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Amotivation is associated with smaller ventral striatum volumes in elderly patients with schizophrenia

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Abstract

Objective—Motivational deficits are prevalent in patients with schizophrenia, persist despite antipsychotic treatment, and predict long-term outcomes. Evidence suggests that patients with greater amotivation have smaller ventral striatum (VS) volumes. We wished to replicate this finding in a sample of older, chronically medicated patients with schizophrenia. Using structural imaging and positron emission tomography (PET), we examined whether amotivation uniquely predicted VS volumes beyond the effects of striatal dopamine (DA) D_{2/3} receptor (D_{2/3}R) blockade by antipsychotics.

Methods—Data from 41 elderly schizophrenia patients (mean age: 60.2±6.7; 11 female) were reanalyzed from previously published imaging data. We constructed multivariate linear step-wise regression models with VS volumes as the dependent variable, and various sociodemographic and clinical variables as the initial predictors: age, gender, total brain volume, and antipsychotic striatal D_{2/3}R occupancy. Amotivation was included as a subsequent step to determine any unique

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Conflict of Interests

The other authors have no conflicts of interest to declare in relation to the current manuscript.

relationships with VS volumes beyond the contribution of the covariates. In a reduced sample ($n=36$), general cognition was also included as a covariate.

Results—Amotivation uniquely explained 8% and 6% of the variance in right and left VS volumes, respectively (right: $\beta=-.38$, $t=-2.48$, $p=.01$; left: $\beta=-.31$, $t=-2.17$, $p=.03$). Considering cognition, amotivation levels uniquely explained 9% of the variance in right VS volumes ($\beta=-.43$, $t=-.26$, $p=.03$).

Conclusion—We replicate and extend the finding of reduced VS volumes with greater amotivation. We demonstrate this relationship uniquely beyond the potential contributions of striatal $D_{2/3}R$ blockade by antipsychotics. Elucidating the structural correlates of amotivation in schizophrenia may help develop treatments for this presently irremediable deficit.

Introduction

Motivational deficits in patients with schizophrenia are persistent¹, prevalent from the earliest stages of the disease², and may uniquely predict outcomes beyond other symptoms^{3–6}. Across several neuropsychiatric disorders, including schizophrenia⁷, amotivation is associated with abnormal functioning of frontal-striatal circuits involving the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), and ventral striatum (VS)^{8–10}. In schizophrenia, amotivation has been associated with reduced frontal lobe volumes¹¹, and cortical thinning in the left ACC and left orbitofrontal cortex¹². A better understanding of the neurochemical and structural correlates of amotivation in patients with schizophrenia may help guide future treatments for this currently unamenable deficit, which severely impacts everyday functioning.

While several studies have focused on the cortex, few studies have specifically examined the relationship between VS morphology and amotivation in patients with schizophrenia. Examination of the VS as a substrate for amotivation in schizophrenia is particularly relevant given its proposed role in regulating motivated behaviour^{10,13}. To our knowledge, only one study by Roth and colleagues has specifically explored this relationship¹⁴. They observed that patients ($n=23$) with more severe amotivation demonstrated reduced grey matter (GM) volumes in the right VS. While several lines of preclinical evidence suggest that reduced dopamine (DA) functioning at $D_{2/3}R$ receptors ($D_{2/3}R$) in the VS increases amotivation^{7,15,16}, there have been mixed observations in schizophrenia. In untreated patients, greater amotivation has been associated with lower endogenous DA at $D_{2/3}R$ in the VS ($r^2=.47$, $p=.001$)¹⁷. However, treatment with antipsychotics, which antagonize $D_{2/3}R$, does not seem to significantly worsen nor improve motivational deficits in patients with schizophrenia¹⁸. Consistently, several studies suggest that occupancy of striatal $D_{2/3}R$ by antipsychotics is related to improvements in positive symptoms, with no relationship to negative symptoms^{19–22}. In a sample of elderly, chronically treated patients, estimated antipsychotic occupancy of $D_{2/3}R$ in the VS was not found to be related to amotivation²³. Reducing the dose of antipsychotics in the same sample failed to significantly improve motivation. Thus, the functional status of striatal $D_{2/3}R$ in motivated behaviour may be different in patients with schizophrenia who are treated acutely versus chronically with antipsychotics.

We wished to replicate previous findings of a relationship between reduced VS volumes and greater amotivation in a sample of elderly, chronically medicated patients with schizophrenia. This would help inform whether reduced VS volumes are a correlate of amotivation across the lifespan. We wanted to examine this relationship whilst controlling for estimated striatal D_{2/3}R occupancy by antipsychotic drugs, evaluated using positron emission tomography (PET). This would help elucidate whether antipsychotic D_{2/3}R blockade modulates the relationship between motivation and brain morphology. Notably, estimated striatal D_{2/3}R occupancy provides a more biologically and clinically relevant correlate of antipsychotic action in the brain than dose²⁴. Thus, above and beyond the effects of antipsychotic induced striatal D_{2/3}R blockade, we hypothesized that levels of amotivation would be negatively correlated with VS volume.

Methods

Participants

This is an extension of a previous study; the methods and main results have been published elsewhere²⁵. Patients were recruited based on the following: 1) DSM-IV diagnosis of schizophrenia or schizoaffective disorder, confirmed by the SCID Axis I Disorders²⁶, 2) 50 years old, 3) clinically stable (i.e., no inpatient hospitalization in the past 6 months), and, 4) receiving the same dose of risperidone or olanzapine monotherapy for at least 6 months. Exclusion included: meeting criteria for a substance-use disorder (past 6 months), a positive urine screen for substances of abuse, changing their dose of any psychotropic for mental health reasons (past 6 months), and having an unstable medical condition. Fourteen subjects were current smokers: (mean±SD) 8±15 cigarettes a day.

The study was approved by the institutional Research Ethics Board at the Centre for Addiction and Mental Health, authorized by Health Canada, and registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT00716755). All participants provided written informed consent. Competence to consent was determined using the MacCAT-CR²⁷.

PET Imaging

[¹¹C]-raclopride scans were acquired on a CPS-HRRT PET camera, measuring radioactivity in 207 brain slices with a thickness of 1.2mm each. The in-plane resolution was ~2.8mm full-width at half-maximum. Transmission scans were acquired using a single photon point source for attenuation correction (¹³⁷Cs; T_{1/2}=30.2yr, E=662KeV). A custom-fitted thermoplastic mask was used to decrease head-motion. The mass injected, radioactivity dose, and specific activity of [¹¹C]-raclopride was 2.71(±1.96)µg, 9.69(±0.79)mCi, and 1650.89(±701.51)mCi/µmol. Emission data were acquired in list-mode for 60 minutes, reconstructed by filtered back projection, and redefined into 28 frames.

Time activity curves (TACs) were obtained from dynamic PET images co-registered to MRIs, using the normalized mutual-information algorithm²⁸ in SPM2 (<http://www.fil.ion.ucl.ac.uk/spm>). The Simplified Reference Tissue Method (SRTM)²⁹ was used to calculate binding potential non-displaceable (BP_{ND})³⁰ using cerebellum as reference. The basis function of the SRTM³¹ was applied to generate parametric BP_{ND} maps using PMOD

(v2.7). Images were spatially normalized into MNI space by Nearest Neighbour Interpolation (voxel-size 2mm³) using SPM2.

Estimated Striatal D_{2/3}R Occupancy

We were not able to obtain BP_{ND} data from our participants while they were off antipsychotics. To compute D_{2/3}R occupancy, we estimated participants' baseline BP_{ND} values using data from antipsychotic-free patients with schizophrenia as a reference (mean ±SD; age: 66.1±11.5 years; age range: 50–83 years; 4 women; duration of antipsychotic-free state: 12.5±18.6 years), as previously employed^{32–34}. These subjects come from a previously published study examining D_{2/3}R availability in elderly patients with schizophrenia who had been antipsychotic free for an extended period³⁵. This study demonstrated D_{2/3}R availability measured with [¹¹C]-raclopride in un-medicated, elderly patients with schizophrenia did not differ from age- and sex- matched healthy controls. Using this antipsychotic-free sample, age- and sex-corrected measures of baseline BP_{ND} were estimated for each ROI using a linear regression equation³⁵. D_{2/3}R occupancy was calculated using the following formula:

$$D_{2/3}R \text{ occupancy} = ([BP_{ND_Antipsychotic-free} - BP_{ND_Medicated}] / [BP_{ND_Antipsychotic-free}]) \times 100$$

where BP_{ND_Antipsychotic-free} is the age- and sex-corrected BP_{ND} derived from antipsychotic-free participants with schizophrenia, and BP_{ND_Medicated} is the BP_{ND} obtained from participants receiving oral risperidone or olanzapine. Since it is often impossible to have a complete wash-out of antipsychotic medications to provide a true baseline PET scan in patients with schizophrenia, this estimation method has been employed by our research group^{36–38} and several others^{32–34}. It has been suggested that the error associated with this estimation ranges from 0–9% for patients with 50% occupancy, and 0–4% for patients who have 80% occupancy^{32,39}. This source of error is unlikely to introduce a systematic bias across subjects.

Magnetic Resonance Imaging (MRI)

Each participant underwent T1-weighted magnetic resonance imaging (MRI; inversion time, 650 milliseconds; field of view, 23cm; 256×256; slice thickness, 0.9mm; flip angle, 8°), performed on a GE Discovery MR750 3.0-T scanner (General Electric Medical Systems).

Subcortical Volume Analyses

The Multiple Automatically Generated Templates (MAGeT-Brain) algorithm^{40,41} was employed to provide fully-automated segmentation of striatal subdivisions in participants' native space⁴². The MAGeT-Brain algorithm is a modified multi-atlas segmentation technique, which employs a limited number of high-quality manually segmented atlases as an input to reduce bias and enhance segmentation accuracy. MAGeT-Brain propagates atlas segmentations to a template library, formed from a subset of target images, via transformations estimated by nonlinear image registration. The resulting segmentations are then propagated to each target image and fused using a label fusion method.

A subset of subjects (n=21) were used as template libraries through which the final segmentation was bootstrapped; chosen based on representative subject characteristics⁴³. Volumes (mm³) were extracted bilaterally from the VS and the whole striatum. Figure 1 in the Supplementary Material demonstrates the results of the automatic striatal subdivision labelling in a single subject.

Total Brain Volume Analysis

The procedure for total brain volume (TBV) analysis has been published elsewhere⁴⁴. TBV was obtained using the Brain Extraction based on non-local Segmentation Technique (BEaST) method⁴⁵. This includes CSF (in the ventricles, cerebellar cistern, deep sulci, along surface of brain, and brainstem), the brainstem, and cerebellar white matter and GM in the brain mask, while excluding the skull, skin, fat, muscles, dura, eyes, bone, exterior blood vessels, and exterior nerves.

Symptom Assessments

Clinical status was evaluated using the Positive and Negative Syndrome Scale (PANSS)⁴⁶, and symptom scores were evaluated using consensus-defined factors⁴⁷. Given the burgeoning evidence for a two-factor structure of negative symptoms in schizophrenia^{48,49}, we calculated two additional scores to evaluate amotivation and expressive deficits separately. Specifically, a social amotivation score (Amotivation Factor) was derived by summing the following items from the PANSS: Emotional Withdrawal, Passive Apathetic Withdrawal, and Active Social Avoidance⁵⁰. A diminished expression score (Diminished Expression Factor) was calculated by summing the following items from the PANSS: Blunted Affect, Poor Rapport, Lack of Spontaneity & Flow of Conversation, and Motor Retardation⁵⁰. Higher scores on each of these measures reflect greater negative symptom severity. Cognitive functioning was assessed using The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)⁵¹. Given this previous literature elucidating the factor analytic structure of PANSS negative symptoms, we did not explore how modifications (i.e., removing certain items) to factor scores could affect our results.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS (v.20) and GraphPad Prism (v.7.0). Normality of variables was determined using the D'Agostino-Pearson test. Our analyses focused on VS volumes as the main outcome variable for each hemisphere separately, as previous work found a specific relationship between amotivation and right VS volume¹⁴. We constructed multivariate linear step-wise regression models with VS volumes as the dependent variable, and various sociodemographic and clinical variables as the initial predictors. Amotivation was included as a subsequent step in this predictive model to determine whether this variable demonstrated a significant relationship with VS volumes over and above the contribution of other covariates. Roth and colleagues included age, gender, depression and total GM as covariates. We extended this list to include age, gender, TBV and striatal D_{2/3}R occupancy as an initial step, and positive and depressive symptoms as the second. Amotivation scores were included as the third step. Several groups, including ourselves, have demonstrated that while amotivation and cognition are distinct constructs, they have some shared variance⁵. Thus, we wished to explore whether the relationship

between amotivation and VS volume would persist considering the potential variance in amotivation accounted for by cognition. A subset of the sample also had cognitive scores available. For these subjects, we recomputed our models including global cognition in the second step to determine whether the relationship of interest would hold while controlling for this variable as well. In the Supplementary Material, we present the correlations between all the variables included in our multivariate regression models. In our current sample, there is a trend correlation ($p=.08$) between amotivation and RBANS total scores. Moreover, D_{2/3}R occupancy is negatively correlated with VS volumes and TBV. While this is consistent with some (but not all) findings that antipsychotic exposure is related to reductions in both striatal volume and TBV^{52,53}, our sample is not poised to directly address causality regarding the issue of how antipsychotic exposure may change brain morphology in schizophrenia.

We conducted several analyses to explore the specificity of the amotivation-VS volume relationship. Specifically, we recomputed the above analyses with total striatal volume as the dependent variable. In addition, in separate models, we explored whether another negative symptom, namely diminished expression, would be related to VS volumes.

The alpha level of significance for all our *a priori* hypotheses and confirmatory analyses was set at $p<.05$ (two-tailed).

Results

Participant characteristics are detailed in Table 1. In our multivariate regression model (see Table 2), age, gender, TBV, and striatal D_{2/3}R occupancy together explained 47% of the variance in right VS volumes. Considering these variables, in addition to positive and depression symptoms, amotivation significantly explained an additional 8% of the variance in right VS volumes. Thus, over and above the contribution of participant characteristics, striatal D_{2/3}R occupancy, positive symptoms, and depression symptoms, levels of amotivation were negatively associated with right VS volumes (see Figure 1a). Similarly, in the left VS amotivation significantly explained an additional 6% of the variance above and beyond that explained by the other variables (see Table 2 & Figure 1b). Since years of education and the number of cigarettes smoked per day could theoretically influence the relationship between symptoms and VS volume, we explored including these variables as an additional step in our multivariate regression model (see Supplementary Material).

We wished to explore whether amotivation could account for a significant proportion of the variance in VS volumes after considering global cognitive functioning assessed with total RBANS scores. Five participants did not provide total RBANS scores. After considering global cognitive functioning, amotivation continued to explain a significant proportion (9%) of the variance in right VS volumes, but not left VS volumes (see Table 3). Since there could be potential interactions between cognition and symptomatology on brain morphology, we explored whether amotivation could continue to account for a significant proportion of the variance in right VS volumes after the inclusion of cognition*symptom interaction terms. Amotivation continued to explain a significant proportion (9%) of the variance in right VS

volumes, but not left VS volumes, after considering these potential interactions (see Table 4).

We explored the specificity of our findings to amotivation, rather than to other negative symptoms. We constructed separate regression models using diminished expression scores instead of amotivation scores as the final predictive step (these negative symptoms were positively correlated with each other: $r=.75$, $p<.0001$). Notably, diminished expression scores failed to account for any additional variance in right (final step: $\beta=.13$, $t=.81$, $p=.42$; overall model: $r^2=.37$, $F_{1,33}=.66$, $p=.42$) and left (final step: $\beta=.02$, $t=.15$, $p=.88$; overall model: $r^2=.54$, $F_{1,33}=.02$, $p=.88$) VS volumes. We explored whether the effect with amotivation was specific to the VS, rather than the striatum in general. Amotivation scores failed to account for any additional variance in left (final step: $\beta=-.13$, $t=-.91$, $p=.37$; overall model: $r^2=.60$, $F_{1,33}=.83$, $p=.37$) and right (final step: $\beta=-.17$, $t=-1.19$, $p=.24$; overall model: $r^2=.61$, $F_{1,33}=1.41$, $p=.24$) total striatal volume.

Discussion

We found amotivation in elderly, chronically medicated patients with schizophrenia is significantly related to smaller VS volumes. This relationship persisted after considering several *a priori* variables often associated with amotivation and brain morphology. These findings are consistent with the theorized role of the VS in motivation¹⁶, and replicates and extends previous findings¹⁴. Controlling for age, gender, depression (BDI-II scores), and total GM, Roth and colleagues found that amotivation, measured with the Apathy Evaluation Scale, was associated with smaller right VS volumes in schizophrenia patients. Using different volumetric quantification methods, and a different measure of amotivation, we replicate these findings while additionally controlling for general positive symptoms and estimated antipsychotic D_{2/3}R occupancy. Thus, our data suggests that amotivation is uniquely associated with reduced VS volumes, above and beyond striatal D_{2/3}R blockade by antipsychotics.

Besides including estimated striatal D_{2/3}R occupancy, our study has several strengths which serve to extend previously published work. First, our study included additional covariates – positive symptom severity and cognition – and found the relationship between amotivation and VS volumes to hold even after statistically controlling for these. Second, our study examined the specificity of this relationship. We failed to find an association between negative symptoms in general and VS volumes. Rather, the relationship was specific to amotivation. Furthermore, the relationship between amotivation and striatal morphology was specific to the VS, as a significant association was not observed with total striatal volumes. Collectively, this study provides a more comprehensive approach to the question of whether amotivation is related to VS morphology in schizophrenia; suggesting a specific relationship. An additional strength is that the patients in our sample were clinically stable, and had received the same dose of medication monotherapy for the last 6 months.

Several functional MRI studies have linked amotivation in schizophrenia with reduced activation of the VS^{54–56}. Our findings raise the possibility that previously reported VS hypoactivation may be the result of, or related to, reduced VS volume. The neurofunctional

significance of reduced VS volumes in schizophrenia remains unclear. Future studies should employ multimodal brain imaging to determine whether amotivation-associated reductions in VS activation is associated with reduced neuronal integrity and/or reduced endogenous DA levels. A better understanding of the biological mechanisms underlying reduced VS volume and activity may help guide future treatments for amotivation in schizophrenia. For example, these findings support theories that deep brain stimulation of the VS may improve motivational deficits in schizophrenia^{57–59}, as in depression⁶⁰. Volumetric reductions are usually interpreted as reflecting neurodegeneration. However, multiple interpretations exist. In healthy persons, several common genetic variants have been associated with natural variation in putamen and caudate volumes, but not VS volumes⁶¹. In rodents, reductions in cortical and striatal volume have been related to reduced markers of GABA neuron expression/function^{62–64}. We speculate that reduced GABA-ergic interneuron expression, structure, or function in the VS may be related to greater amotivation. However, this speculation requires confirmation by future longitudinal studies combining *in vivo* MRI volume measures with post-mortem measures.

Both our study and Roth et. al's found that amotivation was more strongly related to VS morphology in the right hemisphere versus the left. The reason for this laterality effect remains unclear. Evidence suggest that DA release in the right VS may be more strongly related to processing of un-expected monetary rewards⁶⁵. Moreover, functional connectivity data suggests that the left VS may be more strongly related to internally directed processes (i.e., saliency and self-control), while the right VS may be related to externally directed processes (i.e., action/attention toward behavioural contingencies)⁶⁶. Interestingly, reduced glucose metabolism in the right VS, but not the left, is predictive of increased amotivation after deep-brain stimulation of the subthalamic nucleus in Parkinson's disease⁶⁷. Collectively, we tentatively speculate that the right VS may be more strongly related to motivated behaviour (i.e., translating reward contingencies into action). However, larger studies are needed to clarify the role of VS laterality on amotivation in healthy persons and those with neuropsychiatric diseases.

There are several limitations. First, included patients were 50 years of age. While our findings replicate those observed in younger patients, the generalizability of our findings may still be limited. Our assessment of motivational deficits was incomplete: only clinician rated and evaluating a single domain (i.e., social amotivation). Future studies should employ multiple measures of amotivation, including objective task measures⁷. Future studies should include matched healthy controls to fully characterize how differences in VS volume may relate to differences in motivation. Finally, while our estimate of antipsychotic D_{2/3}R blockade is superior to estimated chlorpromazine dose-equivalents, patients did not provide a true baseline PET scan. In the Supplementary Material, we provide our main analyses of interest using chlorpromazine equivalents instead of occupancy to allow comparison with future studies that may use this measure. Prospective longitudinal PET studies including neuroleptic naïve patients could examine the relationships between D_{2/3}R blockade, amotivation, and brain morphology. Finally, the variables included in our regression models were based on previous work, and were *a priori*. Studies with larger sample sizes and sufficient statistical power should explore whether other variables may mediate the relationship between amotivation and VS volume in schizophrenia.

Our data suggests reduced VS volumes are associated with amotivation in elderly patients with schizophrenia. This relationship was not found to be significantly related to striatal D_{2/3}R blockade by antipsychotics. Our findings add to a growing literature aimed at better understanding the neural correlates of amotivation in schizophrenia. These findings may help guide novel treatments for this currently unamenable, debilitating symptom.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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A. **B.** **Figure 1.**

Table 1

Subject characteristics.

	Total (n = 41)
	Mean $\pm$ SD (range) or n (%)
Age (year)	60.2 $\pm$ 6.7 (50 – 79)
Female (n)	11 (26.8)
African (n)	4 (9.8)
Asian (n)	2 (4.9)
Caucasian (n)	35 (85.4)
Schizophrenia (n)	33 (80.5)
Schizoaffective (n)	8 (19.5)
Age of onset (year-old)	25.1 $\pm$ 9.7 (7 – 48)
Duration of illness (year)	34.3 $\pm$ 10.6 (8 – 55)
Number of episode (n)	5.7 $\pm$ 4.8 (1 – 20)
Number of hospitalization (n)	5.9 $\pm$ 5.4 (0 – 20)
Year of antipsychotic exposure (year)	30.0 $\pm$ 11.7 (4 – 55)
PANSS total score	60.2 $\pm$ 13.5 (30 – 82)
Positive subscale score	12.8 $\pm$ 3.9 (7 – 20)
Negative subscale score	17.9 $\pm$ 5 (7 – 28)
General psychopathology subscale score	29.5 $\pm$ 6.8 (16 – 43)
PANSS factor scores	
Positive	11.24 $\pm$ 3.22 (5 – 17)
Negative	22.83 $\pm$ 6.70 (10 – 36)
Depression	8.02 $\pm$ 2.88 (5 – 15)
Disorganized	7.24 $\pm$ 2.44 (3 – 13)
Excited/Activation	6.37 $\pm$ 1.67 (5 – 12)
Amotivation Factor	7.88 $\pm$ 2.68 (3 – 13)
Diminished Expression Factor	9.51 $\pm$ 3.20 (4 – 16)
OLZ (n)	24 (58.5)
Daily dose (mg)	20.6 $\pm$ 6.7 (10 – 35)
RIS (n)	17 (41.5)
Daily dose (mg)	4.3 $\pm$ 2.5 (2 – 12)
CPZ equivalent dose (mg)	419.5 $\pm$ 186.4 (200 – 1200)
D _{2/3} R occupancy (%)	70.4 $\pm$ 11.9 (40.6 – 91.2)
	(n=36)
RBANS Total Scores	76.53 $\pm$ 11.64 (52 – 99)

Abbreviations: PANSS, Positive and Negative Syndrome Scale; OLZ, Olanzapine; RIS, Risperidone; CPZ, Chlorpromazine; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

Table 2

Stepwise multiple regression model predicting right and left ventral striatum volumes.

Right Ventral Striatum					
Step	Variable Added ^a	β	<i>t</i> -statistic	<i>p</i> -value	R ² Change
1	Age	.11	.76	.44	.47
	Gender	.24	1.41	.17	
	Total Brain Volume	.56	3.98	.0004	
	Striatal D _{2/3} Receptor Occupancy	-.03	-.17	.87	
2	Positive Symptoms ^c	.14	.75	.46	.004
	Depressed Symptoms ^c	-.12	.76	.45	
3	Amotivation Factor ^c	-.38	-2.48	.01	.08
Left Ventral Striatum					
Step	Variable Added ^b	β	<i>t</i> -statistic	<i>p</i> -value	R ² Change
1	Age	.05	.36	.73	.53
	Gender	-.03	-.17	.87	
	Total Brain Volume	.68	5.08	.00002	
	Striatal D _{2/3} Receptor Occupancy	-.06	-.43	.67	
2	Positive Symptoms ^c	.10	.60	.55	.003
	Depressed Symptoms ^c	.02	.12	.91	
3	Amotivation Factor ^c	-.31	-2.17	.03	.06

Note: For ease of presentation, only the regression weights from the final model are shown.

^aOverall model: $r^2 = .55$, $F_{1,33} = 6.14$, $p = .01$.

^bOverall model: $r^2 = .60$, $F_{1,33} = 4.42$, $p = .03$.

^cCalculated using derived factor scores from the Positive and Negative Syndrome Scale.

Table 3

Stepwise multiple regression model predicting right and left ventral striatum volumes.

Right Ventral Striatum					
Step	Variable Added ^a	β	<i>t</i> -statistic	<i>p</i> -value	R ² Change
1	Age	.09	.56	.57	.40
	Gender	.23	1.14	.26	
	Total Brain Volume	.51	2.27	.01	
	Striatal D _{2/3} Receptor Occupancy	-.04	-.18	.86	
2	Positive Symptoms ^c	.22	.91	.37	.008
	Depressed Symptoms ^c	-.14	-.75	.46	
	RBANS Total	-.06	-.39	.70	
3	Amotivation Factor ^c	-.43	-.26	.03	.09
Left Ventral Striatum					
Step	Variable Added ^b	β	<i>t</i> -statistic	<i>p</i> -value	R ² Change
1	Age	.06	.40	.70	.50
	Gender	-.10	-.52	.61	
	Total Brain Volume	.64	3.46	.002	
	Striatal D _{2/3} Receptor Occupancy	-.12	-.58	.57	
2	Positive Symptoms ^c	.13	.57	.58	.006
	Depressed Symptoms ^c	-.02	-.08	.93	
	RBANS Total	-.06	.43	.67	
3	Amotivation Factor ^c	-.21	-1.10	.28	.02

Note: For ease of presentation, only the regression weights from the final model are shown.

^aOverall model: $r^2 = .50$, $F_{1,27} = 5.12$, $p = .03$.

^bOverall model: $r^2 = .53$, $F_{1,27} = 1.21$, $p = .28$.

^cCalculated using derived factor scores from the Positive and Negative Syndrome Scale.

Table 4
Stepwise multiple regression model predicting right and left ventral striatum volumes.

Right Ventral Striatum					
Step	Variable Added ^a	β	<i>t</i> -statistic	<i>p</i> -value	R ² Change
1	Age	.09	.57	.58	.40
	Gender	.23	1.10	.28	
	Total Brain Volume	.51	2.63	.02	
	Striatal D _{2/3} Receptor Occupancy	-.02	-.08	.94	
2	Positive Symptoms ^c	.19	.72	.48	.008
	Depressed Symptoms ^c	-.12	-.63	.53	
	RBANS Total	-.05	-.32	.75	
3	RBANS*Positive Symptoms ^d	.02	.11	.92	.004
	RBANS*Depressed Symptoms ^d	.04	.19	.85	
4	Amotivation Factor ^c	-.43	-2.15	.04	.09
Left Ventral Striatum					
Step	Variable Added ^b	β	<i>t</i> -statistic	<i>p</i> -value	R ² Change
1	Age	.06	.37	.72	.50
	Gender	-.11	-.51	.61	
	Total Brain Volume	.63	3.31	.003	
	Striatal D _{2/3} Receptor Occupancy	-.14	-.61	.55	
2	Positive Symptoms ^c	.15	.60	.56	.006
	Depressed Symptoms ^c	-.03	-.13	.90	
	RBANS Total	.06	.36	.72	
3	RBANS*Positive Symptoms ^d	-.02	-.10	.92	.001
	RBANS*Depressed Symptoms ^d	-.03	-.17	.87	
4	Amotivation Factor ^c	-.21	-1.08	.29	.02

Note: For ease of presentation, only the regression weights from the final model are shown.

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^aOverall model: $r^2 = .31$, $F_{1,25} = 4.63$, $p = .04$.
^bOverall model: $r^2 = .34$, $F_{1,25} = 1.16$, $p = .29$.
^cCalculated using derived factor scores from the Positive and Negative Syndrome Scale.
^dCentered values