Online Resource Material for:

Prefrontal Dopamine D1 Receptors and Working Memory in Schizotypal Personality Disorder: A PET Study with [11C]NNC112, *Psychopharmacology*

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The following Online Resource file contains supplementary text regarding the PET-imaging methodology and analyses used, and supplemental results. This file also contains the following:
-Online Resource Table 1: Total distribution volumes of [11C]NNC112 by diagnostic group for prefrontal-cortical and striatal regions of interest;
-Online Resource Table 2: Bivariate correlations between working memory (WM) performance and [11C]NNC112 BP in the prefrontal cortex (PFC) among schizotypal personality disorder (SPD) participants;
-Online Resource Table 3: Partial correlations between WM performance and [11C]NNC112 BP in the PFC when controlling for age among SPD participants;
-Online Resource Figures 1a-d: Scatterplots illustrating the distribution of [11C]NNC112 BP_F by group (SPD, controls) in the dorsolateral PFC (DLPFC), medial PFC (MPFC), orbitofrontal cortex (OFC), and ventral striatum;
-Online Resource Figures 2a, b: Scatterplots illustrating the relation of [11C]NNC112 BP_F and BP_P in the DLPFC with performance on the Paced Auditory Serial Addition Test (PASAT) in participants with SPD.

Supplemental Methods

Radiochemistry

[11C]NNC112 was prepared by *N*-methylation of the precursor using [11C]methyl triflate, as previously described (Halldin et al. 1998).

PET Acquisition

Emission scan data were collected for 90 minutes. Data were binned into 18 frames of increasing duration (3 x 20 sec, 3 x 1 min, 3 x 2 min, 2 x 5 min, and 7 x 10 min).

Receptor Parameter Estimation

As described in the primary text, PET data were analyzed with kinetic modeling and arterial plasma input to derive the total distribution volume (V_T) for each region. V_T was derived from the estimated rate constants in the respective compartment model; 2-tissue compartment modeling was used in the regions of interest (ROIs) and 1-tissue compartment modeling in the cerebellum (CER). Fits were performed with programs developed in-house in Matlab (Mathworks, Natick, MA, USA). The binding potential measure BP_P was estimated as: $BP_P = V_T(ROI) - V_T(CER)$. BP_P is equivalent to f_p * B_{avail}/K_D. Here, B_{avail} (nM) is the regional density of receptors available for radioligand binding, and K_D (nM) is the reciprocal of the affinity of radioligand for the target receptor. We also present results for both BP_F and BP_{ND} (see primary text). BP_F accounts for f_p and is defined as: $BP_F = \frac{BP_P}{fp}$; it is equivalent to B_{avail}/K_D. BP_{ND}, calculated as: $BP_{ND} = \frac{BP_P}{V_T(CER)}$, is equivalent to f_{ND} * B_{avail}/K_D. Here, f_{ND} is the fraction of free plus non-specifically bound radioligand in brain tissue.

Partial Volume Effect Correction

Given significant group differences in some of the cortical-ROI volumes, there was the potential for partial volume effects (PVE) to influence PET measures differentially across groups. Thus PET data for cortical ROIs were adjusted to correct for PVE using a voxel-based approach (Meltzer et al. 1996) in which cortical white matter was used to estimate the activity in white matter, and correction was applied to each frame of data. TACs were then generated as the

average PVE-corrected activity in each ROI. The striatal ROI data were not PVE-corrected, as there were no significant group differences in striatal subregion volumes.

Supplemental Results

Clinical Characteristics of SPD Participants

Among the SPD participants, current comorbid Axis-I conditions included binge-eating disorder (n=1), depersonalization disorder (n=1), dysthymia (n=1), generalized anxiety disorder (n=2), intermittent-explosive disorder (n=3), obsessive-compulsive disorder (n=1), social phobia (n=5), and specific phobia (n=1). Past Axis-I conditions included alcohol abuse (n=3), alcohol dependence (n=4), binge-eating disorder (n=1), cannabis abuse (n=1), cannabis dependence (n=1), cocaine abuse (n=1), dissociative amnesia (n=1), hallucinogen abuse (n=1), intermittent-explosive disorder (n=4), major depressive disorder (n=8), and post-traumatic stress disorder (n=2). Comorbid personality disorders were antisocial (n=3), avoidant (n=4), borderline (n=1), narcissistic (n=2), obsessive-compulsive (n=4), paranoid (n=6), and schizoid (n=1).

Associations of Age with Binding-Potential and WM Measures

As noted in the primary text, age was significantly related to BP_F in the DLPFC among the SPD participants (r_s=0.494, p=0.037), indicating that older SPD participants tended to have higher BP_F in this region; this same association was in the weak range among controls (r_s=0.150). In contrast, age was significantly negatively related to BP_{ND} in several of the striatal subregions in the total sample and in both groups separately. Specifically, in the total sample (N=39), age was significantly negatively related to BP_{ND} in the postcommissural putamen (postPU; r_s=-0.367, p=0.022), precommissural dorsal putamen (preDPU; r_s=-0.464, p=0.003), precommissural dorsal caudate (preDCA; r_s=-0.543, p<0.001), postcommissural caudate (postCA; r_s=-0.353, p=0.027), and whole striatum (STR; r_s=-0.477, p=0.002). When examining these associations separately

within each group, they remained significant among the controls (n=21; postPU; r_s=-0.497, p=0.022; preDPU; r_s=-0.612, p=0.003; preDCA; r_s=-0.621, p=0.003; postCA; r_s=-0.553, p=0.009; STR; r_s=-0.600, p=0.004). Among the SPD participants, age was significantly negatively related to BP_{ND} in the preDCA (r_s=-0.494, p=0.037), whereas nonsignificant negative associations were observed for BP_{ND} in the other striatal subregions (range of r_s=-0.150 to -0.315; whole STR: r_s=-0.366, p=0.135). Age was not significantly related to BP_F or BP_P in the striatum. Among the SPD participants, age was not significantly related to performance on either the PASAT or 2-back task.

Group Differences in [^{11}C]NNC112 BP_F, BP_{ND}, and BP_P: Striatum

As noted in the primary text, between-group planned comparisons indicated that SPD participants had higher BP_F in the VST compared to controls (p=0.025); the effect size for this difference was in the medium-to-large range (0.763), but this difference was not considered significant after multiple-comparisons correction. There were no significant differences in BP_F in the other striatal subregions or in the striatum as a whole. Effect sizes for group differences in BP_F in striatal subregions (other than VST) and whole striatum were in the medium range (0.443 to 0.569). BP_F results were nearly identical when including age as a covariate, although the trend-level effect of diagnosis that was observed with mixed modeling became nonsignificant [F(1, 36.01)=2.75, p=0.106]. For BP_{ND}, between-group planned comparisons indicated that SPD participants had higher BP_{ND} in the VST compared to controls at trend level (p=0.064); the effect size for this difference was in the medium range (0.612). There were no significant differences in other striatal subregions or in the striatum as a whole (effect sizes ranged from 0.013 to 0.161). Results were similar when using age as a covariate, although the p value for the

VST group comparison reduced to 0.030; this difference was not considered significant after multiple-comparisons correction. We found no significant group differences in BP_P in the striatal subregions or the striatum as a whole (VST effect size=0.307 [SPD>controls], all others ranged from -0.031 to 0.050).

PASAT and 2-back Performance

On the PASAT, the SPD participants had a mean score (number correct) of 32.50 ± 12.53 (range=9 to 47; n=18), and on the 2-back, their mean hit rate was 0.82 ± 0.10 (range=0.65 to 0.97; n=16 for the 2-back due to missing scores).

References

Halldin C, Foged C, Chou YH, Karlsson P, Swahn CG, Sandell J, Sedvall G, Farde L (1998) Carbon-11-NNC 112: a radioligand for PET examination of striatal and neocortical D1-dopamine receptors. J Nucl Med 39:2061-2068

Meltzer CC, Zubieta JK, Links JM, Brakeman P, Stumpf MJ, Frost JJ (1996) MR-based correction of brain PET measurements for heterogeneous gray matter radioactivity distribution. J. Cereb. Blood Flow Metab. 16:650-658

Online Resource Table 1

Total Distribution Volumes (V_T, mL/cm^3) of [^{11}C]NNC112 by Diagnostic Group for PFC[a] and Striatal ROIs

ROI	Controls (n=21)	SPD (n=18)	p[b]
PFC:			
DLPFC	5.25 ± 1.12	4.97 ± 1.37	0.475
MPFC	5.35 ± 1.09	5.01 ± 1.36[c]	0.396
OFC	5.34 ± 1.16	5.21 ± 1.37	0.747
Striatal:			
VST	7.82 ± 1.78	8.22 ± 2.06	0.523
preDCA	8.67 ± 1.79	8.61 ± 2.42	0.937
preDPU	9.07 ± 1.82	9.03 ± 2.53	0.957
postCA	7.11 ± 1.52	7.01 ± 2.19	0.861
postPU	8.80 ± 1.79	8.67 ± 2.33	0.847
whole STR	8.59 ± 1.74	8.60 ± 2.38	0.989

Note. Mean ± Standard Deviation.
DLPFC=dorsolateral prefrontal cortex; MPFC=medial prefrontal cortex; OFC=orbitofrontal cortex; PFC=prefrontal cortex; postCA=postcommissural caudate; postPU=postcommissural putamen; preDCA=precommissural dorsal caudate; preDPU=precommissural dorsal putamen; ROI=region of interest; SPD=schizotypal personality disorder; STR=striatum; VST=ventral striatum.
[a]V_T values for all PFC (but not striatal) ROIs were adjusted to correct for partial volume effects (PVE); see primary and Online Resource text.
[b]Independent-samples *t*-test.
[c]n=17: One SPD participant's values were excluded due to excessive noise in the V_T measurement.

Online Resource Table 2

Bivariate correlations[a] between WM Performance and [^{11}C]NNC112 BP in the PFC among SPD Participants (n=18)

PFC ROI	PASAT	2-back[b]
BP	r_s	r_s
DLPFC:		
BP_F	-0.460‡	-0.281
BP_P	-0.421‡	-0.033
BP_{ND}	-0.194	0.030
MPFC[c]:		
BP_F	-0.551*	-0.345
BP_P	-0.488*	0.007
BP_{ND}	-0.207	0.108
OFC:		
BP_F	-0.303	-0.186
BP_P	-0.339	-0.068
BP_{ND}	-0.178	-0.047

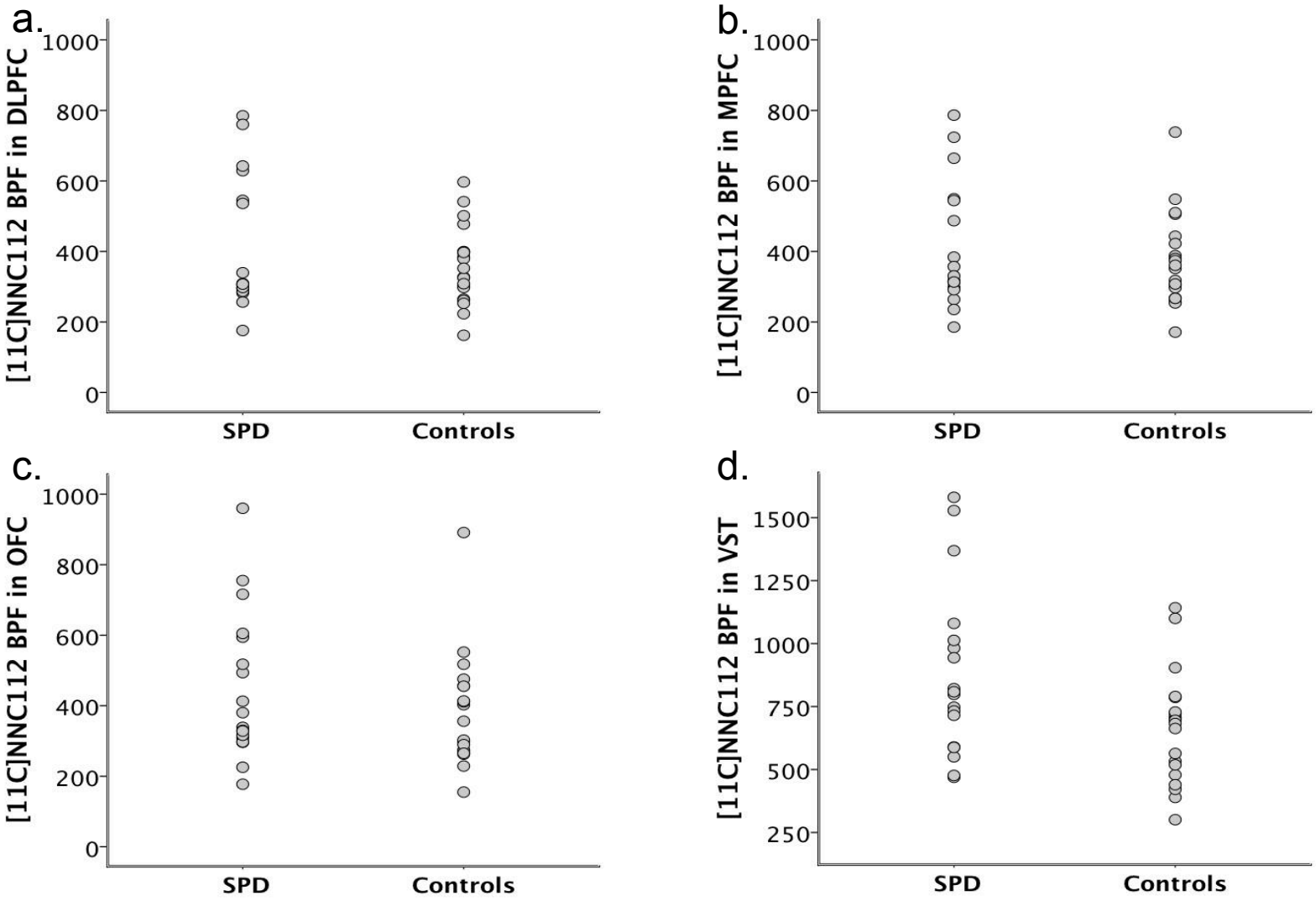
* $\leq$ 0.05
‡ $\leq$ 0.10
BP=binding potential; DLPFC=dorsolateral prefrontal cortex; MPFC=medial prefrontal cortex; OFC=orbitofrontal cortex; PASAT=Paced Auditory Serial Addition Test; PFC=prefrontal cortex; ROI=region of interest; SPD=schizotypal personality disorder; WM=working memory
[a]Spearman rank correlations (r_s) were used due to non-normal distributions observed for several variables.
[b]n=16 due to missing scores for 2 participants.
[c]n=17 for PASAT and n=15 for 2-back; one SPD participant's MPFC values were excluded due to excessive noise in the V_T measurement.

Online Resource Table 3

Partial correlations[a] between WM Performance and [^{11}C]NNC112 BP in the PFC when controlling for age among SPD Participants (n=18)

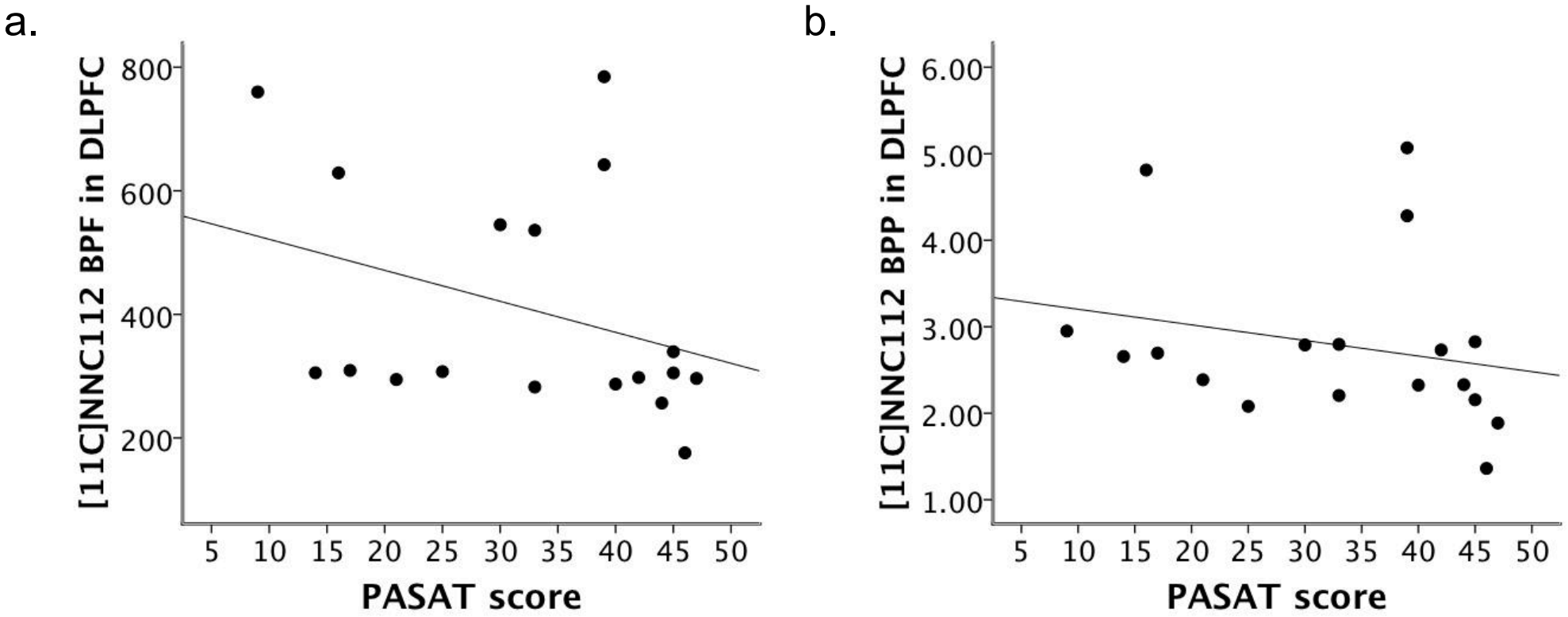
PFC ROI	PASAT	2-back[b]
BP	**pr_s**	**pr_s**
DLPFC:		
BP_F	-0.354	-0.201
BP_P	-0.357	0.035
BP_{ND}	-0.121	0.089
MPFC[c]:		
BP_F	-0.474‡	-0.282
BP_P	-0.498*	0.022
BP_{ND}	-0.145	0.164
OFC:		
BP_F	-0.214	-0.123
BP_P	-0.287	-0.020
BP_{ND}	-0.110	0.003

* $\leq$ 0.05
‡ $\leq$ 0.10
BP=binding potential; DLPFC=dorsolateral prefrontal cortex; MPFC=medial prefrontal cortex; OFC=orbitofrontal cortex; PASAT=Paced Auditory Serial Addition Test; PFC=prefrontal cortex; ROI=region of interest; SPD=schizotypal personality disorder; WM=working memory
[a]Partial Spearman rank correlations (pr_s) were used due to non-normal distributions observed for several variables.
[b]n=16 due to missing scores for 2 participants.
[c]n=17 for PASAT and n=15 for 2-back; one SPD participant's MPFC values were excluded due to excessive noise in the V_T measurement.



Online Resource Figure 1.

a) Distribution of [^{11}C]NNC112 BP_F in the dorsolateral prefrontal cortex (DLPFC) of participants with schizotypal personality disorder (SPD, n=18) and healthy-control participants (n=20); the groups did not differ significantly on this measure (p=0.306). b) BP_F in the medial prefrontal cortex (MPFC) of SPD participants (n=17) and controls (n=20); the groups did not differ significantly on this measure (p=0.466). c) BP_F in the orbitofrontal cortex (OFC) of SPD participants (n=18) and controls (n=20); the groups did not differ significantly on this measure (p=0.248). d) BP_F in the ventral striatum (VST) of SPD participants (n=18) and controls (n=20); results indicated that SPD participants may be characterized by higher BP_F in the VST compared to controls (p=0.025; see primary text).



Online Resource Figure 2.
a) The relation between [^{11}C]NNC112 BP_F in the dorsolateral prefrontal cortex (DLPFC) and performance on the Paced Auditory Serial Addition Test (PASAT) in participants with schizotypal personality disorder (SPD), n=18; r_s=-0.460, p=.055.
b) The relation between BP_P in the DLPFC and PASAT performance in SPD participants, n=18; r_s=-0.421, p=.082.