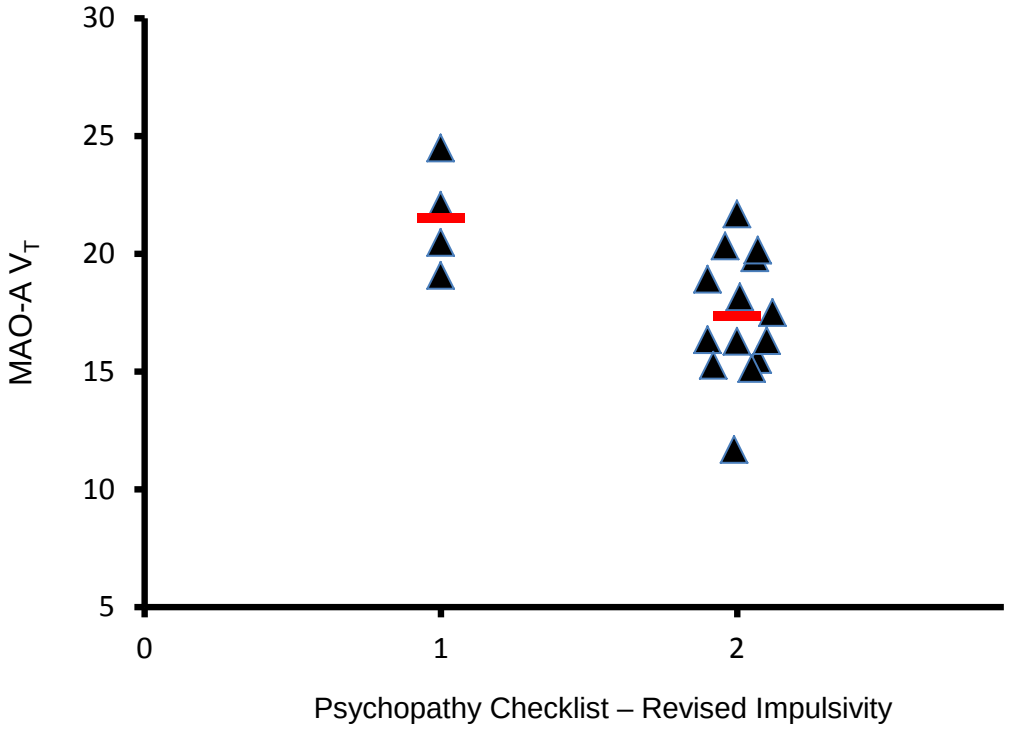
Figure 3-3



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).

Figure 3-4

Ventral Striatum MAO-A V_T is Lower in Antisocial Personality Disorder with Greater Psychopathy Checklist – Revised Impulsivity



ASPD subjects rated the most impulsive on the PCL-R had lower VS MAO-V_T than subjects rated less impulsive (Means [red bars]: 17.4 vs. 21.5; t_{16} = 1.7, p = 0.013).

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, Nelen, Breakefield, 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 C to T 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. While 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 decreased 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 KO 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 KOs also exhibit cognitive and physiological responses characteristic of ASPD with high psychopathic traits, such as decreased startle reflex (Popova et al., 2001), reduced anxiety (Popova et al., 2001), impaired risk assessment (Godar et al., 2011), and attenuated stress reaction (Popova et al., 2006). While 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 phenotypes do not match. For instance, 5-HT_{1B} KO conditions are associated with increased impulsive violence in mice (Saudou et al., 1994), but 5-HT_{1B} receptor binding in postmortem PFC does not differ between pathologically aggressive and healthy individuals (Huang, Grailhe, Arango, Hen, & Mann, 1999). Moreover, molecular imaging studies find a relationship between decreased 5-HT_{1B} receptor expression and internalizing conditions, such as posttraumatic stress disorder and MDD, that are not, on average, associated with high aggression or impulsivity (Murrough, Czermak, et al., 2011; Murrough, Henry, et al., 2011). By contrast, the consistency in phenotype between the MAO-A KO and ASPD with high psychopathic traits (e.g., increased aggression, high impulsivity, low anxiety, fearless dominance, and low stress hormones) suggests that the MAO-A KO is an important model for understanding the pathophysiology of ASPD.

We 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, Colledge, Leonard, & Blair, 2002; Vollm et al., 2010) that underlies the reckless and impulsive behaviors of these conditions (Blair, 2008). Mounting evidence suggests that exaggerated DA response to highly salient stimuli increases vulnerability to impulsive and reward-seeking

behaviors (Leyton & Vezina, 2014). One model of impulsivity in individuals with high antisocial-impulsive psychopathic traits posits that neurochemical hypersensitivity of the mesolimbic DA 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 DA synthesis capacity and vesicular storage capacity, was associated with greater behavioral disinhibition (Lawrence & Brooks, 2014). Thus, it has been proposed that individuals at high risk for externalizing conditions have larger amounts of pre-synaptic DA (Lawrence & Brooks, 2014). Since DA is a high affinity substrate for MAO-A in humans (O'Carroll, Fowler, Phillips, Tobbia, & Tipton, 1983) and MAO-A inhibition potentiates striatal DA efflux (Finberg et al., 1995), we interpret the association between decreased VS MAO-A V_T and increased impulsivity as supportive of the model linking greater VS presynaptic DA efflux and/or reward-based DA release to high impulsivity and externalizing behaviors.

3.6 STUDY LIMITATIONS

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, since 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 & Iacono, 2014).

3.7 CONCLUSION

In summary, we found that highly impulsive, violent males with ASPD had reduced MAO-A V_T in the OFC and VS. These results suggest that reduced 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 of reduced MAO-A levels 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. Decreased VS MAO-A levels were additionally associated with greater impulsivity, which, given the role of MAO-A in modulating DA efflux, suggests greater complexity to the model linking elevated VS DA release to rewarding stimuli in externalizing disorders.

CHAPTER 4: Ventral Striatum Monoamine Oxidase-A Distribution Volume Is Associated with Functional Connectivity of the Ventral Striatum in Impulsive Males with Antisocial Personality Disorder

4.1 ABSTRACT

Introduction: Mounting evidence suggests that MAO-A level in the VS is associated with impulsivity, aggression, and the clinical phenotype of ASPD. Although impulsivity is a core feature of ASPD, little is known about the neurocircuitry underlying impulsive behaviors. Therefore, the aim of the study was to explore the relationship in ASPD between VS MAO-A level and functional connectivity (FC) of two seed regions, superior and inferior VS (VSs, VSi), using PET and resting state fMRI, respectively.

Methods: Nineteen males with ASPD underwent [^{11}C] harmine PET scanning to measure VS MAO-A V_T, an index of MAO-A density, and seed-based resting state fMRI that assessed the FC of two bilateral seed regions in the VSi and VSs. Subjects also completed the BIS 11, NEO PI-R impulsivity subscale, and the IGT.

Results: The VSs showed functional coupling with bilateral dorsomedial prefrontal cortex (DMPFC) that was correlated with VS MAO-A V_T (r = 0.47, p = 0.04, R^2 = 0.23), while the VSi showed FC with the right hippocampus that was anti-correlated with VS MAO-A V_T (r = -0.55, p = 0.01, R^2 = 0.31). Additionally, VSs-DMPFC FC was negatively correlated with NEO PI-R impulsivity (r = -0.49, p = 0.03), as was VSi-Hippocampus FC with BIS 11 motor impulsiveness (r = -0.50, p = 0.03).

Conclusions: To the best of our knowledge, this is the first study to investigate the relationship between MAO-A V_T and resting state FC. These preliminary results of a small ASPD sample suggest that VS MAO-A V_T is associated with the FC of striatal

regions implicated in impulsive behavior. Further investigation of a comparison group is warranted to determine the specificity of these results to ASPD.

4.2 INTRODUCTION

Investigating symptom clusters in relation to multiple biomarkers has emerged as a promising approach in psychiatric research (Boksa, 2013). ASPD is a common psychiatric condition that exacts a high healthcare and societal burden due to the impulsive behavior of affected individuals (Scott, Knapp, Henderson, & Maughan, 2001). MAO-A is an enzyme located on outer mitochondrial membranes in glia and monoamine-releasing neurons (Youdim et al., 2006) that has been implicated in impulsive behavior, given the convergence of findings from animal models and PET studies showing an association of low or absent MAO-A brain levels with greater impulsivity (Alia-Klein et al., 2008; Cases et al., 1995; Scott et al., 2008; Soliman et al., 2011). We recently demonstrated that MAO-A V_T, an index of MAO-A density that can be measured using [^{11}C] harmine PET, is lower in ASPD and that low MAO-A V_T in VS is related to greater impulsivity (Kolla et al., 2014). These results suggest that low brain MAO-A V_T is a viable molecular target to pursue in clinically impulsive phenotypes and that MAO-A level may potentially influence the neural circuitry underlying impulsive behaviors in ASPD.

Resting state fMRI can be used to identify brain regions showing a strong coherence in spontaneous blood oxygen-level dependent (BOLD) fluctuations under resting

conditions, which has been interpreted as a measure of FC (Fox & Raichle, 2007). To the best of our knowledge, only three resting state fMRI studies of unique ASPD/psychopathic populations have been reported in the literature. One investigation of young ASPD offenders found decreased FC between the default mode, attention, and cerebellar networks (Tang, Jiang, Liao, Wang, & Luo, 2013), while two seed-based resting-state analyses of psychopathic samples reported reduced resting state cortical-subcortical FC (Contreras-Rodriguez et al., 2014; Motzkin, Newman, Kiehl, & Koenigs, 2011). One of these studies (Contreras-Rodriguez et al., 2014) reported one measure of self-reported impulsivity but did not examine FC in relation to this symptom. Despite the strong association between impulsivity and criminal offending in antisocial populations (Bechtold, Cavanagh, Shulman, & Cauffman, 2014), the relationship between impulsivity in ASPD and the FC of brain regions subserving impulsive behavior is presently unknown.

A growing number of fMRI-genetic studies in healthy males have reported correlations between the low-transcription MAO-A genetic variant; personality traits related to impulsivity, such as anger control or reactivity; and altered BOLD signaling in brain regions involved in emotional arousal (Alia-Klein et al., 2009; Denson, Dobson-Stone, Ronay, von Hippel, & Schira, 2014). Since MAO-A brain level has not been shown to vary according to the low or high activity MAO-A genotype (Fowler et al., 2007), it has been suggested that the BOLD responses underpinning anger expression in the aforementioned studies relate to effects induced by lower MAO-A gene expression during early maturation of brain

networks. However, to answer the critical question of whether brain MAO-A level is associated with the neural mechanisms thought to underlie impulsive behavior, the application of complementary PET and fMRI imaging techniques is necessary.

The VS is a core component of the cortico-limbic-striatal neurocircuitry that receives input from the midbrain dopaminergic system and is linked to impulsive responding (Basar et al., 2010; Dalley et al., 2011; Dalley et al., 2007). Given that functional alterations of the VS relate to impulsivity in antisocial groups (Glenn & Yang, 2012) and VS MAO-A V_T is decreased in impulsive offenders with ASPD (Kolla et al, 2014), the main study objective was to investigate the relationship between VS MAO-A V_T and VS FC in a sample of men with ASPD. We specifically hypothesized that VS MAO-A V_T would show an association with the FC of two VS seed regions and that these associations would be correlated with measures of impulsivity.

4.3 METHOD AND MATERIALS

Nineteen males with ASPD completed the study protocol. 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.

4.3.1 PARTICIPANTS

Subjects were recruited from the community and probation services. All participants were clinically assessed by a forensic psychiatrist (NJK) and diagnosed using the SCID-II (First et al., 1997) and SCID I (First et al., 2002). All subjects were additionally administered the Wechsler Test of Adult Reading – Revised that provides an estimate of full-scale IQ (Wechsler, 1981).

Each ASPD participant had a history of impulsive violent offending that included conviction or admission of assault, sexual assault, robbery, uttering threats, and manslaughter. Exclusion criteria included history of a psychotic, major depressive, or bipolar disorder; current drug abuse or dependence; use of psychotropic medication; and cigarette smoking in the last month. Non-smoking status was determined by breathalyzer testing for carbon monoxide (MicroSmokerlyzer; Bedfont Scientific Ltd., Kent, United Kingdom). Study subjects refrained from the use of tea, coffee, or caffeinated beverages on the day of PET scanning. Subjects provided negative urine toxicology screens on all study days.

4.3.2 POSITRON EMISSION TOMOGRAPHY IMAGING

Participants underwent a single [^{11}C] harmine PET scan at the Centre for Addiction and Mental Health Research Imaging Centre. PET data for 18 of the study subjects have been presented in another study (Kolla et al., 2014). All participants in the

current investigation completed the same PET scan protocol that has been used for previous [^{11}C] harmine PET studies in our laboratory (Bacher et al., 2011; Kolla et al., 2014; Meyer et al., 2009). Interested readers are referred to these reports for specific details about the protocol.

The VS was chosen as the primary PET ROI, given its relationship to impulsivity in ASPD (Glenn & Yang, 2012; Kolla et al., 2014). The VS was based on the definition provided by Mawlawi and colleagues (Mawlawi et al., 2001).

4.3.3 RESTING STATE FUNCTIONAL MAGNETIC RESONANCE IMAGING SCAN

None of the resting state fMRI data in the current report has been previously published. Nine of the 19 subjects had their PET and fMRI scans on the same day or one day apart. Scans were separated by 14.6 ± 16.5 days for the remaining participants.

4.3.3.1 IMAGE ACQUISITION

Images were acquired with a 3.0-T GE Discovery MR750 scanner (GE Medical Systems, Milwaukee, WI) equipped with a standard 8-channel head coil at the Centre for Addiction and Mental Health Research Imaging Centre. Each participant completed a 6-minute fMRI scan (TE = 30 ms, TR = 2000 ms, flip angle = 60º, slice

thickness = 5.0 mm, 31 axial slices, FOV = 220 mm, matrix = 64 x 64; voxel size = 3.4 mm x 3.4 mm x 5.0 mm) performed in the resting state with eyes closed. To improve the registration process, the T1 anatomical scan used for the PET ROI analysis (TE = 3.0 ms, TR = 6.7 ms, flip angle = 8º, slice thickness = 0.9 mm, 200 slices, FOV = 240 mm, matrix = 256 x 256, voxel size = 0.9 mm x 0.9 mm x 0.9 mm) was also used for spatial normalization and localization of the functional MRI scan.

4.3.3.2 IMAGE PREPROCESSING

Preprocessing of resting-state functional neuroimaging data was carried out using the FMRIB software library (http://www.fmrib.ox.ac.uk/fsl/). The first five volumes were discarded to allow for T1 equilibrium effects. Preprocessing steps included slice-time correction, removal of non-brain tissue using the Brain Extraction Tool (BET) (Smith, 2002), spatial smoothing using a Gaussian kernel of 6 mm FWHM, and mean-based intensity normalization by a single multiplicative factor of all images. Six motion parameter time series (3 translational and 3 rotational parameters) were included as covariates of no interest in the general linear model (GLM), and the aCompCor method (Behzadi, Restom, Liau, & Liu, 2007) was applied using an in-house MATLAB-based script to correct for cerebrospinal and white matter noise sources. De-noised scans were bandpass filtered between 0.009 and 0.9 Hz. fMRI volumes were registered to each participant's structural scan and

the MNI-152 stereotactic space using the Linear Image Registration Tool (FLIRT) (Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson & Smith, 2001).

4.3.3.3 SEED REGION OF INTEREST SELECTION

Two seed ROIs in the VS were manually selected in standard space: bilateral VSs and bilateral VSi. The VSs seed included the ventral caudate (MNI: $x = \pm 10$, $y = 15$, $z = 0$, with 3 mm radius), and the VSi seed included both ventral caudate and nucleus accumbens (MNI: $x = \pm 9$, $y = 9$, $z = -8$, with 3 mm radius). The VS seed coordinates were derived from a previously published study (Di Martino et al., 2008) that assessed striatal FC patterns. We tested both seeds because the VS ROI used for the PET analysis encompasses both inferior and superior ventral striatal regions (Mawlawi et al., 2001).

4.3.3.4 FUNCTIONAL MAGNETIC RESONANCE IMAGING STATISTICAL ANALYSIS

Seed ROIs were registered to each subject's functional space utilizing the transformation matrix from the initial registration to standard space in FLIRT. Average time courses for each masked ROI were extracted and fitted with a linear model to detect correlated and anti-correlated voxels associated with the seed ROI. These correlations with the time series were interpreted as the degree of FC with each seed region for every subject. To identify voxels whose correlation with the

ROI time series was associated with MAO-A V_T, the spatially normalized effect size and standard error volumes provided input to a group analysis using FSL's FLAME mixed effect model (Beckmann, Jenkinson, & Smith, 2003). Demeaned VS MAO-A V_T values for each subject were included as regressors in two GLMs that fitted correlated voxels with the VSs or VSi seed time series. The modeled group effect sizes and standard errors for each of the two GLMs were divided to yield volumes that were *T* scores. *T* scores were then transformed to *Z* scores. Corrections for multiple comparisons were carried out using Gaussian random field theory cluster-based correction ($Z > 1.98$, cluster significance $p < 0.05$, corrected), which generated corrected *Z*-score maps correlating the FC of each seed (VSi or VSs) to MAO-A V_T.

Single-subject connectivity values between seed and target regions for the group level analyses were extracted by transforming masks of defined clusters into individual space and obtaining *Z*-score values from the connectivity map of interest. To ensure anatomical specificity of the extracted regions, the target region was masked with the anatomical map from the Harvard-Oxford atlas (50% probability).

4.3.4 CLINICAL MEASURES OF IMPULSIVITY

4.3.4.1 BARRATT IMPULSIVENESS SCALE – 11

The BIS 11 is self-report instrument indexing an impulsivity construct that consists of three subscales: motor impulsiveness, attentional impulsiveness, and non-

planning impulsiveness (Patton et al., 1995). The ICC of the BIS 11 total score in prisoner populations is 0.80 (Patton et al., 1995), and the motor impulsiveness subscale has been shown to discriminate clinically impulsive groups from healthy controls (Nasser, Gluck, & Geliebter, 2004).

4.3.4.2 NEO PERSONALITY INVENTORY – REVISED

The NEO PI-R (Costa Jr., 1992) is an extensively validated questionnaire based on the FFM of personality (Goldberg, 1990) that yields norm-referenced test scores for dimensional personality domains and traits, including impulsivity.

4.3.4.3 IOWA GAMBLING TASK

The IGT is a computerized, performance-based card game that measures choice impulsivity (Bechara et al., 1994). The goal is to win the most virtual money possible by choosing cards from different decks (A, B, C, or D) one at a time. Decks C and D yield consistently high rewards with higher overall losses, whereas decks A and B yield lower rewards with smaller overall losses. Participants are told from the outset that some decks offer better overall returns and that they can win by avoiding these decks. Twenty trials were administered over five blocks for a total of 100 trials. Highly impulsive subjects show the greatest impairment in performance during the latter trials of the IGT (Sweitzer et al., 2008). The net IGT score 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)].

4.3.5 STATISTICAL ANALYSIS

Pearson's correlation coefficients were used to measure the strength of the associations between observed FC patterns and impulsivity measures. Estimated full-scale IQ was included as a covariate in these analyses given the relationship between IQ and FC (van den Heuvel, Stam, Kahn, & Hulshoff Pol, 2009) and IQ and impulsivity (de Wit, Flory, Acheson, McCloskey, & Manuck, 2007).

4.4 RESULTS

4.4.1 SUBJECT CHARACTERISTICS

Subjects were aged 18 to 48 years. Estimated full-scale IQ scores for the group ranged from 85 to 123.

[Insert Table 4-1]

Table 4-1. Clinical and Demographic Characteristics of Antisocial Personality Disorder Subjects[1]

Characteristics	**ASPD (n=19)**
Age	36.0 (9.1)
Ethnicity	
- % Caucasian	47.4
- % African Canadian	26.3
- % Asian	10.5
- % Other	15.8
Estimated IQ	105.7 (10.9)
Education, years	13.9 (2.4)
VS MAO-A V_T	18.2 (3.1)
Impulsivity Measures	
- BIS II	
- Motor Impulsiveness	30.3 (4.3)
- Non-planning Impulsiveness	30.7 (6.8)
- Attentional Impulsiveness	19.1 (5.7)
- NEO-PI-R Impulsivity (*T*-score)	59.1 (13.0)
- IGT Net Score[2]	5.6 (-16 to 20)
Antisociality Measures	
- Number of Conduct Disorder Symptoms	7.7 (3.6)
- Number of ASPD Symptoms	5.6 (1.2)
PCL-R	
- Total Score	26.3 (6.6)
- PCL-R Factor 1 Score	9.5 (3.2)
- PCL-R Factor 2 Score	14.7 (3.8)
Conviction Data	
- Number of Convictions[2]	14.2 (0 to 56)
- Number of Violent Convictions[2]	2.1 (0 to 13)

[1] values are expressed as mean (standard deviation) or percentages, except where indicated; [2] mean (range)

4.4.2 FUNCTIONAL CONNECTIVITY: SUPERIOR VENTRAL STRIATUM SEED

Examination of FC during resting-state conditions revealed patterns of connectivity between VSs and frontal cortical regions, including bilateral DMPFC, bilateral pre- and post-central gyrus, and right superior frontal gyrus, that were correlated with VS MAO-A V_T (r = 0.47, p = 0.04, R^2 = 0.23; correlation with bilateral DMPFC). No FC involving the VSi seed was anti-correlated with VS MAO-A V_T.

4.4.3 FUNCTIONAL CONNECTIVITY: INFERIOR VENTRAL STRIATUM SEED

The VSi seed predicted patterns of activity in limbic regions (e.g., right hippocampus and parahippocampal gyrus) and posterior cortical regions, such as superior/middle temporal gyrus and occipital cortex, that were anti-correlated with VS MAO-A V_T (r = -0.55, p = 0.01, R^2 = 0.31; correlation with right hippocampus and parahippocampal gyrus). No FC involving the VSs seed was correlated with VS MAO-A V_T.

[Insert Table 4-2 and Figures 4-1, 4-2, 4-3, 4-4]

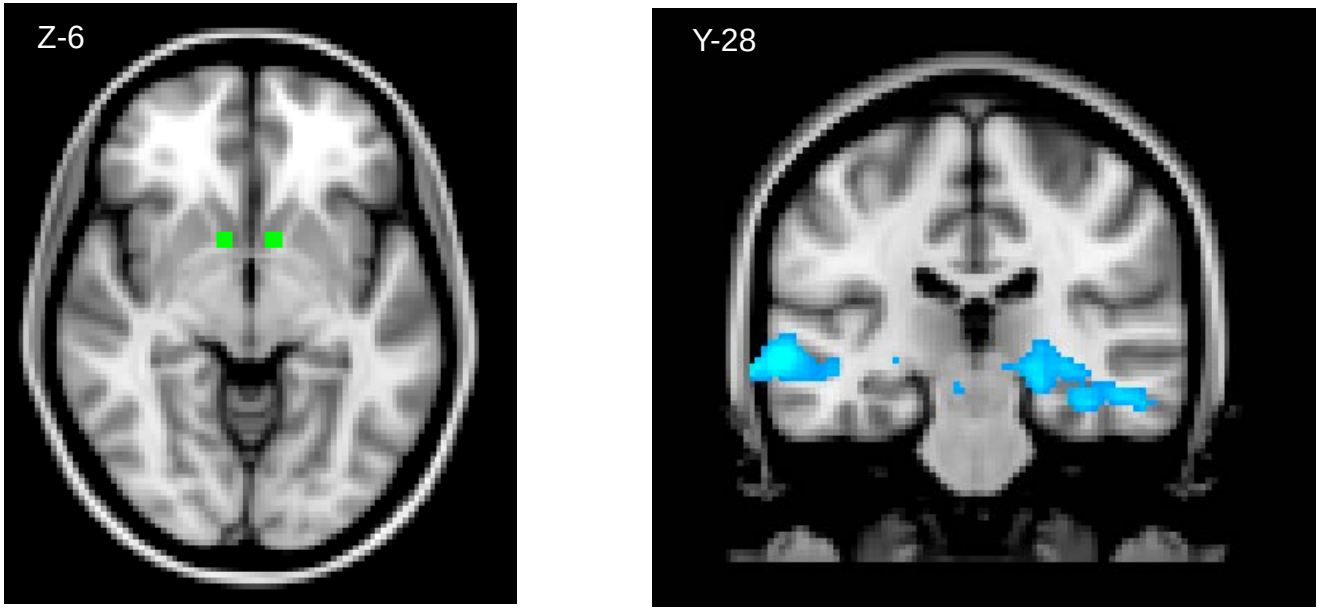
Table 4-2: Activation Peaks for the Functional Connectivity of Regions Associated with Ventral Striatum MAO-A V_T

Seed	Functional Region	Brodmann Area	MNI			Peak *Z*-score
			x	*y*	*z*	
Vsi	***Anticorrelated with MAO-A V_T***					
	Parahippocampal Gyrus, Hippocampus		20	-28	-6	3.12
	Calcarine Sulcus	17, 18	-6	-92	18	3.24
	Lateral Occipital Cortex, Superior/Middle Temporal Gyrus	19, 22, 39	-64	-24	-2	4.02
	Lateral Occipital Cortex, Middle Temporal Gyrus	19, 22, 39	56	-68	18	3.93
VSs	***Correlated with MAO-A V_T***					
	Pre/Postcentral Gyrus	3, 4, 5, 6	-10	-32	58	4.72
	Dorsomedial Prefrontal Cortex	8	8	40	50	3.28
	Superior Frontal Gyrus	6	18	22	44	4.33

Note: *Z*-scores indicate the degree of correlation between connectivity and MAO-A V_T. Peaks are from significant clusters ($p < 0.05$, corrected).

Figure 4-1

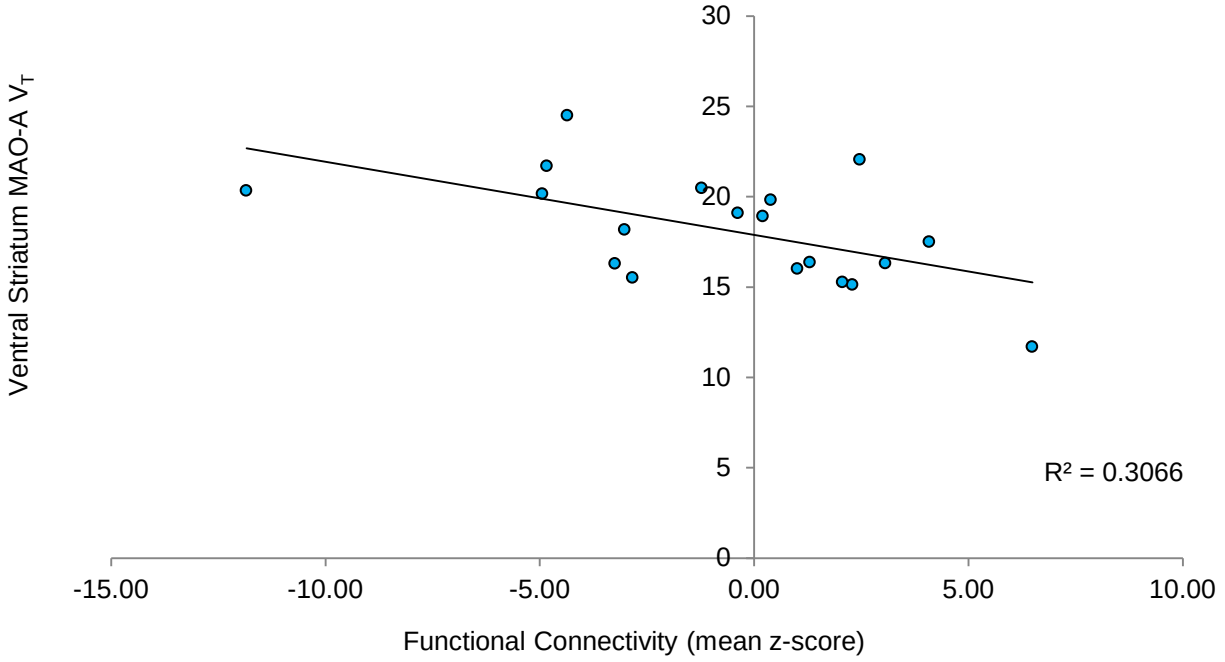
Functional Connectivity of Inferior Ventral Striatum



Regions (blue) where FC with the VSi coordinates (green) were significantly anti-correlated with VS MAO-A V_T.

Figure 4-2

Inferior Ventral Striatum Functional Connectivity is Anti-correlated with MAO-A V_T



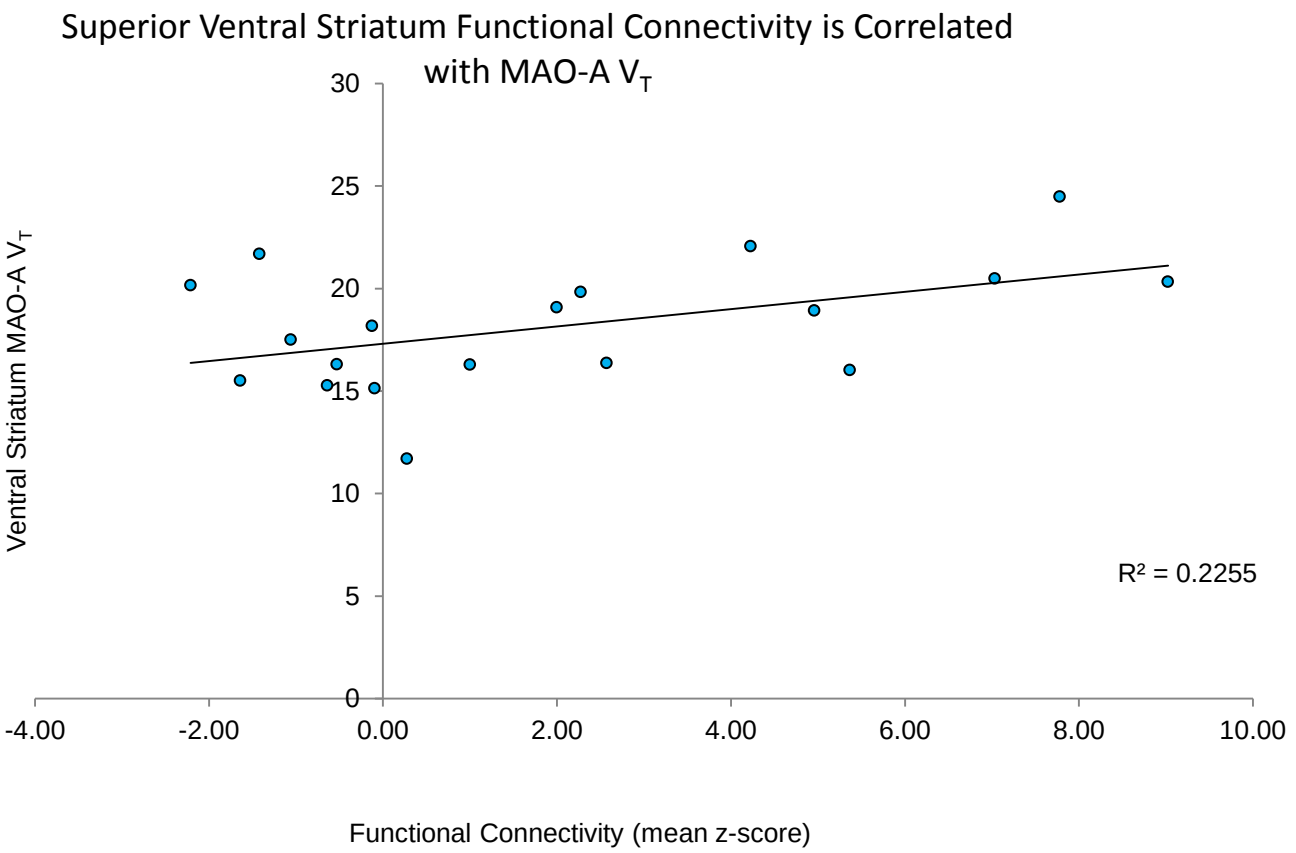
Resting state FC from VSi (mean z-score) is anti-correlated with ventral striatum VS MAO-A V_T: r = 0.55, p = 0.01, R^2 = 0.31

Figure 4-3

Functional Connectivity of Superior Ventral Striatum

Regions (orange) where FC with the VSs coordinates (green) were significantly correlated with VS MAO-A V_T.

Figure 4-4



Resting state FC from superior ventral striatum (mean z-score) is correlated with VS MAO-A V_T: r = 0.47, p = 0.04, R^2 = 0.23

4.4.4 RELATIONSHIP BETWEEN VENTRAL STRIATUM MONOAMINE OXIDASE-A TOTAL DISTRIBUTION VOLUME, FUNCTIONAL CONNECTIVITY, AND IMPULSIVITY

VS MAO-A V_T was negatively correlated with NEO PI-R impulsivity (r = -0.45, p = 0.05) and IGT performance (r = -0.48, p = 0.05). In other words, individuals who reported greater NEO-PI-R impulsivity and performed more poorly on the IGT had higher VS MAO-A V_T. VS MAO-A V_T was not correlated with any of the BIS 11 subscales. DMPFC-VSs FC was negatively correlated with NEO PI-R impulsivity (r = -0.49, p = 0.03), while hippocampal-VSi connectivity was negatively correlated with BIS 11 motor impulsivity (r = -0.50, p = 0.03).

[Insert Table 4-3]

4.5 DISCUSSION

This is the first study to explore the association of VS MAO-A brain level with VS FC. We chose to investigate impulsive males with ASPD, because VS MAO-A V_T has shown a robust relationship to several measures of impulsivity in a subset of this sample (Kolla et al., 2014). Consistent with our hypotheses, we found that FC to both VS seed regions was associated with VS MAO-A V_T. We also found that these patterns of FC were related to self-reported impulsivity measures. These results shed new light on the relationship between MAO-A level and striatal-based FC in ASPD

Table 4-3: Correlations between VS MAO-A V_T, FC, and Measures of Impulsivity

	VS MAOA V_T	VSi-Hippocampus FC	VSs-DMPFC FC	NEO-PI-R	Net IGT Score	Barratt Attentional	Barratt Motor	Barratt Nonplanning
VS MAOA V_T	-	-	-	-	-	-	-	-
VSi-Hippocampus FC	-0.55**	-	-	-	-	-	-	-
VSs-DMPFC FC	0.47*	-0.34	-	-	-	-	-	-
NEO-PI-R[a]	-0.45*	0.14	-0.49*	-	-	-	-	-
Net IGT	0.48*	-0.20	0.16	-0.35	-	-	-	-
Barratt Attentional	0.17	-0.27	-0.36	0.30	0.09	-	-	-
Barratt Motor	0.15	-0.50*	-0.28	0.21	0.16	0.75***	-	-
Barratt Nonplanning	0.05	-0.40	-0.18	0.41	0.14	0.71***	0.65***	-

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; [a] = *T*-score

and suggest a potential role for MAO-A as a neuromodulatory influence on the neural circuitry subserving impulsive behaviors.

We show, for the first time, that individual differences in VS MAO-A V_T relate to variation in seed-based VS FC among impulsive males with ASPD. Several approaches have been adopted to investigate the influence of neurotransmitter systems on neurobehavioral circuits, including within-subject designs that test the effect of exogenous neuroreceptor agonists and antagonists on resting state fMRI connectivity patterns (McCabe & Mishor, 2011; Scheidegger et al., 2012). However, varying levels of affinity of some pharmacologic agents for multiple targets renders it difficult to attribute connectivity patterns to a single neurotransmitter system, and it is not possible to ascribe FC patterns to absolute levels of enzyme inhibition or receptor occupancy using fMRI alone. By combining fMRI and PET techniques, we were able to quantify and relate a regionally-specific *in vivo* neurochemical marker (e.g., VS MAO-A V_T) to the FC of seeds derived from the same anatomical region. Hence, the application of complementary neuroimaging techniques expands on previous paradigms and offers a more nuanced understanding of how MAO-A brain level in ASPD could affect the hemodynamic response to neural processing.

One of our two main findings is that VS MAO-A V_T was correlated with DMPFC-VSs FC. That is, greater resting state functional coupling between bilateral DMPFC and VSs was associated with higher VS MAO-A V_T. In addition, we found that VSs-DMPFC FC was negatively correlated with NEO PI-R impulsivity. This

finding is consistent with a recent investigation describing reduced functional coupling between prefrontal regulatory regions and subcortical drive structures, including caudate and nucleus accumbens, as a function of increasing trait impulsivity (Davis et al., 2013). Interestingly, administration of L-dopa to healthy subjects decreases FC between the ventral caudate and cortical structures (Kelly et al., 2009), and clinical samples of impulsive individuals exhibit greater striatal DA release following amphetamine challenge that is associated with poor response inhibition (Cherkasova et al., 2014). Since DA exhibits high affinity substrate binding to MAO-A (O'Carroll et al., 1983) and MAO-A inhibition promotes DA release from the VS (Finberg et al., 1995), a model linking increased VS DA signaling to decreased DMPFC-VSs coupling is consistent with the observed association of increased VS MAO-A V_T and greater DMPFC-VSs functional coupling. While this study cannot inform on the extent to which the observed FC patterns were modulated by VS DA levels, the results tentatively suggest that the corticostriatal networks implicated in impulsivity may be associated with VS MAO-A level.

Our second main finding is that VS MAO-A V_T was anti-correlated with hippocampus-VSi FC. In keeping with a model linking VS MAO-A level to DA-modulated VS FC, animal studies have demonstrated that under conditions promoting receipt of rewards, subregions of the hippocampus project excitatory inputs to the nucleus accumbens that has the effect of increasing VS phasic DA release to maintain goal-directed behavior (Sesack & Grace, 2010). In disorders

such as ASPD or psychopathy that exhibit dysfunctional reward processing, lower VS MAO-A V_T may serve to amplify these connections, such that hippocampal input to reward-based structures becomes dysregulated. Although VS MAO-A V_T was not associated with BIS 11 scores, we detected a negative association between VSi-hippocampal FC and motor impulsivity. Interestingly, hippocampus-lesioned rats make more impulsive choices than rats with intact hippocampi (Cheung & Cardinal, 2005; Mariano et al., 2009; Rawlins, Feldon, & Butt, 1985), and violent, impulsive offenders exhibit decreased hippocampus metabolism (Soderstrom, Tullberg, Wikkelso, Ekholm, & Forsman, 2000), suggesting that disrupted hippocampal circuits may be related to highly impulsive phenotypes.

4.6 STUDY LIMITATIONS

This preliminary investigation has several limitations. The most important is the absence of a control group. Although we demonstrated that VS MAO-A V_T was associated with seed-based VS FC in ASPD, without a comparison group or information about the relationship between VS MAO-A V_T and VS FC in healthy controls, we cannot conclude that the observed results are specific to ASPD. Still, we were able to show that VS MAO-A V_T was related to patterns of VS FC associated with self-reported impulsivity, which could suggest a model of VS FC as an endophenotype of impulsivity that differs as a function of VS MAO-A V_T. A second limitation is that some of the individual subject PET and MRI scans were obtained on different days. However, seed-ROI-based resting state FC for

statistically significant correlations shows high test-retest reliability in subjects scanned five months apart (Shehzad et al., 2009), and test-retest reliability of striatal MAO-A V_T is also high (Sacher et al., 2012). A third limitation is that the sample size was small, which may have limited the power to detect more robust associations between VS MAO-A V_T, VS resting state FC, and indices of impulsivity. A fourth limitation, common to virtually all neuroimaging studies of offender populations, is that our investigation was limited to males. However, ASPD is more common in males compared with females by a factor of 5-7 to 1 (Hamdi & Iacono, 2014).

4.7 CONCLUSION

In conclusion, we found in this preliminary investigation that the FC of regions encompassing the ventral caudate and nucleus accumbens varied as a function of VS MAO-A V_T in impulsive offenders with ASPD. The observed connectivity patterns were additionally associated with several measures of impulsivity. Our results add to the accumulating data on MAO-A as a key target in ASPD and merit similar investigations in healthy individuals to determine whether linkages between VS MAO-A V_T and FC patterns related to impulsivity are unique to the clinical phenotype of ASPD.

CHAPTER 5: Synthesis of Results, General Discussion, Future Directions, and Final Conclusion

5.1 SYNTHESIS OF RESULTS AND GENERAL DISCUSSION

The results of the previous experiments highlight first and foremost the strong associations of MAO-A with both specific psychiatric disorders and symptom clusters that transcend single diagnostic entities. For example, we demonstrated that increased MAO-A level was present in the PFC and ACC of BPD with high borderline symptomatology and that elevated MAO-A V_T was also associated with greater suicidality, mood symptoms, and neurocognitive deficits in BPD. We additionally showed that MAO-A V_T was lower in the OFC and VS of ASPD and that VS MAO-A V_T was negatively correlated with self-report and behavioral measures of impulsivity. Finally, we reported that VS MAO-A V_T in ASPD was associated with VS FC, which, in turn, showed a relationship with self-reported impulsivity, suggesting that VS MAO-A may influence the neural circuitry linked to impulsive behavior. The results of these investigations clearly indicate that ASPD and BPD are associated with altered brain MAO-A level and further suggest that the two disorders have distinct neurochemical underpinnings. However, given that ASPD and BPD display overlapping symptom clusters that might presumably comprise a similar neurobiology, further discussion is warranted to outline additional factors that could have influenced the obtained results.

Although BPD and ASPD are both associated with high levels of impulsivity, a relationship between MAO-A V_T and impulsivity was only detected in ASPD. A potential explanation for this discrepancy is the regional specificity of the finding.

For instance, the relationship between impulsivity and MAO-A V_T in ASPD was limited to the VS. We did not sample VS MAO-A V_T in BPD, because, to the best of our knowledge, no postmortem samples and very few neuroimaging investigations have reported abnormalities of this region in BPD. Resting state hypometabolism of the right VS was reported in a small sample of BPD patients versus 15 healthy subjects using 2-[^{18}F]-fluoro-2-deoxy-D-glucose PET imaging (De La Fuente et al., 1997), although the relationship between regional glucose metabolism and BPD symptomatology was not explored. Similarly, although greater VS mu-opioid receptor binding was noted in a PET study of BPD, this measure was not significantly correlated with impulsivity (Prossin et al., 2010). We did not detect any correlation of BIS 11 impulsivity subscale scores with MAO-A V_T for any of the regions examined in the BPD sample, but the possibility that VS MAO-A V_T is associated with the impulsivity of BPD cannot be excluded.

Another possibility for the divergence in average MAO-A level between ASPD and BPD samples could relate to the presence of comorbid conditions. Our finding that PFC and ACC MAO-A V_T were highly elevated in both moderate and severe BPD with comorbid MDE adds to the substantial body of PET research reporting robust links between increased MAO-A level and MDE (Chiuccariello et al., 2014; Meyer et al., 2006; Meyer et al., 2009; Sacher et al., 2014). The fact that a linear relationship between PFC/ACC MAO-A V_T and depression severity has been reported adds further weight to these findings (Chiuccariello et al., 2014). On the other hand, PET studies of healthy subjects have failed to detect a relationship

between personality traits predisposing to MDE, such as neuroticism or negative emotionality, and MAO-A level (Alia-Klein et al., 2008; Soliman et al., 2011), suggesting that it is the severity of symptoms comprising an MDE or expression of select symptoms that may mediate the association of elevated MAO-A V_T with MDE. Indeed, reversed neurovegetative symptoms characteristic of atypical depression were previously shown to relate to elevated PFC and ACC MAO-A V_T in MDE (Chiuccariello et al., 2014). We did not find a relationship between OFC or ACC MAO-A V_T and HDRS score in our ASPD participants, most of whom reported high levels of neuroticism but did not endorse a MDE. This result could be due to the reduced variability of HDRS scores in our sample but is also consistent with the notion that personality traits increasing risk for MDE are less strongly related to elevated MAO-A V_T in the absence of a full-blown mood disorder.

It is possible, although less likely, that the decision to limit the study of BPD to females and ASPD to males may have biased average MAO-A V_T values toward opposite directions. In the very few neuroimaging studies of ASPD that included males and females (de Oliveira-Souza et al., 2008; Raine, Yang, Narr, & Toga, 2011; Sato et al., 2011; Yang, Raine, Narr, Colletti, & Toga, 2009), no gender differences in imaging results were reported. Among neuroimaging investigations of BPD that sampled both sexes, most, but not all studies (Leyton et al., 2001; Soloff, Nutche, Goradia, & Diwadkar, 2008; Soloff et al., 2014; Soloff, Kelly, Strotmeyer, Malone, & Mann, 2003; Soloff, Meltzer, Becker, Greer, & Constantine, 2005), reported no difference in the imaging results obtained between males and females,

although the majority of these analyses were likely underpowered to compare women and men. The lack of a consistently reported gender effect in neuroimaging studies of BPD or ASPD subjects makes it less plausible that the difference in average MAO-A V_T values between the two samples was due to a strong effect of gender. Moreover, MAO-A V_T has not been shown to differ by gender in other clinical samples when controlling for menopausal or postpartum status in females (Bacher et al., 2011; Chiuccariello et al., 2014; Matthews et al., 2013; Meyer et al., 2009).

5.2 FUTURE RESEARCH DIRECTIONS

5.2.1 COMPARISON OF MONOAMINE OXIDASE-A TOTAL DISTRIBUTION VOLUME IN BORDERLINE PERSONALITY DISORDER AND ANTISOCIAL PERSONALITY DISORDER

The present studies tested MAO-A V_T in BPD and ASPD samples but did not compare results between groups. All of the BPD subjects had comorbid MDE, an illness that is independently associated with increased MAO-A V_T, while three of the ASPD participants had comorbid BPD. Although PFC and ACC MAO-A V_T were higher in severe BPD compared with MDE after controlling for depressive symptoms, investigating BPD and ASPD groups without additional comorbid psychopathology to isolate the effect of diagnosis on MAO-A V_T would represent an important future research direction. Similarly, data obtained from multimodal [^{11}C]

harmine PET and resting state fMRI studies in BPD could be compared to the results of the ASPD sample.

5.2.2 THE RELATIONSHIP OF MONOAMINE OXIDASE-A TO OTHER NEUROTRANSMITTER SYSTEMS

MAO-A is inextricably linked to myriad other molecular signaling systems given that one of its primary functions is to terminate the activity of neurotransmitters (Youdim et al., 2006). Investigating additional neurotransmitter systems that are either directly or indirectly modulated by MAO-A, and for which there is a strong rationale to suspect their involvement in the pathophysiology of BPD, ASPD, and/or related symptom clusters, would be a logical next step to pursue.

5.2.2.1 ENDOCANNABINOID SYSTEM

The endocannabinoid system (ECS) has recently emerged as an exciting new target in molecular neuroscience. Stimulated by Δ9-THC (tetrahydrocannabinol), the ECS controls the release of a large number of brain neurotransmitters and is a potent modulator of many neural circuits influencing human behavior (Basavarajappa, 2007). Endogenous cannabinoid ligands (endocannabinoids) are fatty acid amides and monoacylglycerols that function as lipid neuromodulators. Unlike most other neurotransmitters that are stored in vesicles, endocannabinoids exhibit rapid, on-demand synthesis in response to neuronal activation, and once synthesized, undergo

retrograde synaptic transmission to the extracellular space where they bind to presynaptic endocannabinoid receptors (Basavarajappa, 2007). This style of neurotransmission is known to precisely regulate information flow within most major neurotransmitter pathways and contributes to the synaptic plasticity of brain regions implicated in neuropsychiatric disorders (Basavarajappa, 2007).

Cannabinoid receptors are the most abundant G protein-coupled receptors in the brain, and they bind endocannabinoids with high affinity. Cannabinoid subtype 1 receptors (CB1) are densely expressed in the CNS, including PFC, hippocampus, and amygdala, in addition to peripheral tissues (Di Marzo & De Petrocellis, 2012). Fatty acid amide hydrolase (FAAH) is a brain enzyme that modulates the ECS (Cravatt et al., 1995). FAAH metabolizes anandamide (AEA), an endogenous endocannabinoid that binds to CB1 receptors (Ahn, McKinney, & Cravatt, 2008) and stimulates neurotransmission. A critical mechanism governing CB1 receptor-mediated signaling is the active catalysis of AEA by FAAH (Cravatt et al., 1995). Because of its role in modulating AEA, FAAH has been actively investigated as a therapeutic target. FAAH inhibitors have already shown efficacy in preclinical models of depressive disorders (Bambico, Duranti, Tontini, Tarzia, & Gobbi, 2009) and anxiety (Moreira, Kaiser, Monory, & Lutz, 2008).

5.2.2.2 [^{11}C] CURB BINDING PROVIDES A MEASURE OF FATTY ACID AMIDE HYDROLASE LEVEL

FAAH level can be measured using [^{11}C] CURB, a novel PET radiotracer that binds selectively, specifically, and irreversibly to FAAH and shows good test-retest reliability in healthy humans (Rusjan et al., 2013; Wilson et al., 2011).

5.2.2.3 RELATIONSHIP BETWEEN MONOAMINE OXIDASE-A ACTIVITY AND THE ENDOCANNABINOID SYSTEM

Growing research suggests that MAO-A activity and ECS signaling are intimately connected. For example, upregulated PFC CB1 receptor density *in vivo* and decreased PFC AEA tissue content have been reported in rats administered the MAOI tranylcypromine for 21 days (Hill, Ho, Hillard, & Gorzalka, 2008), while MAO-A activity in pig brain cortex is competitively inhibited by high concentrations of AEA (Fisar, 2010). Moreover, elevated MAO-A gene expression has been detected in the amygdala and median and dorsal raphe nuclei of CB1 receptor KO mice compared with wild type (Rodriguez-Arias et al., 2013). Similar to the connections between increased MAO-A activity, disrupted mitochondrial membrane function, and stimulation of pro-apoptotic signaling pathways, AEA and synthetic cannabinoid receptor agonists were shown to inhibit the mitochondrial membrane respiratory chain in rat heart mitochondria and induce morphological changes consistent with apoptotic cell death in human non-neuronal cell lines

(Athanasiou et al., 2007). These results suggest that MAO-A activity and ECS signaling may reciprocally influence each other and/or play a synergistic role in the pathophysiology of clinical disorders.

5.2.2.4 INVESTIGATING FATTY ACID AMIDE HYDROLASE IN BORDERLINE PERSONALITY DISORDER WITH HIGH SUICIDALITY

Several compelling reasons link increased FAAH levels to BPD with suicidality. First, cerebrospinal fluid levels of AEA are reduced in BPD, suggesting higher central levels of FAAH (Koethe, 2014). Second, postmortem brain samples of suicide victims show up-regulation of CB1 receptors and higher FAAH levels (Erdozain et al., 2014; Hungund et al., 2004; Vinod et al., 2005; Vinod et al., 2010). Third, stress exposure and depressive-like symptoms are associated with elevated brain FAAH in animal models (Hill et al., 2009; Hill et al., 2010; Kamprath et al., 2006; Mikics, Vas, Aliczki, Halasz, & Haller, 2009; Reich, Taylor, & McCarthy, 2009; Sanchis-Segura, Cline, Marsicano, Lutz, & Spanagel, 2004), which is pertinent to the suicidality of BPD, because dysphoric symptoms and stressful events are well-known risk factors for suicidal behavior in BPD (Goodman, Roiff, Oakes, & Paris, 2012). Taken together, these findings merit the investigation of FAAH as a prospective therapeutic target in BPD with suicidality.

5.2.2.5 INVESTIGATING FATTY ACID AMIDE HYDROLASE IN ANTISOCIAL PERSONALITY DISORDER WITH HIGH PSYCHOPATHIC TRAITS

Notwithstanding research linking genetic disruption of the CB1 receptor gene in animal models to an aggressive, impulsive phenotype (Martin, Ledent, Parmentier, Maldonado, & Valverde, 2002; Rodriguez-Arias et al., 2013), several persuasive lines of evidence indicate that decreased brain FAAH level may relate to the pathophysiology of ASPD. For example, preclinical studies suggest that pharmacological inhibition of FAAH reduces anxiety-like behaviors in the context of threatening stimuli (Kathuria et al., 2003), and individuals with ASPD also exhibit psychophysiological responses consistent with low arousal or anxiety upon exposure to stressful conditions (Raine, Lencz, Bihrle, LaCasse, & Colletti, 2000). In a large fMRI study of healthy volunteers, carriers of a functional polymorphism of the FAAH gene (rs324420, C385A) that is associated with lower *in vivo* production of FAAH displayed decreased amygdala activation to threat-related stimuli (Hariri et al., 2009), which resembles the deficit observed in antisocial populations with high psychopathic traits (Jones, Laurens, Herba, Barker, & Viding, 2009). Carriers of this same FAAH genetic polymorphism (C385A) additionally showed enhanced reward-related ventral striatal reactivity that was associated with behavioral measures of impulsivity (Hariri et al., 2009). The implication of a dysfunctional ECS in ASPD and impulsive phenotypes insinuates that applying [^{11}C] CURB PET to the study of this population could yield important gains.

5.2.3 MONOAMINE OXIDASE-A AND INFLAMMATION

Since depressive-like states in animal models are associated with both increased production of pro-inflammatory cytokines and greater MAO-A gene expression and activity in the PFC (Filipenko et al., 2002; Grunewald et al., 2012; Liu et al., 2013), while phenelzine, an MAOI, attenuates disease severity in a murine model of autoimmune encephalomyelitis (Musgrave et al., 2011), there is a strong rationale to test whether neuroinflammation contributes to the pathology of episodic, intense dysphoria in BPD.

5.2.3.1 [^{18}F] FEPPA MEASURES A MARKER OF NEUROINFLAMMATION

Microglia are resident macrophages of the CNS that play a key role in immune surveillance (Gehrmann, Matsumoto, & Kreutzberg, 1995). During brain inflammation, microglia become active and migrate to the site of injury to phagocytize the insult, possibly in response to cytokines (Gehrmann et al., 1995). Activated microglia, therefore, represent an important marker of neuroinflammation (Venneti, Wiley, & Kofler, 2009). Translocator protein (TSPO) can be used to identify activated microglia in the brain (Chen & Guilarte, 2008). In the human brain, TSPO is predominantly located on the outer mitochondrial membranes of microglia and astrocytes (Hertz, 1993). During CNS injury and inflammation, microglia become active, and greater TSPO binding occurs (Batarseh & Papadopoulos, 2010). [^{18}F] FEPPA is a radiotracer that has excellent properties for

PET imaging in humans. It has very high affinity for TSPO, a very good specific-binding-to-nonspecific-binding ratio, good reversibility, and its metabolites do not cross the BBB (Wilson et al., 2008).

5.2.3.2 INVESTIGATING NEUROINFLAMMATION IN BORDERLINE PERSONALITY DISORDER WITH ACUTE DYSPHORIA

The reasons for investigating neuroinflammation in BPD with acute dysphoria are convincing. For example, when the immune system is overly active from administration of cytokines for therapeutic purposes, dysphoric moods can occur (Brydon, Harrison, Walker, Steptoe, & Critchley, 2008; Musselman et al., 2001). Moreover, increased levels of peripheral and central cytokines have been detected in BPD and related trauma disorders (Baker et al., 2001; Diaz-Marsa et al., 2012). Elevated TSPO binding has been reported in MDE (Setiwan et al., 2014), which lends further support to the notion that neuroinflammation is present in disorders characterized by high levels of dysphoria, including BPD.

5.2.4 CLINICAL TRIALS OF REVERSIBLE INHIBITORS OF MONOAMINE OXIDASE-A IN BORDERLINE PERSONALITY DISORDER WITH SEVERE SYMPTOMS

The available evidence indicates that classic, irreversible MAOIs are effective treatments for BPD. One randomized controlled trial (RCT) found that

tranylcypromine improved mood in BPD, even in the absence of a concurrent MDE, and that it provided beneficial effects for anger, anxiety, and anhedonia (Cowdry & Gardner, 1988). Another RCT (Soloff et al., 1993) demonstrated that phenelzine was superior to placebo in reducing assaultiveness and resentment scores on the Buss-Durkee Hostility Inventory (Buss & Durkee, 1957). However, the relatively high fatal toxicity index of irreversible MAOIs (Henry & Antao, 1992) precludes the routine use of these agents in BPD patients who are actively suicidal or have a history of overdose. On the other hand, moclobemide is a reversible inhibitor of MAO-A that possesses several advantages over irreversible MAOIs, including lax or absent dietary restrictions, low risk of hypertensive crisis, and a shorter washout period. To the best of our knowledge, moclobemide has never been tested in BPD. Given the favorable safety profile of moclobemide and the results of the present studies linking increased MAO-A V_T to more severe presentations of BPD and greater mood symptoms and suicidality, an argument could be made for conducting clinical trials of moclobemide in BPD subgroups with these same symptoms.

5.2.5 INVESTIGATING THE RELATIONSHIP BETWEEN PRENATAL CIGARETTE SMOKING AND INHIBITION OF MONOAMINE OXIDASE-A IN THE DEVELOPING BRAIN

Several longitudinal studies have found that maternal cigarette smoking during pregnancy is strongly related to the development of conduct disorder in exposed offspring, independent of other relevant socioeconomic variables (Gaysina et al.,

2013). Cigarette smoking is associated with lower MAO-A brain level (Fowler et al., 1996), which has been attributed to the non-nicotinic components of cigarette tobacco, such as aromatic β carbolines, that are known or suspected inhibitors of MAO-A (Herraiz & Chaparro, 2005). Some experts have suggested that the MAO-A inhibitory activity of these substances could extend to the developing brain of an exposed fetus and interfere with optimal monoamine levels for synaptogenesis (Baler, Volkow, Fowler, & Benveniste, 2008). The timing of this hypothesized brain insult in concert with possible genetic influences could alter developmental brain trajectories such that conduct-disordered behavior is more likely to emerge later in life (Baler et al., 2008). The ideal time to test the relationship between prenatal cigarette smoke exposure and brain MAO-A V_T would be shortly after birth. However, safety concerns prohibit the use of PET in individuals less than 18 years old. An alternative approach to addressing this question would involve sampling MAO-A V_T in adulthood and relating this measure to self-report and collateral information (e.g., from subjects' mothers) about *in utero* cigarette smoke exposure. There are several disadvantages inherent to this type of design, including response bias and the inability to control for all lifetime exposures that could potentially affect MAO-A V_T. Yet, with a large enough sample and reliable information about prenatal exposures, this type of study could provide initial correlational data. Should the results support an association of greater prenatal cigarette smoke exposure with low MAO-A V_T in ASPD, these findings could bolster public health approaches to help reduce smoking in pregnant women by providing education about the risk of

brain changes predisposing to antisocial behavior in individuals exposed to cigarette smoke *in utero*.

5.4 CONCLUSION

Given the evidence linking MAO-A V_T to MDE, substance use disorders, high risk physiological states in women for MDE and now ASPD and BPD, it is not surprising that MAO-A is one of the most intensely investigated molecular targets in psychiatry (Craig, 2007). The present PET and fMRI studies of ASPD and BPD unambiguously show that these disorders present alterations in brain MAO-A level that are illness specific. While the pathoetiology of these conditions is undeniably complex and multifactorial, the burgeoning field of neurobiological research in BPD and ASPD has already and will continue to make a vital contribution to understanding the complicated interaction of psychological, social, and biological influences that make these disorders a challenge to research and treat.

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