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Association of ventral striatum monoamine oxidase-A binding and functional connectivity in antisocial personality disorder with high impulsivity: A positron emission tomography and functional magnetic resonance imaging study

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Abstract
Impulsivity is a core feature of antisocial personality disorder (ASPD) associated with abnormal brain function and neurochemical alterations. The ventral striatum (VS) is a key region of the neural circuitry mediating impulsive behavior, and low monoamine oxidase-A (MAO-A) level in the VS has shown a specific relationship to the impulsivity of ASPD. Because it is currently unknown whether phenotypic MAO-A markers can influence brain function in ASPD, we investigated VS MAO-A level and the functional connectivity (FC) of two seed regions, superior and inferior VS (VSs, VSi). Nineteen impulsive ASPD males underwent [^{11}C] harmine positron emission tomography scanning to measure VS MAO-A V_T, an index of MAO-A density, and resting-state functional magnetic resonance imaging that assessed the FC of bilateral seed regions in

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the VSi and VSs. Subjects also completed self-report impulsivity measures. Results revealed functional coupling of the VSs with bilateral dorsomedial prefrontal cortex (DMPFC) that was correlated with VS MAO-A V_T ($r=0.47$, $p=0.04$), and functional coupling of the VSi with right hippocampus that was anti-correlated with VS MAO-A V_T ($r=-0.55$, $p=0.01$). Additionally, VSs-DMPFC FC was negatively correlated with NEO Personality Inventory-Revised impulsivity ($r=-0.49$, $p=0.03$), as was VSi-hippocampus FC with Barratt Impulsiveness Scale-11 motor impulsiveness ($r=-0.50$, $p=0.03$). These preliminary results highlight an association of VS MAO-A level with the FC of striatal regions linked to impulsive behavior in ASPD and suggest that phenotype-based brain markers of ASPD have relevance to understanding brain function.

1. Introduction

Antisocial personality disorder (ASPD) is a serious psychiatric condition that exacts a high healthcare and societal burden due to the impulsive behavior of affected individuals (Scott et al., 2001). Studies parsing impulsivity subtypes in ASPD have identified deficits in behavioral inhibition (Swann et al., 2009) and excessive discounting of delayed rewards (Petry, 2002). Psychopathy is a personality disorder that shares some clinical overlap with ASPD but can be distinguished by its high reliance on the use of proactive or instrumental aggression. The Psychopathy Checklist-Revised (PCL-R) (Hare, 2003), a common tool for assessing psychopathic personality traits, includes impulsivity as a core component of psychopathy (Hare, 2003), although not all individuals with the disorder endorse high impulsiveness or impulsive aggression (Snowden and Gray, 2011). Hence, exploring the neural correlates of ASPD with high psychopathic traits and a history of impulsive violence can refine our knowledge of this specific phenotype.

A promising direction to understanding the impulsivity of ASPD with high psychopathic traits that has not yet been explored is to use phenotype-based neurobiological markers that can predict brain function. One marker of interest is monoamine oxidase-A (MAO-A), an enzyme located on outer mitochondrial membranes in glia and neurons that metabolizes monoamine neurotransmitters (Youdim et al., 2006). A growing corpus of animal and human studies points to connections between low or absent brain MAO-A level and impulsive aggression. At least two MAO-A knockout models are associated with high impulsive aggression in adult mice (Cases et al., 1995; Scott et al., 2008). Moreover, males from a Dutch pedigree with deficient MAO-A activity secondary to a non-conservative point mutation of the MAO-A gene were reported to exhibit impulsive, aggressive behavior (Brunner et al., 1993). Two positron emission tomography (PET) studies of healthy humans and one of alcohol dependence have additionally detected relationships between lower widespread MAO-A level and indices of greater impulsivity and aggression (Alia-Klein et al., 2008; Matthews et al., 2014; Soliman et al., 2011). Most recently, low brain MAO-A has emerged as a candidate endophenotype of ASPD with high psychopathic traits and impulsive violence (Kolla et al., 2015). As activation of brain networks implicated in impulsive behavior may be influenced by MAO-A genotype (Clemens et al, 2015), it seems logical to examine phenotypic MAO-A markers in relation to other markers of brain activity that may underlie the impulsivity of ASPD.

Resting-state functional magnetic resonance imaging (fMRI) is another technique that can be applied to identify a potential nexus between clinically impulsive phenotypes and patterns of neural functioning. Few resting state fMRI studies of ASPD/psychopathic populations have been reported in the literature. One investigation of young ASPD offenders found decreased resting-state brain activity in temporal and frontal regions (Liu et al., 2014), while three seed-based resting-state analyses of psychopathic samples reported reduced resting-state cortical-subcortical (Contreras-Rodriguez et al., 2015; Motzkin et al., 2011) and cortical-cortical functional connectivity (FC) (Philippi et al., 2015). One of these studies (Contreras-Rodriguez et al., 2015) provided information on a self-report measure of impulsivity but did not examine FC in relation to this symptom. Despite the strong association of impulsivity with violence in antisocial populations (Blackburn and Coid, 1998), very little is known about the FC of brain regions subserving impulsive behavior in ASPD.

Considerable pharmacological evidence links brain dopaminergic systems to facilitation of aggressive behavior. Increased dopamine turnover is observed in the nucleus accumbens of rodents engaging in aggressive behavior (Haney et al., 1990; Louilot et al, 1986). Further, optogenetic stimulation of dopaminergic neurons in mouse midbrain has been shown to induce protracted aggressive responding (Yu et al., 2014). In a sample of violent offenders, cerebrospinal fluid dopamine metabolites predicted psychopathic traits and were most strongly related to items tapping behavioral measures on the PCL-R (Soderstrom et al., 2001). Impulsive-antisocial psychopathic traits are also associated with enhanced activity of mesolimbic dopaminergic neurons to pharmacological reward (Buckholtz et al., 2010). By contrast, a 6-[^{18}F]-fluoro-L-DOPA PET study of healthy subjects reported an inverse correlation between striatal dopamine synthesis capacity and impulsive aggressive responding following provocation (Schlüter et al., 2013). Since MAO-A expression and activity are highly correlated in the striatum (Meulendyke et al., 2014; Tong et al., 2013), and MAO-A inhibition leads to increased striatal dopamine level (Yu et al., 2014), a plausible mechanism to account for increased striatal dopaminergic tone in impulsive aggression is lower co-localized MAO-A activity.

The VS is a core component of the cortico-limbic-striatal neurocircuitry that receives input from the midbrain