

## REGULAR RESEARCH ARTICLE

# Corticostriatal Connectivity in Antisocial Personality Disorder by MAO-A Genotype and Its Relationship to Aggressive Behavior

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## ABSTRACT

**Background:** The influence of genetic variation on resting-state neural networks represents a burgeoning line of inquiry in psychiatric research. Monoamine oxidase A, an X-linked gene, is one example of a molecular target linked to brain activity in psychiatric illness. Monoamine oxidase A genetic variants, including the high and low variable nucleotide tandem repeat polymorphisms, have been shown to differentially affect brain functional connectivity in healthy humans. However, it is currently unknown whether these same polymorphisms influence resting-state brain activity in clinical conditions. Given its high burden on society and strong connection to violent behavior, antisocial personality disorder is a logical condition to study, since *in vivo* markers of monoamine oxidase A brain enzyme are reduced in key affect-modulating regions, and striatal levels of monoamine oxidase A show a relation with the functional connectivity of this same region.

**Methods:** We utilized monoamine oxidase A genotyping and seed-to-voxel-based functional connectivity to investigate the relationship between genotype and corticostriatal connectivity in 21 male participants with severe antisocial personality disorder and 19 male healthy controls.

**Results:** Dorsal striatal connectivity to the frontal pole and anterior cingulate gyrus differentiated antisocial personality disorder subjects and healthy controls by monoamine oxidase A genotype. Furthermore, the linear relationship of proactive aggression to superior ventral striatal-angular gyrus functional connectivity differed by monoamine oxidase A genotype in the antisocial personality disorder groups.

**Conclusions:** These results suggest that monoamine oxidase A genotype may affect corticostriatal connectivity in antisocial personality disorder and that these functional connections may also underlie use of proactive aggression in a genotype-specific manner.

**Keywords:** antisocial personality disorder, monoamine oxidase A, resting-state functional magnetic resonance imaging

## Significance Statement

Antisocial personality disorder (ASPD) is a serious psychiatric condition that presents with high aggression and violence. Monoamine oxidase A (MAO-A) is a gene comprising different variants that show a relation to brain activity in healthy humans. However, it has not been demonstrated whether these variants are also associated with brain activation patterns in ASPD. Therefore, we used resting-state functional magnetic resonance imaging to study brain activity in healthy control participants and subjects with ASPD. We found that the high-activity MAO-A variant was related to stronger brain connections in ASPD between the dorsal caudate, a brain region involved in decision making, and frontal brain areas. Functional connectivity from the superior ventral striatum to the angular gyrus also revealed an interaction between ASPD and proactive or premeditated aggression. Our results suggest that brain connections in ASPD and violence may be under control by the MAO-A gene.

## Introduction

Antisocial personality disorder (ASPD) is a chronic psychiatric condition characterized by aggressive behavior that frequently leads to criminal offending (Barratt et al, 1997). Longitudinal studies show that ASPD-afflicted males experience severe life-long interpersonal problems (Paris, 2003). Furthermore, some estimates suggest that 7% of the general population (Swanson et al, 1994) and nearly 50% of incarcerated individuals (Fazel and Danesh, 2002) meet criteria for ASPD. This evidence provides a compelling rationale to intensify research efforts.

Increasingly, studies have identified genetic polymorphisms in psychiatric populations that may influence brain endophenotypes, including neural circuitry. For example, monoamine oxidase A (MAO-A) is one gene vigorously pursued as a psychiatric endophenotype, as it functions to degrade monoamine neurotransmitters (Youdim et al, 2006). MAO-A is particularly implicated in impulsive, aggressive phenotypes, as positron emission tomography (PET) studies demonstrate lower brain MAO-A levels in ASPD and aggressive individuals (Kolla et al, 2015). A common variable nucleotide tandem repeat (VNTR) polymorphism in the MAO-A promoter region affects transcriptional activity in cell lines. Alleles with 3.5 or 4 copies of the VNTR are transcribed more efficiently (high activity: MAOA-H) than alleles with 2 or 3 VNTR repeats (low activity: MAOA-L) (Sabol et al, 1998).

Resting-state fMRI (rs-fMRI) is a functional neuroimaging technique that measures spontaneous neural activity in the absence of a task stimulus. To our knowledge, a single rs-fMRI study investigated its relation to MAO-A VNTR genetic polymorphisms (Clemens et al, 2015). Comprised of healthy individuals, the study reported similarly low aggression levels in the MAOA-L and MAOA-H groups. Using independent components analysis, the authors found regional distinctions of executive and salience resting-state network nodes: low right middle frontal gyrus activity in MAOA-L carriers and high dorsal anterior cingulate cortex activity among MAOA-H participants. Furthermore, alternate resting-state modalities have not yet been applied to distinguish MAO-A genotypes. Seed-based correlational analysis is one such technique that correlates time series data from a priori seed regions and whole-brain time courses. This data-driven, simple, and easily interpretable analysis is ideal for demarcating functional connectivity (FC) (van den Heuvel and Hulshoff Pol, 2010).

We previously reported that seed-based FC of ventral striatal (VS) seed regions in ASPD correlated with VS MAO-A level using PET (Kolla et al, 2016). However, MAO-A VNTR genotypes show no relationship with in vivo levels of brain MAO-A, at least in healthy males (Fowler et al, 2007). Yet, the fMRI-genetic study of healthy humans cited above suggests that there may exist distinct profiles of functional brain activity based on MAO-A genotype. These findings indicate that

MAO-A genotypic effects, in combination with in vivo brain markers, may influence FC. Clinically, differential FC in ASPD with MAOA-L or MAOA-H could indicate biological subtypes, reflected by propensity for aggression, violent recidivism, and manifestation of substance misuse (Kolla and Vinette, 2017). Since no study has ever examined whether MAO-A polymorphisms differentially affect FC in ASPD, we investigated the FC of previously employed VS seeds (Kolla et al, 2016) and a dorsal caudate seed from the same striatal parcellation. Our aim was to determine whether resting-state FC differed by MAO-A genotype in ASPD and healthy controls. Based on the rs-fMRI results in healthy individuals (Clemens et al, 2015), we hypothesized that differences would emerge in corticostriatal resting-state FC by diagnosis (control and ASPD), genotype (high- and low-activity MAO-A), and in the interaction of group  $\times$  genotype.

## Methods

### Subjects

Twenty-one males with ASPD and 19 sex-matched healthy controls completed the study. A total of 163 individuals who contacted the study authors to be part of the experimental group were excluded based on our inclusion and exclusion criteria. Sixty-nine participants who contacted the study authors to form part of the healthy control group were also excluded based on our inclusion and exclusion criteria. All subjects provided informed, written consent, and the Research Ethics Board at the Centre for Addiction and Mental Health, Toronto, Ontario, approved all study components. All subjects were clinically assessed by a forensic psychiatrist (N.J.K.) using the Structured Clinical Interview for DSM-IV Axis II, Personality Disorders (SCID-II) (First et al, 1997) and SCID-I (First et al, 2002). Official documentation confirmed that all ASPD subjects had a criminal record and no healthy controls had a record of criminal offending. A subset of 20 healthy (Kolla et al, 2017) and 18 ASPD participants (Kolla et al, 2015) had previously participated in imaging studies in our laboratory. Exclusion criteria included history of major depressive disorder, bipolar disorder, or a schizophrenia spectrum illness. Current nonalcohol drug abuse or dependence additionally excluded participation. Use of psychotropic medication was also exclusionary as was cigarette smoking. Nonsmoking status was verified by breathalyzer testing for carbon monoxide (MicroSmokerlyzer, Bedfont Scientific Ltd.) on assessment and scanning days. All subjects' urine toxicology samples were uniformly negative for drugs of abuse on the day of scanning and all assessment days.

## Seed Selection and Rationale

We selected three brain regions of interest (ROIs): superior VS (VSs), inferior VS (VS<sub>i</sub>), and the dorsal striatum/caudate (Di Martino et al, 2008). We previously selected these VS seeds, demonstrating that the striatal resting state connectivity was related to brain MAO-A level (Kolla et al, 2016). Furthermore, the neural circuitry of impulsive behaviors has been associated with the VS (Basar et al, 2010), and VS circuitry is associated with emotional processing, reward pathways, and cognitive control (Haber, 2016). The dorsal caudate (DC) seed was created from the same striatal parcellation (Di Martino et al, 2008) and was selected based on its role in the abnormal reward processing and impaired evaluation of contingency changes reported in antisocial individuals (Glenn and Yang, 2012). To correct for the comparison of 3 seed regions, we applied a Bonferroni correction to all posthoc analyses on extracted cluster parameters. All ROIs were spheres centered on the coordinates outlined by Di Martino and colleagues, with a radius of 4 mm and masked by the subject's T1 gray matter segmentation.

## Image Acquisition

Each participant underwent a T1-weighted anatomical scan (TE=3.0 milliseconds, TR=6.7 milliseconds, flip angle=8°, slice thickness=0.9 mm, 200 slices, FOV=240 mm, matrix=256×256, voxel size=0.9 mm×0.9 mm×0.9 mm; 3.0-T GE Discovery MR750 scanner, GE Medical Systems) for the ROI analysis. To obtain resting-state activity patterns, participants completed a 6-minute fMRI scan (TE=30 milliseconds, TR=2000 milliseconds, flip angle=60°, slice thickness=5.0 mm, 31 axial slices, FOV=220 mm) performed in the resting state with their eyes closed.

## Data Preprocessing

The first five volumes of each subject's resting-state fMRI scan were removed prior to data preprocessing to allow for signal equilibrium. Data preprocessing was performed using SPM12 (<http://www.fil.ion.ucl.ac.uk/spm/doc/>) and the CONN FC toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012), implemented in Matlab v8.5.0.197613 (<https://www.mathworks.com/products/matlab/>). Preprocessing steps included the following: slice-time correction (interleaved), motion correction (e.g., realignment and scrubbing), linear affine registration of the functional image to the anatomical T1 image, nonlinear registration of the functional and anatomical images to the MNI standard brain, and spatial smoothing with a 6-mm full-width half-maximum. Anatomical T1 images were additionally segmented into gray matter, white matter, and CSF for the removal of physiological noise.

Physiological noise and noise from other sources were removed via linear regression. To remove physiological noise, aCompCor (Behzadi et al, 2007) was performed using segmented white matter and CSF images. The first 5 principal components of each tissue segment were removed in addition to the 12 motion parameters, their first derivative, and the linear motion trend. Functional data were then bandpass filtered at 0.008 to 0.09 Hz.

## Resting-State fMRI Statistical Analysis

Whole-brain seed-to-voxel-based FC was performed for each ROI for each subject. Each ROI resulted in a bivariate correlation map for each subject; these maps were then Fisher-transformed to normalized z-scores and were entered into a second-level,

mixed-effects general linear model to identify group effects. For each ROI, we compared any difference between the four groups using 2×2 between-subjects ANOVA, which was based on MAO-A genotype and diagnosis, covarying for IQ. The resultant group-level analyses were thresholded at  $P < .001$  (cluster-corrected using the false discovery rate [FDR], with a height threshold of  $P < .01$ ). The resulting clusters were then displayed on the MNI brain. To determine any significant statistical differences between groups, posthoc parameter estimates for the mean effect size for each resulting cluster were extracted, and a *t* test for each combination of groups was performed. The cutoff *P* value for each test was .0033 (.01/3 ROIs).

## Genetics Analysis

Standard PCR procedures that used primers as previously reported (Deckert et al, 1999) were employed to amplify the MAO-A VNTR locus. Minor changes were implemented, including the labeling of the forward primer with 5' HEX modifier, which permitted electrophoresis and visualization on a capillary sequencer. Briefly, 125 ng of total genomic DNA was added to the following components: 1x P<sub>CR</sub> Amplification Buffer, 1.5 mM MgSO<sub>4</sub>, and 1x P<sub>CR</sub> Enhancer Solution that accompanied the Invitrogen P<sub>CR</sub> Enhancer Kit, 0.2 mM of each dNTP, 0.0975 ug of each primer, and 0.5 U Taq polymerase. This combination produced a total reaction volume of 20 µL. The cycling conditions mirrored those as previously reported (Deckert et al, 1999), except for an additional denaturation step of 5 minutes at 95°C. The ABI 3130 Genetic Analyzer system and GeneMapper software (ThermoFisher Scientific) electrophoresed and helped visualize 1 µL of the amplified product. Subjects with 2, 3, or 5 copies of the MAO-A VNTR were designated as MAOA-L carriers, while individuals with 3.5 or 4 copies were assigned the MAOA-H genotype.

## Clinical Measures

### Intelligence

Participants were administered the Wechsler Test of Adult Reading (Wechsler, 1981) to provide an estimate of full-scale IQ.

### Buss-Perry Aggression Questionnaire

The Buss-Perry Aggression Questionnaire (Buss and Perry, 1992) conceptualizes human aggression as a 4-factor model, including physical aggression, verbal aggression, anger, and hostility. The 29-item Aggression Questionnaire has been validated in aggressive populations (Gallagher and Ashford, 2016).

### Hare Psychopathy Checklist-Revised

A trained forensic psychiatrist (N.J.K.) conducted interviews with participants and obtained criminal records to score the Hare Psychopathy Checklist-Revised (PCL-R) (Hare, 2003). The PCL-R includes 20 items comprising 4 facets that measure interpersonal, affective, lifestyle instability, and antisocial behavior. Each PCL-R item is rated from 0 to 2 based on the presence or absence of the trait (0=no; 1=possible; 2=yes) to generate a final score between 0 and 40.

### Barratt Impulsiveness Scale-11

The Barratt Impulsiveness Scale -11 (Patton et al, 1995) is a self-report instrument that indexes motor impulsiveness, attentional impulsiveness, and nonplanning impulsiveness subscales. The Barratt Impulsiveness Scale-11 displays strong psychometric properties in offender populations (Patton et al, 1995).

### Reactive-Proactive Aggression Questionnaire—

The Reactive-Proactive Aggression Questionnaire (Raine et al, 2006) is a self-report measure that assesses both verbal and physical forms of aggressive behavior. Eleven items index reactive forms of aggression, while the other 12 items measure proactive aggression. The Reactive-Proactive Aggression Questionnaire has been used in adult ASPD populations (Kolla et al, 2013).

## RESULTS

### Demographic and Clinical Variables

ASPD subjects ( $n=21$ ) and controls ( $n=19$ ) were similar in age (ASPD= $36.2\pm 8.7$  years; controls= $34.2\pm 7.7$  years,  $t=0.78$ ,  $P=.44$ ) and proportion of individuals by MAO-A genotype (L/H: ASPD= $11/10$ ; controls= $9/10$ ,  $\chi^2=0.1$ ,  $P=.75$ ). However, the groups showed differences in IQ (ASPD= $106.0\pm 10.6$ ; controls= $112.3\pm 8.2$ ,  $t=-2.1$ ,  $P=.043$ ). As a result, IQ was covaried in the functional analyses.

The two ASPD groups and two healthy groups were stratified by genotype, and comparisons were performed using 1-way ANOVA for variables relating to aggression, anger, impulsivity, and psychopathic traits. Because the analyses produced 16 separate ANOVAs, a Bonferroni correction was applied for multiple testing, which resulted in a significant threshold  $P$  value of .0031 (0.05/16 tests). For each significant ANOVA, posthoc tests using Tukey's HSD were then calculated to analyze differences between the 4 groups (ASPD MAOA-L; ASPD MAOA-H; healthy control MAOA-L; and healthy control MAOA-H). As depicted in Table 1 and the tables included as supplementary results, the ANOVAs for all variables were significant with the exception of Barratt Attentional Impulsiveness. Posthoc tests revealed that both ASPD groups differed from the healthy participants

Table 1. Comparisons between the Four Groups on Clinical Variables

Measure	ANOVA		Posthoc Tests*
	F-Test	P Value	
Buss Perry Aggression Scale			
Physical aggression	22.4	<.0001	
Verbal aggression	16.1	<.0001	
Anger	28.1	<.0001	
Hostility	8.8	<.0001	
Total	28.4	<.0001	
Hare Psychopathy Checklist-Revised			
Interpersonal (facet 1)	21.0	<.0001	
Affective (facet 2)	41.3	<.0001	
Impulsive (facet 3)	34.0	<.0001	
Antisocial (facet 4)	48.4	<.0001	
Total PCL-R score	65.5	<.0001	
Barratt Impulsiveness Scale-11			
Motor impulsiveness	10.8	<.0001	
Attentional impulsiveness	4.8	.007	
Nonplanning impulsiveness	10.7	<.0001	
Reactive-Proactive Aggression Questionnaire			
Reactive aggression	20.9	<.0001	
Proactive aggression	14.6	<.0001	1 > 2 ( $P=.043$ )
Total aggression	21.7	<.0001	

\*Only those tests where differences emerged between (1) ASPD MAOA-L and (2) ASPD MAOA-H groups or (3) healthy control MAOA-L and (4) healthy control MAOA-H groups are specified.

for each variable except nonplanning impulsiveness, where no difference between ASPD MAOA-H and healthy control MAOA-L groups was discerned ( $P=.13$ ). The only variable that distinguished the 2 ASPD groups was proactive aggression: MAOA-L carriers with ASPD endorsed greater proactive aggression than ASPD MAOA-H carriers ( $P=.043$ ) and both healthy control groups (healthy control MAOA-L:  $P<.001$ ; healthy control MAOA-H:  $P<.001$ ).

### fMRI Results

#### Main Effect of Diagnosis

The  $2\times 2$  between-subjects ANOVA revealed no significant difference in the FC of any ROIs between the ASPD group and controls.

#### Main Effect of MAO-A Genotype

The  $2\times 2$  between-subjects ANOVA revealed no significant difference in the FC of any ROIs between the high- and low-activity MAO-A genotypes.

### Interaction Between Genotype and Diagnosis

#### Dorsal Caudate

The  $2\times 2$  ANOVA revealed a significant interaction effect of MAO-A genotype and diagnosis in FC from the dorsal caudate (Figure 1A). This interaction was found in one significant cluster: bilateral anterior cingulate cortex (ACC) and right frontal pole (312 voxels,  $T=3.59$ , cluster  $P\text{-FDR}=.000077$ ; Figure 1B). Subsequent posthoc analyses indicated that the ASPD MAOA-H group displayed greater mean FC to the frontal pole and ACC relative to ASPD subjects with MAOA-L (Figure 1B; ASPD MAOA-H  $MPE=0.26\pm 0.04$  SE, ASPD MAOA-L  $MPE=0.02\pm 0.03$  SE,  $t(19)=26.00$   $P=.0001$ ), and healthy control MAOA-H subjects (Figure 1B; healthy control MAOA-H  $MPE=-0.03\pm 0.04$  SE,  $P=.00024$ ). The healthy control MAOA-L group displayed greater mean FC to the frontal pole and ACC relative to the healthy control MAOA-H group (Figure 1B; healthy control MAOA-L  $MPE=0.17\pm 0.05$  SE,  $P=.0037$ ) and ASPD MAOA-L group (Figure 1B;  $P=.037$ ). Given that our Bonferroni-corrected cluster- $P$  threshold was .01/3 ROIs=.0033, the differences observed in the healthy control MAOA-L group do not survive multiple comparisons correction.

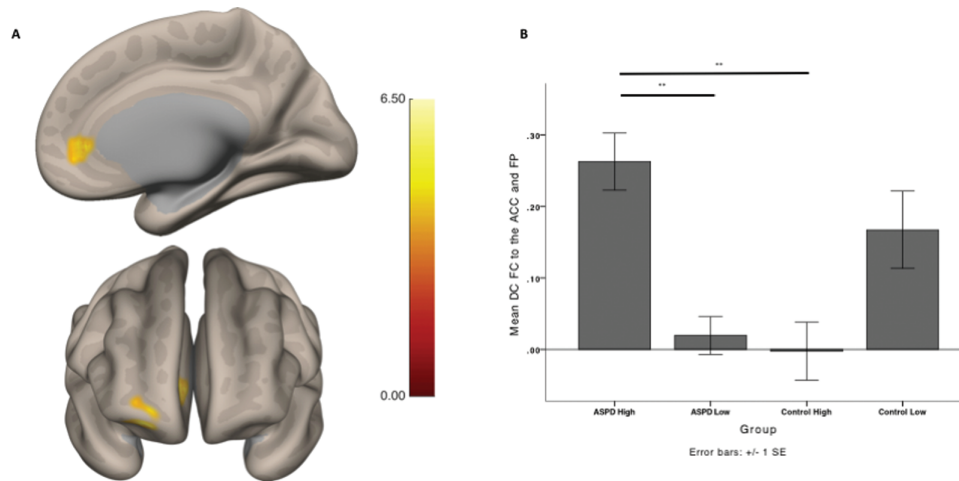
#### VSi and VSs

No clusters met the threshold of cluster  $P < .001$  FDR-corrected with a height threshold of  $P < .01$ .

### Exploratory Analyses

Since proactive aggression was the only continuous variable that differed between ASPD MAOA-L and MAOA-H groups, we modeled a 2-group (ASPD MAOA-L and ASPD MAOA-H) with continuous covariate interaction with the FC of the three ROIs, covarying for IQ. Statistical significance was defined according to a voxel-level, cluster-defined height threshold of  $P < .005$ , where clusters were retained that met an FDR-cluster level correction of  $P < .01/3$  ROIs=.0033. While there were no significant clusters associated with the dorsal caudate ROI before or after correcting for multiple comparisons, there were significant clusters related to the VS<sub>i</sub> and VS<sub>s</sub> seeds. First, VS<sub>s</sub> FC to the right angular gyrus displayed a significant ASPD  $\times$  proactive aggression interaction in ASPD subjects, even after correction for multiple comparisons (396 voxels, cluster- $P$   $FDR=.00071$ ; Figure 2Ai). Extracting the mean parameter estimate representing VS<sub>s</sub>-angular gyrus





**Figure 1.** Dorsal striatal functional connectivity that showed a genotype  $\times$  diagnosis interaction. (A) Significant clusters of functional connectivity (FC) to the dorsal caudate (DC) that differed between groups. (B) Posthoc mean parameter estimates of DC FC to the anterior cingulate cortex (ACC) and frontal pole (FP). \*\* $P$  value  $< .0033$ , corrected.

FC revealed a trend correlation between VSs-angular gyrus connectivity and proactive aggression in the ASPD MAOA-L group ( $r=0.62$ ,  $P=.054$ ) and no correlation in the ASPD MAOA-H group ( $r=-0.056$ ,  $P=.89$ ; [Figure 2Aii](#)). Similarly, VSi FC to the left and right precuneus displayed a significant interaction in ASPD subjects; however, both clusters did not meet significance following multiple comparisons correction (right precuneus cluster: 274 voxels, cluster- $P$  FDR = .0043; left precuneus cluster = 257 voxels, cluster- $P$  FDR = .0043) ([Figure 2Bi](#)). Mean parameter estimates of VSi-precuneus connectivity showed a negative correlation between FC and proactive aggression in ASPD MAOA-L participants (left VSi-precuneus FC:  $r=-0.71$ ,  $P=.022$ ; right VSi-precuneus FC:  $r=-0.62$ ,  $P=.056$ ) and no association in the ASPD MAOA-H group (left VSi-precuneus:  $r=0.30$ ,  $P=.43$ ; right VSi-precuneus:  $r=0.40$ ,  $P=.29$ ) ([Figure 2Bii](#)).

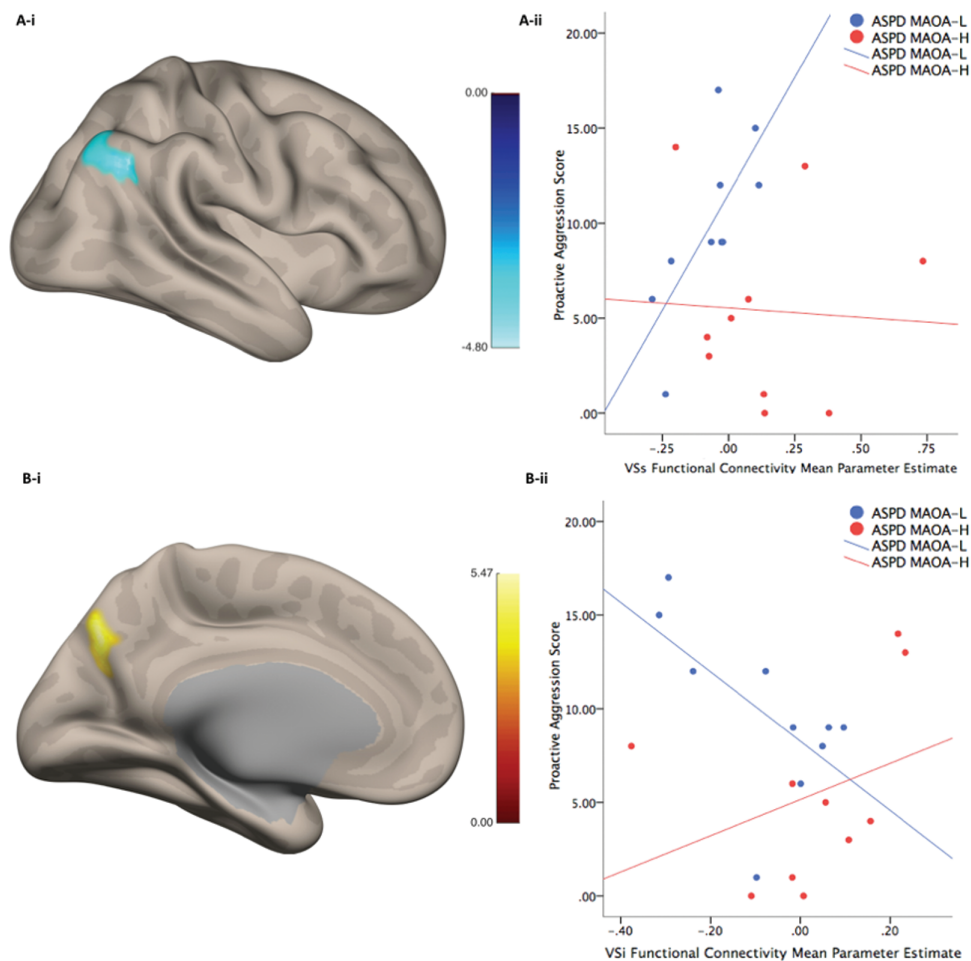
## Discussion

To our knowledge, this study is the first to examine the association of MAOA polymorphisms with resting-state FC in a sample with clinical level severity of symptoms. We chose to investigate genotype-based brain activity in medication-free, nonsmoking, and non-substance-using ASPD participants to eliminate potential confounds. Furthermore, previous findings correlated *in vivo* MAOA levels and FC in this population ([Kolla et al, 2016](#)). Inconsistent with our hypothesis, we did not find any differences in frontostriatal connectivity between ASPD subjects and healthy controls or between MAOA genotypes regardless of diagnosis. However, we did detect a dorsal caudate-frontostriatal interaction by genotype and diagnosis. A subsequent exploratory analysis revealed that ventral striatal FC was associated with different linear relationships with proactive aggression in MAOA-H and MAOA-L ASPD groups. These findings expand upon a litany of prior genetic research linking MAOA-VNTR genotypes to aggression ([Kolla and Vinette, 2017](#)) and helps establish that MAOA polymorphisms are differentially associated with resting-state FC in ASPD.

Our principal finding is that ASPD MAOA-H subjects exhibited increased caudate FC to the right frontal pole and ACC relative to ASPD MAOA-L carriers and MAOA-H healthy controls. Notably, we recently reported that medio-frontostriatal FC was positively correlated with MAOA-V<sub>r</sub>, a measure of MAOA density,

so that higher frontostriatal FC was associated with greater MAOA density ([Kolla et al, 2016](#)). Frontostriatal connectivity was also positively correlated with NEO-PI-R impulsivity in our previous study. Our current result replicates our previous finding that increased medio-frontostriatal connectivity may reflect differential MAOA density. Further work is needed to confirm its relationship to impulsivity and ASPD, especially as we were unable to replicate an association between MAOA genotype, frontostriatal connectivity, and impulsivity. As the extant literature is silent on how MAOA polymorphisms may impact FC underlying pathological behaviors, we must extrapolate from the results of healthy control MAOA-A fMRI studies. These studies incorporate behavioral paradigms typically employed to study high-aggression populations. For example, one task-based fMRI study reported that MAOA-H carriers exhibited increased activation of the dorsal ACC during response inhibition compared with their MAOA-L counterparts ([Meyer-Lindenberg et al, 2006](#)). OFC activity was similarly elevated among MAOA-H participants vs MAOA-L carriers when individuals were exposed to emotionally arousing stimuli. Another research group reported a relative deactivation of the left middle frontal gyrus in MAOA-L subjects vs MAOA-H carriers upon hearing the word “no” ([Alia-Klein et al, 2007](#)). Given these previous task-based findings and our own results, we suggest that increased caudate FC at rest to the frontal pole and ACC could relate to the neural basis of pathological behavior and aggression in ASPD offenders with the MAOA-H genotype.

We also found an inverse relationship between MAOA genotype and frontostriatal connectivity in the healthy control groups relative to the antisocial groups. Only ASPD MAOA-H FC significantly differed between control MAOA-H and ASPD MAOA-L groups after correcting for multiple comparisons. We speculate that these differences displayed by the ASPD MAOA-H group may be genotype specific. In healthy humans, frontostriatal FC from dorsal prefrontal regions such as the ACC is associated with response selection ([Walton et al, 2007](#)), decision-making ([Walton et al, 2007](#)), and habit-learning ([Packard and Knowlton, 2002](#)), while ventral frontostriatal connectivity, including the paracingulate gyrus and frontal pole, is related to reward-processing ([Knutson et al, 2001](#)). These studies suggest that frontostriatal connectivity differences between ASPD and healthy groups may reflect the combined effect of MAOA genotype and pathological



**Figure 2.** Ventral striatum (VS) functional connectivity in antisocial personality disorder (ASPD) participants that showed a monoamine oxidase A (MAO-A) genotype  $\times$  proactive aggression score interaction. (Ai) Significant functional connectivity (FC) to the superior VS (VSs). (Aii) Scatter plot of VSs FC and proactive aggression in MAOA-L and MAOA-H ASPD groups. (Bi) FC to the inferior VS (VSi); note that this cluster did not survive after correcting for multiple comparisons. (Bii) Scatter plot of VSi-left precuneus FC and proactive aggression in MAOA-L and MAOA-H ASPD groups. Again, this relationship did not survive after correcting for multiple comparisons.

mechanisms of ASPD on reward-based decision-making processes. Interestingly, increased resting-state caudate FC has been reported in externalizing disorders (Tomasi and Volkow, 2012) and is consonant with our findings in ASPD MAOA-H subjects. Since enhanced corticostriatal connectivity is present in our ASPD MAOA-H subjects, we attribute the relative increase of FC in the ASPD MAOA-H group vs healthy MAOA-H carriers to the effect of ASPD diagnosis.

ASPD MAOA-L carriers endorsed significantly higher levels of proactive aggression relative to our other groups, and the linear relationship of proactive aggression to ventral striatal FC differed by MAO-A genotype in the ASPD groups. Before correction, ventral striatal FC to the angular gyrus and precuneus displayed near significant correlations with proactive aggression only in the ASPD MAOA-L carriers and not in ASPD MAOA-H carriers; only VSs-angular gyrus FC differed significantly postcorrection. Proactive aggression refers to the deliberate, purposeful behavior that is enacted to achieve a desired goal, whereas reactive aggression encapsulates angry or impulsive actions that occur following provocative stimuli (Crick and Dodge, 1996). Some studies (Caspi et al, 2002), but not all (Kolla et al, 2014), report a connection between the MAOA-L allele and higher proactive aggression. In the latter study, violent offenders had substantially lower PCL-R scores, whereas in the current investigation, PCL-R scores were much higher. The relationship between

MAO-A genotype and proactive aggression in offender populations may, therefore, depend on manifestation of psychopathic traits. In any event, future research with larger samples that takes into account salient environmental influences is needed to parse the relationship between MAO-A genotypes and aggression subtypes. Our exploratory analysis revealed that proactive aggression in the ASPD MAOA-L group was positively associated with ventral striatal FC to the angular gyrus and negatively associated with FC to the precuneus. We are unaware of any other research examining the association of resting-state FC with proactive aggression. Both the angular gyrus and precuneus are nodes of the default mode network (Vaidya and Gordon, 2013), and it is worthwhile noting the inverse relationship between ventral striatal connectivity to these regions and proactive aggression scores in the MAOA-L ASPD group. Previous studies have shown that poorer inhibitory control in healthy controls (Davis et al, 2013), borderline personality disorder (Wolf et al, 2011), and incarcerated juvenile offenders (Shannon et al, 2011) is associated with altered between and within network default mode connectivity. More specifically, the presence of externalizing symptoms like aggression in childhood attention deficit-hyperactivity disorder is also associated with altered default mode network and subcortical resting-state FC (Cao et al, 2009; Chabernaude et al, 2012). Angular gyrus volume has also been associated with externalizing behaviors in children, such that

greater externalizing behavior was associated with smaller cortical volumes (Caldwell et al, 2015). More generally, angular gyrus function has been implicated in moral cognition and decision-making (Miczek et al, 2007). Given the strong genetic liability underlying pathological use of proactive aggression (Tuvblad et al, 2009), a multitude of genes, perhaps including MAO-A, likely contributes to regulation of functional neural networks that ultimately control expression of this multifaceted and dysfunctional behavior.

Several limitations of the present investigation must be acknowledged. First, the sample size was relatively small for typical imaging-genetic studies. Still, our sample size is comparable with the only other investigation (Clemens et al, 2015) to have examined connections between MAO-A VNTR polymorphisms and resting-state FC. In the aforementioned study, the sample was composed exclusively of healthy subjects, whereas the present study examined healthy controls in addition to ASPD. Given the smaller sample size, we do, however, emphasize the importance of interpreting these results with caution. A second limitation is that we restricted our analysis to 3-seed regions in the dorsal and ventral striatum. These regions were selected, because they had been implicated in previous neuroimaging studies of antisocial populations (Glenn and Yang, 2012). Furthermore, prior work had also demonstrated functional links between the VS and in vivo markers of MAO-A in ASPD (Kolla et al, 2016). It would be advantageous for future studies to consider examining whether other regional FC, such as the amygdala (Hyde et al, 2014) and ventromedial prefrontal cortex (Narayan et al, 2007), also show a relation to MAO-A genetic variants; evidence suggests that these structures may also be under MAO-A genetic control (Buckholtz and Meyer-Lindenberg, 2008; Cerasa et al, 2011). A third limitation is that we only sampled males. One rationale is that ASPD is approximately five to seven times more common in males than females (Hamdi and Iacono, 2014). However, one can include females in a study and genotype for MAO-A alleles. It is just not as straightforward as it is for males, because females can be homozygous or heterozygous for the MAO-A VNTR locus, and there is debate as to whether X-inactivation occurs at this site (Carrel and Willard, 2005). A fourth limitation is that our carbon monoxide breathalyzer was only sensitive to detecting carbon monoxide (e.g., smoking) in the past 24 hours. Although unlikely, it is possible that some smokers were able to refrain from smoking for 24 hours prior to testing and thus were incorrectly classified as nonsmokers. Fifth, use of alcohol was determined solely by self-report. We asked subjects to refrain from drinking the day before and the day of scanning. When asked, all confirmed that they had not consumed alcohol. However, we did not have a biological assay to test for alcohol consumption, and it is possible that some participants misrepresented themselves. Sixth, we cannot declare with certainty that participants did not fall asleep during the scans. Our resting-state instructions asked participants to refrain from sleeping during the scan. Our overall scanning time was relatively short (e.g., approximately 30 minutes), and all participants were asked whether they had slept during the scan. All participants responded negatively. However, some subjects may have been untruthful. Finally, our resting-state parameters were obtained by 6-minute scans with a slice thickness of 5 mm, whereas some might suggest that the gold standard is 10 minutes with 3-mm slice thickness. Our scans were first acquired in 2012 when these parameters were more acceptable. Moreover, the duration of our scanning session, as noted before, was relatively short. Importantly, we have recently published using these same parameters (Kolla et al, 2016). We

also note that a seminal paper reported using 8-minute resting-state scans with a slice thickness of 4 mm (Greicius et al, 2009). Future studies should endeavor to optimize scanning parameters to conform to current gold standards.

In summary, we identified differences in corticostriatal resting-state FC in ASPD participants by MAO-A VNTR polymorphism. We found that DC connectivity to the frontal pole and ACC was significantly greater in ASPD MAOA-H subjects compared with ASPD participants carrying the MAOA-L polymorphism and healthy groups. We additionally discovered that the ASPD MAOA-L group displayed higher levels of proactive aggression relative to ASPD MAOA-H participants and healthy controls. This increase showed a robust correlation with corticostriatal connectivity between the precuneus and angular gyrus; such nodes of the default mode network have been implicated in the genesis of externalizing behavior like aggression and moral judgment. Subtyping externalizing disorders using biological measures, including genetic and neuroimaging markers, holds promise for improving our understanding of illness nosology and endophenotypes. Research indicating that somatic treatments may depend on MAO-A genotype (Domschke et al, 2008) speaks to the translational potential of the present work, especially as emerging neuromodulation techniques have been shown to alter corticostriatal FC (Dunlop et al, 2016). As we continue to learn more about the neural underpinnings of ASPD, a better understanding of how these biological systems interact to instigate violence and aggression will become critical for developing novel treatments.

## Supplementary Material

Supplementary data are available at *International Journal of Neuropsychopharmacology* online.

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## Statement of Interest

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