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Individual differences in schizotypal personality traits correlate with amphetamine induced dopamine release in striatal and extra-striatal brain regions

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Abstract

Objective—Schizotypal personality traits are associated with schizophrenia spectrum disorders. Individuals with schizophrenia spectrum disorders demonstrate increased dopamine transmission in the striatum. We sought to determine if individual differences in normal variation in schizotypal traits correlate with dopamine transmission in the striatum and extra-striatal brain regions.

Method—63 healthy individuals with no history of psychiatric illness completed the Schizotypal Personality Questionnaire and underwent positron emission tomography (PET) imaging with [¹⁸F]fallypride at baseline and after administration of oral (0.43 mg/kg) d-amphetamine. Dopamine release, quantified by subtracting each subject's d-amphetamine scan from their baseline scan, was correlated with Schizotypal Personality Questionnaire total and factor scores using region-of-interest and voxel-wise analyses.

Results—Dopamine release in the striatum positively correlated with overall schizotypal traits. The association was especially robust in the associative sub-division of the striatum. Voxel-wise analyses identified additional correlations between dopamine release and schizotypal traits in the left middle frontal gyrus and left supramarginal gyrus. Exploratory analyses of Schizotypal Personality Questionnaire factor scores revealed correlations between dopamine release and disorganized schizotypal traits in the striatum, thalamus, medial prefrontal cortex, temporal lobe, insula, and inferior frontal cortex.

Conclusions—The association between dopamine signaling and psychosis phenotypes extends to individual differences in normal variation in schizotypal traits and involves dopamine transmission in both striatal and extra-striatal brain regions. D-amphetamine induced dopamine release may be a useful endophenotype for investigating the genetic basis of schizophrenia spectrum disorders.

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Introduction

Personality traits often relate to psychopathology (1). Investigating the neural substrates of personality traits may inform etiological and pathophysiological models of psychiatric disorders. In the case of psychosis, attention has focused on the relationship between schizotypal personality traits and schizophrenia spectrum disorders. Schizotypal personality traits encompass a broad range of personality characteristics and experiences, including unusual perceptions and beliefs, social anxiety or withdrawal, and disorganized thoughts or behaviors (2). These traits cluster into positive, negative, and disorganized factors that are conceptually similar to the symptom dimensions of schizophrenia (2–4). The expression of schizotypal traits ranges from benign odd perceptual experiences or beliefs to excessive levels associated with significant psychosocial impairment and schizotypal personality disorder (2). Pre-morbid personality in schizophrenia is marked by an excess of schizotypal traits and schizotypal personality disorder is a risk factor for schizophrenia (5–7). Indicators of cerebral dysfunction observed in schizophrenia spectrum disorders, including cognitive impairment and sensory gating deficits, correlate with schizotypal traits in psychiatrically healthy individuals, further underscoring the link between schizotypal traits and schizophrenia spectrum disorders (8–14).

The neural basis of individual differences in schizotypal personality traits is poorly understood. Dopamine signaling may be associated with normal variation in schizotypal personality traits given that dopamine dysregulation is prominent in schizophrenia spectrum disorders. Positron emission tomography (PET) imaging with displaceable dopamine receptor ligands sensitive to endogenous dopamine levels has shown that patients with schizotypal personality disorder demonstrate exaggerated dopamine release in the striatum following d-amphetamine challenge (15). Schizophrenia patients also demonstrate increased d-amphetamine induced dopamine release in the striatum (16;17). Dopamine release is especially robust in schizophrenia patients experiencing an acute illness exacerbation and, in contrast to schizotypal personality disorder patients, correlates with a transient increase in positive psychotic symptoms (16).

Determining the relationship between dopamine transmission and individual differences in schizotypal traits may further our understanding of dopamine dysregulation in schizophrenia spectrum disorders. While the findings in schizophrenia provide compelling case for a state component to hyper-dopaminergia, the evidence for a trait basis is less conclusive given that it is based largely on findings from one study of schizotypal personality disorder that included relatively few patients (15). Moreover, the extent to which dopamine signaling varies continuously with dimensional measures of schizotypy is unknown. Evidence that dopamine signaling correlates with individual differences in schizotypy would lend considerable support to the hypothesis that there is a trait component to hyper-dopaminergia and may further suggest hyper-dopaminergia is an endophenotype of schizophrenia spectrum disorders.

It is also unknown if dopamine dysregulation in schizophrenia spectrum disorders includes extra-striatal brain regions. There are reasons to suspect it may given reports of elevated L-DOPA uptake in the amygdala and medial prefrontal cortex in schizophrenia (18;19), and findings from a recent meta-analysis showing that dopamine receptor occupancy by antipsychotics in temporal cortex is strongly related to clinical efficacy (20). Examining the relationship between schizotypal personality traits and extra-striatal dopamine transmission may provide testable hypotheses on the role of extra-striatal dopamine transmission in schizophrenia spectrum disorders.

We examined the relationship between d-amphetamine induced dopamine release determined from PET imaging with [^{18}F]fallypride, a ligand that can quantify both striatal and extra-striatal dopamine D_2/D_3 receptors, and schizotypal personality traits in a large sample of healthy individuals. We hypothesized that schizotypal personality traits would correlate positively with d-amphetamine induced dopamine release in the striatum and sought to determine if similar associations exist in extra-striatal brain regions.

Methods

Participants

63 subjects drawn from two studies of individual differences in d-amphetamine induced dopamine release were included in this investigation. Study procedures were identical for the two studies; with the exception that one group of subjects was given identical appearing capsules containing placebo or amphetamine on PET scanning days ('placebo-controlled' cohort; $n=48$), whereas the other group was not blind to amphetamine administration ('open label' cohort; $n=15$). 14 subjects in the open label cohort were included in a prior report (21). Sample characteristics for the total sample and each cohort are reported in Table 1. All subjects received a physical and neurological examination that included EKG, blood chemistries, urine analysis, urine drug screen, and T1, T2, and T2 flair MRI scans. Exclusion criteria included history of neurological or psychiatric disorder, severe past or concomitant medical illness, borderline elevated blood pressure, abnormal EKG, abnormal comprehensive medical panel, abnormal complete blood count, abnormal urine analysis, failed 10-panel urine drug screen, brain abnormalities revealed on MRI scanning, psychotropic medication usage over the preceding 6 months, history of substance abuse or dependence, and pregnancy or lactation. Subjects were also excluded if they had taken cocaine or amphetamines more than once in their lifetime or reported any illicit drug use in the last 2 months. Axis I psychopathology was ruled out using the Structured Clinical Interview for Diagnosing DSM-IV Disorders (SCID: 22). Axis II psychopathology was not formally assessed using a structured clinical interview. This study was approved by the Vanderbilt University Institutional Review Board and informed consent was obtained in writing from each subject.

Assessments and Study Procedures

Study procedures and image acquisition have been described previously by our group (21). Prior to scanning, subjects completed the Schizotypal Personality Questionnaire (2). The focus of this investigation is on the total score; however, factor analytic studies indicate that the Schizotypal Personality Questionnaire can be separated into 'cognitive-perceptual', 'paranoid', 'negative', and 'disorganized' factors (3). Exploratory analyses of the factor scores were undertaken to determine if dopamine release is related to a specific dimension of schizotypy.

Subjects underwent two PET scans with [^{18}F]fallypride. The first scan was a baseline scan and the second scan occurred 3.5 hours after administration of oral d-amphetamine (0.43 mg/kg). The baseline and d-amphetamine scanning sessions took place on separate days and the baseline scan always occurred first. 15 subjects were not blind to d-amphetamine administration whereas 48 were administered identical appearing capsules on scan days that contained either placebo or d-amphetamine. Physiological measures (blood pressure, heart rate, temperature, respirations) were monitored on scan days and subjects completed a brief screen of possible side effects. Participants also completed a brief neurological screen at baseline and at the end of the scan protocol. Complete blood count and comprehensive medical panel were also obtained at baseline and at completion of the scan protocol.

PET Image Acquisition and Data Preprocessing

PET imaging was performed on a GE Discovery LS scanner located at Vanderbilt University Medical Center which was upgraded to a Discovery STE system during the course of the study. 30 and 33 subjects were scanned on the LS and STE systems, respectively. All subjects received their baseline and d-amphetamine scans on the same scanner. To ensure the validity of combining data across scanners, we compared dopamine release in each of the anatomical regions-of-interest described below between scanners. No differences were observed in any region-of-interest. Moreover, voxel-wise analysis comparing dopamine release between the two scanners did not identify any clusters after whole brain correction at $t=2.5$ (lowest cluster-level $p\text{-value} > .90$). 3-D emission acquisitions and transmission attenuation correction scans were performed following a 5.0 mCi slow bolus injection of [^{18}F]fallypride (specific activity greater than 3000 Ci/mmol). Serial scans started simultaneously with the bolus injection of [^{18}F]fallypride and were obtained for approximately 3.5 h. The extended scanning time allowed for stable kinetic model fits in both striatal brain and extra-striatal regions. The initial scan sequence coincided with the start of the [^{18}F]fallypride injection and included the following frames: 8 for 15 s, 6 for 30 s, 5 for 1 min, 2 for 2.5 min, 3 for 5 min, and 3 for 10 min. After the initial scan sequence, a 10-min transmission scan was obtained and the subject was given a break. At approximately 85–90 min post-injection, a second scan sequence of two frames of 25 min each followed by a second transmission scan was obtained. The subject was then allowed a second break and at approximately 165–170 min a 40-min emission scan followed by a third transmission scan was obtained. Serial PET scans were coregistered using a mutual information rigid body algorithm to minimize potential modeling errors due to head motion within and between scans (23). Consistent with our prior studies with [^{18}F]fallypride (e.g. 24), parametric binding potential (BP_{ND}) images of dopamine D_2/D_3 receptor density were calculated using the full (four-parameter) reference region model (25), with the cerebellum serving as the reference region. Prior studies in our lab (26) have shown that this method produces BP_{ND} estimates that closely agree with estimates derived from Logan plots (27) using a metabolite corrected plasma input function. A high-resolution, T1-weighted MRI scan was also obtained on each subject.

PET and high-resolution T1-weighted MRI scans were coregistered to one another (23). Following coregistration, each subject's BP_{ND} image was warped to a canonical brain that had been normalized to the MNI152 template brain and resampled to 2 mm^3 . Parametric images of dopamine release, in percent, were created by subtracting each subject's d-amphetamine scan from their baseline scan and dividing the difference by their baseline scan using the 'ImCalc' function in SPM2 (<http://www.fil.ion.ucl.ac.uk/spm>). In addition, dopamine release for several anatomically defined regions-of-interest was extracted from the parametric images of dopamine release by calculating the mean of the voxels within each region-of-interest. The regions-of-interest included the left and right striatum, thalamus, amygdala, and hippocampus. Dopamine release values were averaged across hemispheres to produce one value for each region-of-interest. The striatum regions-of-interest were taken from the LONI Probabilistic Brain Atlas 40 (LPBA40: 28) and partitioned into limbic, associative, and sensorimotor functional sub-divisions using previously described criteria (29;30). Briefly, the striatum atlas was divided into 5 ROIs, ventral striatum, dorsal caudate rostral to the anterior commissure (AC), dorsal putamen rostral to the AC, post-commissural caudate, and post-commissural putamen. The limbic sub-division comprised the ventral striatum, the associative striatum was the weighted average of the pre and post-commissural dorsal caudate and pre-commissural putamen, and the sensorimotor sub-division consisted of the post-commissural putamen. Dopamine release in the entire striatum, weighted by the size of each sub-division, was also calculated. The thalamus region-of-interest was derived from the ICBM Deep Nuclei Probabilistic Atlas (<http://www.loni.ucla.edu/Atlases>);

thresholded at 80% to avoid partial volume effects. The hippocampus and amygdala regions-of-interest were created using the Wake Forrest University Pick Atlas and manually edited using criteria previously described by our group to avoid partial volume effects from adjacent structures (24).

Statistical Analysis

The relationship between Schizotypal Personality Questionnaire scores and dopamine release was examined with region-of-interest and voxel-wise analyses. First, Schizotypal Personality Questionnaire total scores were correlated with dopamine release in the regions-of-interest. The correlations for the striatum and striatum sub-divisions were thresholded at $p=.05$ given our a-priori hypothesis that dopamine release in the striatum correlates with overall schizotypal traits. Significance was set to $p=.016$ for extra-striatal regions to correct for the number of structures examined. For the voxel-wise analysis, multiple regression analysis with Schizotypal Personality Questionnaire total score entered as a predictor of dopamine release at each voxel was used. Given our hypothesis, we first examined the extent to which dopamine release in the striatum was related to schizotypal traits by restricting the voxel-wise analysis to the LONI LPBA40 striatum atlas using the small volume correction tool in SPM2. Only clusters within the LPBA40 striatum mask that exceeded the cluster-wise corrected threshold at voxel-wise $p\text{-value}=.05$ are reported. Following that we examined positive correlations throughout the brain. Only clusters exceeding the whole brain corrected cluster-wise $\alpha=.05$ for voxel-wise $t=2.5$ are reported (31). The voxel-wise analysis was masked to exclude voxels with mean BP_{ND} values below .40 on the amphetamine scan. Significant clusters were converted to Talairach coordinates using ICBM_SPM2Tal (32). The estimated smoothness of the statistical parametric map generated for the voxel-wise regression analysis was 6.6, 7.5, and 6.4 mm in the x, y, and z planes, respectively. Age, sex, and cohort (open label or placebo-controlled) were included as nuisance covariates in both the region-of-interest and voxel-wise analyses. Scanner was not included as a covariate for two reasons. First, all subjects in the open-label cohort were scanned on the Discovery LS scanner. Thus, inclusion of scanner as a covariate was redundant given that cohort and scanner were not independent. Second, as stated above, both voxel-wise and region-of-interest analyses did not reveal any significant differences in dopamine release between scanners.

Results

Correlation between overall schizotypal traits and dopamine release: Region-of-interest analysis

Correlations between dopamine release and Schizotypal Personality Questionnaire scores in the total sample and placebo-controlled sub-group are presented in Table 2. For the striatum, overall schizotypal traits correlated with dopamine release in the whole striatum and associative sub-division. No correlations reached the corrected alpha level ($p=.016$) in the extra-striatal regions; although, dopamine release in the amygdala correlated with the Schizotypal Personality Questionnaire total score at the un-corrected alpha level. The results were virtually identical when the analysis was restricted to the placebo-controlled sub-group. Peak plasma d-amphetamine level was $72 (\pm 19)$ ng/ml. Consistent with our prior report on the open label cohort (21), peak plasma d-amphetamine level was unrelated to striatal dopamine release. Baseline BP_{ND} values and dopamine release for each region-of-interest are presented in Supplemental Table 1.

Correlation between overall schizotypal traits and dopamine release: Voxel-wise Analysis

The results of the voxel-wise analysis are presented in Table 3 and Figures 1 and 2. Small volume correction within the striatum revealed positive correlations bilaterally in the

striatum. The clusters were centered in the head of the caudate, but extended into the ventral striatum (See Figure 1). The corresponding correlations between mean dopamine release extracted from each cluster and Schizotypal Personality Questionnaire total score, after controlling for age, gender, and cohort, were $r=.41$ ($p=.001$) and $r=.40$ ($p=.002$) for the left and right striatum, respectively. The findings were unchanged when the analysis was restricted to the placebo-controlled cohort (left striatum: $r=.45$, $p=.002$; right striatum: $r=.36$, $p=.014$).

Whole brain analysis identified two additional clusters (See Table 3 and Figure 2). They included a region within the left middle frontal gyrus corresponding to Brodmann's Areas (BA) 9/10 and left supramarginal gyrus within the inferior parietal lobule. The corresponding correlations between mean dopamine release extracted from each cluster and Schizotypal Personality Questionnaire total score, after controlling for age, gender, and cohort, were $r=.44$ ($p=.0004$) and $r=.46$ ($p=.0002$) for the left middle frontal and supramarginal gyrus clusters, respectively. The findings were unchanged when the analysis was restricted to the placebo-controlled cohort (left middle frontal gyrus: $r=.48$, $p=.001$; left supramarginal gyrus: $r=.55$, $p=.0001$).

No inverse correlations between dopamine release and Schizotypal Personality Questionnaire total score were identified in the striatum or whole brain.

Correlation between dopamine release and specific dimensions of schizotypy

We examined the relationship between Schizotypal Personality Questionnaire factor scores and dopamine release in the regions-of-interest to determine if a particular facet of schizotypy was related to dopamine release (See Table 2). No statistical correction was applied given the exploratory nature of this analysis. Robust correlations were observed between disorganized schizotypal traits and dopamine release in the whole striatum and associated sub-divisions, amygdala, and thalamus. Very similar results were observed within the placebo-controlled sub-group. The other factor scores were not correlated with dopamine release in either the entire sample or placebo-controlled sub-group.

Given the widespread correlations observed between dopamine release and disorganized traits in the regions-of-interest analysis, we performed an exploratory voxel-wise multiple regression analysis regressing disorganized factor scores on dopamine release including age, sex, and cohort as nuisance covariates. The results were thresholded at the whole brain cluster-wise corrected $\alpha=.05$ for voxel-wise $t=2.5$. Dopamine release in several sub-cortical and cortical regions correlated with disorganized traits (See Table 3 and Supplemental Figure 1). They included bilateral striatum and right thalamus, pre-genual cingulate/medial prefrontal cortex, bilateral temporal cortex, superior frontal gyrus, and bilateral insula. All of the clusters remained significant when the analysis was restricted to the placebo-controlled sub-group (all cluster p -values $<.003$).

Discussion

Dopamine release in striatal and extra-striatal brain regions correlates with individual differences in schizotypal traits. Our findings suggest the link between d-amphetamine induced dopamine release and schizophrenia spectrum disorders extends to normal variation in schizotypal personality traits. The results parallel prior reports of associations between schizotypal traits and relative impairments in cognition and sensory gating in samples with similar Schizotypal Personality Questionnaire scores (8–14). Moreover, the correlations between dopamine release and schizotypal traits reported here are similar in magnitude to prior investigations of the association between psychometrically measured schizotypy and behavioral measures of cognition or sensory gating.

The current findings may further our understanding of dopamine dysregulation in schizophrenia spectrum disorders. Extrapolating dopamine release based on the correlation we found for the striatum region-of-interest, we obtain predicted dopamine release values of 9–13% for Schizotypal Personality Questionnaire scores between 30 and 40 (the range reported in schizophrenia and schizotypal personality disorder patients (13;33–35)). This is very similar to the 10–12% increase observed in schizotypal personality disorder and remitted schizophrenia patients, but substantially less than the 20–22% increase reported in acutely ill schizophrenia patients (15). Although caution is warranted when making comparisons between studies that used different radioligands, slightly different d-amphetamine doses and delivery routes (i.v. vs. oral); the similarity in mean striatal dopamine release between the control sample (n=57) reported by Abi-Dargham (7–7.5%) and the current study (~6%) supports the validity of this comparison. Thus, our findings support the hypothesis that the modest elevation in dopamine release observed in schizotypal personality disorder and remitted schizophrenia is a stable trait indicator related to schizotypy, while the robust increases reported in acutely ill schizophrenia patients is probably a state component super-imposed upon trait-wise elevation in dopamine transmission (15).

Identifying the neural basis of individual differences in personality traits associated with psychiatric illnesses is similar to imaging genetics approaches which examine relationships between brain structure/function and putative psychiatric disorder risk genes in healthy subjects. By providing further support for a trait basis for dopamine dysfunction, our findings suggest that d-amphetamine induced dopamine release may represent an endophenotype of schizophrenia spectrum disorders. Evidence that unaffected relatives of patients with schizophrenia demonstrate elevated pre-synaptic dopamine synthesis capacity in the striatum also implicates hyper-dopaminergia as an endophenotype for schizophrenia (36). Identification of gene variants associated with psychostimulant induced dopamine release may provide clues to the genetic basis of schizophrenia spectrum disorders.

Imaging studies of dopamine release in clinical studies have been limited to the striatum; however, there are reasons to suspect that hyper-dopaminergia in schizophrenia spectrum disorders extends beyond the striatum (20). Our findings showing a relationship between schizotypal traits and dopamine release in prefrontal regions may, at first glance, appear to contradict the cortical hypo-dopaminergia hypothesis of schizophrenia (37). However, the evidence supporting cortical hypo-dopaminergia in schizophrenia is indirect and inconsistent. PET studies of cortical dopamine D1 receptors in schizophrenia have reported increased, decreased, and unaltered levels (38–40). Moreover, inferences about dopamine function based on differences in receptor levels observed between patients and controls under normal physiological conditions may not generalize to stimulant challenge. We find little evidence that baseline BP_{ND} is associated with dopamine release in our data. Consequently, it is possible that hypo-dopaminergia inferred from differences in baseline BP_{ND} may be un-related to amphetamine induced dopamine release, or may actually co-occur with stimulant induced hyper-dopaminergia. Studies of extra-striatal d-amphetamine induced dopamine release in schizophrenia spectrum disorders are clearly warranted.

Multi-modal imaging may inform the relationship between schizotypy, especially disorganized traits, brain function, and dopamine signaling. The face validity of disorganized factor questions suggests they may relate to subtle limitations in executive cognitive functions. Individual differences in disorganized schizotypal traits correlate with executive function, and abnormal prefrontal cortical functioning during task performance correlates with disorganized symptoms in schizophrenia patients (9;33;41–43). The PFC influences dopamine function directly by altering midbrain dopamine cell firing and indirectly via pre-synaptic innervation of striatal dopamine terminals (44;45). Consequently,

alterations in PFC function may alter the response of both cortical and sub-cortical dopamine systems to d-amphetamine challenge.

There are several limitations of this study. Our findings require replication in a sample of subjects with a broader range of schizotypal traits in order to better characterize the relationship between specific facets of schizotypy and dopamine release. Also, we did not rule out Axis II psychopathology during the screening session. Thus, it's possible that some individuals may have met criteria for a schizotypal personality disorder; although this is unlikely given the range of Schizotypal Personality Questionnaire scores in this sample. It's also unlikely that the results are related to other dimensions of psychopathology, such as anxiety and depression, given that neither is associated with dopamine release (46;47). Interview-based measures may be more sensitive to schizotypal traits than self-report questionnaires raising the possibility that different results might have been obtained had we used interview based methods (48). Finally, combining subjects across d-amphetamine administration protocols and PET scanners is not ideal. However, the findings were largely unchanged when analyses were restricted to the placebo-controlled sub-group and we did not find any differences in dopamine release between scanners.

In conclusion, our findings support the possibility that dopamine dysfunction may be a useful endophenotype for genetic studies by showing that the trait basis for hyperdopaminergia observed in schizophrenia spectrum disorders extends to individual differences in schizotypal traits in non-clinical subjects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Correlation between schizotypal traits and dopamine release in the striatum. (A) Voxel-wise analysis restricted to the striatum revealed positive correlations between Schizotypal Personality Questionnaire total score and dopamine release in bilateral striatum. Image thresholded at $p=.05$ (small volume correction). Scatter plots depicting correlation between SPQ total score and dopamine release in the (B) left (C) right striatum clusters.

Figure 2.

Correlation between schizotypal traits and cortical dopamine release. (A) Schizotypal Personality Questionnaire total score correlated with dopamine release in the left middle frontal gyrus and inferior parietal lobule. Image thresholded at $p=.05$ (whole-brain cluster-level corrected). Scatter plots depicting correlation between dopamine release and schizotypal traits in the (B) left middle frontal gyrus and (C) left supramarginal gyrus.

Table 1

Sample Characteristics

Variable	Cohort					
	Total Sample	Open Label	Placebo-Controlled	χ^2	p	
N	63	15	48			
Gender (male:female)	32:31	7:8	25:23	0.13	.714	
Ethnicity (White:AA:Other)	53:6:4	12:2:1	41:4:3	0.34	.842	
Age	Mean 23.1	SD 3.7	Mean 26.1	SD 3.3	Mean 22.1	SD 3.3
Schizotypal Personality	8.1	8.1	8.7	8.7	7.9	7.9
Questionnaire Total Score						
Cognitive-Perceptual Factor	1.0	1.6	1.3	1.8	1.0	1.5
Paranoid Factor	3.0	3.0	3.2	3.1	2.9	2.9
Negative Factor	3.3	3.8	4.3	4.7	3.0	3.5
Disorganized Factor	2.8	3.4	2.7	4.4	2.9	3.1
					0.42	.824

Table 2

Correlation Between Dopamine Release and Schizotypal Personality Traits: Region-of-Interest Analysis^a

		Schizotypal Personality Questionnaire Scores											
		Total			Cognitive-Perceptual			Paranoid			Negative		
Total Sample (n=63)		r	p		r	p		r	p		r	p	
Whole Striatum		.26	.049		.06	.631		.16	.227		.14	.277	
	Limbic	.22	.094		.02	.903		.14	.285		.12	.353	
	Associative	.27	.038		.11	.413		.18	.170		.18	.161	
	Sensorimotor	.20	.128		.02	.866		.10	.440		.07	.620	
Amygdala		.29	.025		.17	.198		.22	.094		.22	.086	
Hippocampus		.08	.569		-.02	.910		.13	.343		.09	.492	
Thalamus		.21	.100		.08	.544		.15	.267		.17	.208	
Placebo-Controlled subgroup (n=48)		r	p		r	p		r	p		r	p	
Whole Striatum		.32	.029		.25	.092		.26	.086		.20	.188	
	Limbic	.34	.023		.26	.078		.27	.068		.21	.163	
	Associative	.29	.048		.23	.123		.24	.116		.20	.174	
	Sensorimotor	.27	.074		.21	.172		.21	.172		.13	.393	
Amygdala		.35	.018		.26	.079		.27	.066		.24	.107	
Hippocampus		.21	.160		.13	.393		.19	.204		.12	.442	
Thalamus		.29	.049		.24	.115		.21	.172		.19	.218	

^aPartial correlation after covarying for age, gender, and, for total sample, cohort (i.e. open label or placebo controlled)

Table 3
Correlations Between Dopamine Release and Schizotypal Personality Traits: Voxel-wise Analysis

Brain Region	Talairach Coordinates			Volume (Voxels) ^a	Peak t-value
	x	y	z		
Schizotypal Personality Questionnaire: Total Score					
Right Caudate ^b	10	2	23	961	3.20
Left Caudate ^b	-18	0	26	468	3.05
Left Middle Frontal Gyrus (BA 9/10)	-33	40	20	164	3.50
Left Supramarginal Gyrus/Inferior Parietal Lobule (BA 40)	-57	-53	29	153	3.43
Schizotypal Personality Questionnaire: Disorganized Factor Score					
Right Medial Frontal Gyrus (BA 9/10)	3	44	17	255	5.21
Right Temporal Lobe (BA 20, 21, 22)	45	-12	-3	759	5.15
Left Inferior/Middle Temporal Gyrus (BA 20, 21, 37)	-50	-45	10	435	4.38
Left Insula/Inferior Frontal Gyrus (BA 13, 37)	-30	15	-13	814	4.30
Right Insula/Inferior Frontal Gyrus (BA 13, 47)	38	5	7	931	4.30
Left Inferior/Middle Temporal Gyrus (BA 20, 21)	-56	-35	-16	213	4.27
Right Thalamus	6	-4	6	202	4.22
Right Superior Frontal Gyrus (BA 10)	28	47	27	185	4.19
Right Caudate/Putamen	10	13	11	442	3.40
Left Caudate/Putamen	-18	13	9	322	3.51

Abbreviations: BA, Brodmann's Area

^aVoxel size=2 × 2 × 2 mm

^bSmall Volume Correction