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Polymorphism in the Zinc Finger Protein 804A Gene (*ZNF804A*) and Variation in D_1 and $D_{2/3}$ Dopamine Receptor Availability in the Healthy Human Brain: a Dual PET Study

Catherine E. Hegarty, PhD[1,2], **Angela M. Ianni, MD PhD**[1], **Philip D. Kohn, BA**[1], **Bhaskar Kolachana, PhD**[1], **Michael Gregory, MD**[1], **Joseph C. Masdeu, MD PhD**[1], **Daniel P. Eisenberg, MD**[1,*], **Karen F. Berman, MD**[1,*]

[1]Section on Integrative Neuroimaging, Clinical & Translational Neuroscience Branch, Intramural Research Program, National Institute of Mental Health, NIH, DHHS, Bethesda, MD 20892

[2]Neuroscience Graduate Program, Brown University, Providence RI 02912

Abstract

Background: The rs1344706 single nucleotide polymorphism (SNP) in the *ZNF804A* gene has been associated with risk for psychosis in multiple genome-wide association studies, yet mechanisms underlying this association are not known. Given preclinical work suggesting an impact of *ZNF804A* on dopamine receptor gene transcription and clinical studies establishing dopaminergic dysfunction in patients with schizophrenia, we hypothesized that the *ZNF804A* risk SNP would be associated with variation in dopamine receptor availability in the human brain.

Methods: Here, 72 healthy individuals genotyped for rs1344706 completed both [^{18}F]fallypride and [^{11}C]NNC-112 PET scans to measure $D_{2/3}$ and D_1 receptor availability, respectively. Genetic effects on estimates of binding potential (BP_{ND}) for each ligand were tested first with canonical subject-specific striatal regions-of-interest (ROIs) analyses, followed by exploratory whole-brain voxelwise analyses to test for more localized striatal signals and for extra-striatal effects.

Results: ROI analyses revealed significantly less $D_{2/3}$ receptor availability in risk allele homozygotes (TT) compared to non-risk allele carriers (G-carrier group: TG & GG) in the associative (AST) and sensorimotor striatum (SMST), but no significant differences in striatal D_1 receptor availability.

Conclusions: These data suggest that *ZNF804A* genotype may be meaningfully linked to dopaminergic function in the human brain. The results also may provide information to guide future studies of *ZNF804A*-related mechanisms of schizophrenia risk.

Corresponding Author: Karen F. Berman, MD, Clinical and Translational Neuroscience Branch, National Institute of Mental Health, NIH, 9000 Rockville Pike, Building 10, Rm 3C103A, Bethesda MD 20892-1365; Telephone: (301)496-7603; karen.berman@nih.gov.
*These authors contributed equally

Conflicts of Interest

The authors report no biomedical financial interests or potential conflicts of interest.

Keywords

imaging; PET; *ZNF804A* ; dopamine; genetics; schizophrenia

BACKGROUND

Accelerated by advances in genome-wide association (GWA) technology, studies of schizophrenia risk genes have yielded numerous candidates that may be involved in the etiology of this disabling disorder. However, the lack of consistent replication and unclear biological plausibility of most implicated markers have proven critical impediments to understanding the molecular underpinnings of schizophrenia susceptibility. The single nucleotide polymorphism (SNP) rs1344706 in the zinc finger protein 804A gene (*ZNF804A*) has been a statistically reliable candidate, not only showing GWAS-level significance in an early substantive study of psychosis (1), but also being notable as the first to repeatedly reach significance in subsequent independent GWA studies in at least nine European populations (for review see (2)) and three Asian samples (3–5). Indication of risk conferred by rs1344706 has also remained significant when subjected to meta-analyses (6), and in a recent large-scale pooled GWAS, a separate *ZNF804A* SNP in tight linkage disequilibrium with rs1344706 (r^2 = 0.838, D' = 0.963; (7)) reached genome-wide significance (8). Although some negative findings for rs1344706 have been reported in independent European samples (9, 10), most negative findings are in GWA studies (11–13) and meta-analyses (14, 15) of Asian populations. However, two recent meta-analyses of large Asian populations have reported trend-level (16) and marginal (17) associations of the SNP with schizophrenia.

Since its initial identification, rs1344706 has been the focus of several follow-up studies using diverse methods that have provided additional support for its role as a putative genetic risk factor for schizophrenia. For example, the risk allele has been associated with various phenotypes typically exhibited in patients. Specifically, functional MRI studies suggest that the risk allele is associated with reduced activation in the prefrontal cortex (PFC) and cingulate gyrus during working memory (18), theory of mind (19) and interference monitoring and suppression tasks (20), as well as reduced functional connectivity of the dorsolateral prefrontal cortex (DLPFC) (21–23) during a variety of behavioral probes. The risk allele has also been associated with deficits in executive function in healthy individuals, as measured by the attention network test (24) and the Trails A task (25), but has also been associated with preserved cognitive function in patients with schizophrenia (26, 27). Of note, some structural MRI studies have found that the risk allele (T) is associated with reduced cortical thickness and gray matter volume in frontal and temporal regions in both healthy adults (25, 28, 29) and patients with schizophrenia (29); however, a recent large study conducting whole-brain voxel-based morphometry did not corroborate these findings (30). There is also evidence that rs1344706 is relevant to clinical intervention. Specifically, the risk allele may be associated with worse clinical outcome (31) and poorer response to antipsychotic treatment, as measured by symptom severity, in patients with both chronic (32) and first-episode (33) schizophrenia.

Some molecular insights have been offered by investigations of post-mortem brain tissue from patients with schizophrenia, which exhibited elevated cortical ZNF804A levels compared to those observed in post-mortem tissue from controls without psychiatric illness (34). Among controls, the risk allele (T) was also associated with elevated cortical expression of the gene, which, along with bioinformatics analyses, suggests that this intronic SNP may regulate transcription (34). Recently, an important contribution to our understanding of how the ZNF804A protein affects brain function on the molecular level has been provided by Deans et al. (35), who showed that ZNF804A localizes to somatodentric compartments and plays an active role in regulation of synaptic structure and function.

As a potential bridge between these clinical and preclinical findings, increasing the expression of *ZNF804A* in rat cortical progenitor cells caused significant alterations in select dopamine-related genes, such as decreased expression of *DRD2*, which encodes the D_2 dopamine receptor, and increased expression of *COMT* (36), which has been implicated in modulating D_1 receptor expression (37). Furthermore, recent evidence suggests that the effect of *ZNF804A* on prefrontal gray matter volume may be dependent upon *COMT* genotype (38). Although *ZNF804A* likely regulates and interacts with a host of diverse genes (36, 39, 40), its impact on dopamine receptor-related genes is particularly of interest in light of well-studied striatal dopaminergic abnormalities in schizophrenia, including enhanced amphetamine-mediated decrements in striatal D_2 receptor availability and increased baseline striatal D_2 receptor availability, as well as the D_2 receptor targeting of antipsychotic medication (for review see (41)).

Notably, in addition to striatal findings, there is also evidence of dopamine-related abnormalities in limbic and cortical regions of patients with schizophrenia, including reduced $D_{2/3}$ receptor expression in the thalamus (42) and increased dopamine levels in the amygdala (43). Additionally, hippocampal D_2 receptors have been implicated in connections between the PFC and hippocampus (44) as well as in executive function and verbal fluency (45), both of which are disrupted in schizophrenia (46, 47). D_1 receptor-related abnormalities in cortex have also been implicated in the prefrontal dysfunction of schizophrenia (48–50). However, reports of D_1 receptor availability in the PFC of patients relative to controls have been inconsistent, reporting either no significant difference, reductions, or elevations (for review see (41)). Variability in these PET studies may be partially attributed to methodology, and it is important to note that those studies using [^{11}C]NNC-112, a well-validated radiotracer with greater D_1 receptor affinity than its predecessors (51), have generally found higher binding potential in the DLPFC of patients (52–54), with one exception (55).

Here, we studied a large group of healthy adult volunteers and tested for genetic association between *ZNF804A* rs1344706 and two positron emission tomography (PET) measures of dopamine function: $D_{2/3}$ receptor availability measured with [^{18}F]fallypride (56), and D_1 receptor availability measured with [^{11}C]NNC-112 (57). Our *a priori* regions of interest were striatal subregions, where dopamine receptors are most abundant and evidence for schizophrenia-related dopaminergic abnormalities is best established, but we additionally conducted an exploratory, voxelwise examination of the DLPFC, amygdala, hippocampus, and thalamus. We hypothesized that the risk allele would be associated with phenotypes

consistent with illness, specifically, increased $D_{2/3}$ receptor availability in the associative striatum.

METHODS

Participants

All participants were screened and studied at the National Institute Health's Clinical Center, and all provided written informed consent for protocols approved by the Combined Neuroscience Institutional Review Board and the National Institutes of Health Radiation Safety Committee. Participants completed clinician-acquired history and physical examination, a semi-structured clinical interview for psychiatric disorders (SCID) (58), and routine laboratory testing (including urine toxicology) to ensure they did not have a psychiatric illness, history of substance dependence, or exclusionary medical condition. Additionally, a structural MRI of the brain was performed and read by a neuroradiologist to confirm the absence of significant neurostructural abnormalities. Dominant hand information was determined using the Edinburgh Handedness Inventory. Statistical analysis of demographic information was performed in SPSS (SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.; http://www.spss.com.hk/statistics/).

ZNF804A rs1344706 Genotyping

Blood samples were acquired from each participant, and DNA was extracted using standard techniques. *ZNF804A* rs1344706 genotypes were determined by TaqMan 5' exonuclease assay (Applied Biosystems, Foster City, CA).

PET Acquisition

[^{18}F]fallypride and [^{11}C]NNC-112 scans were collected on a Siemen's ECAT HRRT scanner (Siemens Medical Solutions, Knoxville TN; 207 planes) on separate days. An eight-minute transmission scan was collected for each scan series and used for attenuation correction. Continuous optical head position tracking was performed throughout each scan session and was used for motion correction. For [^{18}F]fallypride scans, three dynamically binned emission scan series were collected over four hours immediately after intravenous tracer injection (5 mCi). For [^{11}C]NNC-112, a single series of dynamically binned emission frames was collected over a 90-minute period following injection (20 mCi).

ROI Delineation and PET Processing

A T1-weighted MRI scan for each subject was segmented in each participant's native anatomical space using Freesurfer (http://freesurfer.net), and striatal and cerebellar regions were examined and then manually corrected for errors with ITKsnap (59) by operators blinded to genotype status. Custom scripts enacted division of the striatum into five anatomical subregions: ventral striatum and pre- and post- commissural dorsal putamen and dorsal caudate. These subregions were then combined into previously described 'functional subregions': the associative striatum (AST), sensorimotor striatum (SMST), and ventral striatum (VST) (60). The AST consists of the pre-commissural dorsal regions and post-commissural caudate. The SMST consists only of the post-commissural putamen. The VST

includes the ventral putamen, ventral caudate, and nucleus accumbens. So too, cerebellar ROIs for each individual were further refined by custom scripts to exclude both the vermis and lateral/superior regions abutting the transverse venous sinuses. The MRI images along with the delineated ROIs were coregistered to the attenuation- and motion-corrected reconstructed PET data in each individual's native space, and time-activity curves for the ROIs and cerebellar reference region were extracted from each frame. The AST, SMST, and VST data formed the basis for our between-genotypes ROI analyses.

For *post hoc* voxelwise analyses, ANTS software (61) was used to apply the transform between an individual's coregistered MRI and the Montreal Neurological Institute (MNI) DARTEL template (62), generated from 240 healthy subjects, to the individual's corresponding coregistered PET image in order to warp the individual PET data into standard MNI-space. To improve signal-to-noise ratios, warped PET images were smoothed with an 8mm isotropic Gaussian kernel using SPM (Wellcome Department of Cognitive Neurology, University College London, London, UK; http://www.fil.ion.ucl.ac.uk/spm/).

Non-striatal masks for use in exploratory extra-striatal voxelwise analyses were generated by Freesurfer segmentation as above (amygdala, hippocampus and thalamus), or by delineation on the MNI template brain according to previously established boundaries (DLPFC) (63).

Estimation of Dopaminergic Parameters

We estimated the BP_{ND} associated with each ligand using two methods. Our primary method was ROI-based, while the post-hoc and exploratory analyses were conducted using voxel-based analyses. The same native-space cerebellar reference region time activity curves defined as above were used for both.

For the ROI approach, which was used for *a priori* striatal regions of interest, modeling was performed independently for each bilateral ROI in PMOD (www.pmod.com) using the cerebellar reference region and the simplified reference tissue model (SRTM) to estimate the non-displaceable binding potential (BP_{ND}) for the [^{18}F]fallypride and [^{11}C]NNC-112 scans (64). For the VST and AST values, a mean of the modeled value (i.e., BP_{ND}) for the component regions, weighted by their volume, was used.

For the voxel-based methods, used for post hoc striatal and exploratory analyses, BP_{ND} for each voxel was calculated in PMOD on the warped PET images, using SRTM and the native space cerebellar time activity curve for the reference region input function.

Statistical Tests

Consistent with much of the previously published *ZNF804A* literature (24, 25, 28, 65, 66), we first examined effect of genotype by comparing risk-allele homozygotes (TT) to all non-risk allele-carrying participants (GG and TG) together. In order to elucidate a more complete understanding of the effect of the risk-allele on the physiologic parameters measured, we further investigated significant striatal findings from the 2-group analysis by subsequently comparing all three individual genotype groups to each other, as some other groups investigating *ZNF804A* have done (24, 25, 66).

We performed multivariate analyses of ROI data in SPSS, with genotype group (G-carriers or TT homozygotes) and sex as fixed factors and age as a covariate, to determine if rs1344706 genotype was associated with our dopaminergic measurements in the functional subregions of the striatum. Significant genotype effects identified in the multivariate analyses were further explored with univariate tests, Bonferroni-corrected for the three striatal regions, to determine which subregion(s) contributed to the overall effect. Finally, to determine the direction of the effects and the relationship between the three individual genotypes, we conducted *post hoc* pairwise comparisons, controlling for age and sex, and visualized these results by generating bar graphs using Stata (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP).

Similarly, for voxelwise t-tests used to further localize significant effects across the two groups, we used a general linear model in SPM5 (TT vs. GG & TG, combined). As in our ROI analysis, we used genotype and sex as fixed factors and age as a covariate. Given *a priori* interest in the striatum, we applied a small-volume-correction (SVC) to striatal findings for t-tests conducted, with a significance threshold of False Discovery Rate (FDR) $q < 0.05$. We also reported any difference between non-risk carriers and risk-allele homozygotes in our exploratory non-striatal regions (DLPFC, amygdala, hippocampus and thalamus) that met a significance of $p < 0.005$, uncorrected, with a minimum cluster size of 10 voxels.

RESULTS

Demographics and Genotyping

A total of 72 participants (average age: 38.54± 11.16 years, range 18–59 years; 30 women) were studied with both [^{18}F]fallypride, and [^{11}C]NNC-112. *ZNF804A* rs1344706 genotype frequencies (GG=12, TG=32, TT=28) were in Hardy-Weinberg Equilibrium ($\chi^2 = 0.30$, p=0.582). There were no significant differences across the two groups (G-carriers and TT homozygotes) or three groups (GG, TG, and TT) in age, gender, handedness, or administered tracer dose, mass or specific activity (Table 1).

[^{18}F]fallypride

Multivariate analysis comparing risk-allele homozygotes (TT) to non-risk allele carriers (TG and GG, combined) revealed a significant effect of *ZNF804A* rs1344706 genotype on striatal [^{18}F]fallypride BP_{ND} (Pillai's Trace = 0.171, F(3, 65) = 4.483, p=0.006). Subsequent univariate tests indicated that the effect of genotype on [^{18}F]fallypride BP_{ND} was attributable to the AST (F(1, 67)=10.85, p=0.006, corrected) and, to a lesser extent, the SMST (F(1, 67)=5.12 p=0.081, corrected), such that risk allele homozygotes showed significantly lower BP_{ND} that non-risk carriers (Figure 1a). Voxelwise analysis localized this effect most strongly to clusters in the AST (voxelwise false discovery rate (FDR) $q < 0.05$, small-volume correction for the striatum). Additionally, exploratory examination of extrastriatal regions indicated that non-risk allele carriers showed trends toward greater [^{18}F]fallypride BP_{ND} than risk-allele homozygotes in the left hippocampus and left thalamus (Table 2, Figure 2a). There were no regions in which risk-allele homozygotes had higher [^{18}F]fallypride BP_{ND} than non-risk carriers.

[^{11}C]NNC-112

In the striatum, there were no significant ROI multivariate or voxelwise associations between genotype and [^{11}C]NNC-112 BP_{ND} (Figure 1b). Voxelwise evaluation of extrastriatal regions showed a trend for risk-homozygotes to have higher BP_{ND} than non-risk carriers in the left amygdala and in the DLPFC bilaterally (Table 2, Figure 2b). There were no voxels within these regions in which non-risk carriers had higher BP_{ND} values.

DISCUSSION

The GWAS-supported schizophrenia risk SNP, *ZNF804A* rs1344706, or related variants in close linkage disequilibrium, appears to be associated with dopamine regulation in healthy individuals. Both ROI and voxelwise analyses support the notion that the risk allele (T) is linked with significantly lower levels of $D_{2/3}$ receptor availability in a dose-dependent fashion. Interestingly, these findings are in the opposite direction of the expected schizophrenia phenotype, i.e., higher striatal availability of $D_{2/3}$ receptors (for review see (41)). Our data are, however, consistent with preclinical and postmortem investigations suggesting that, in healthy controls, the risk allele is associated with increased expression of the ZNF804A protein (34), which in turn would decrease expression of *DRD2* (36). Mirroring the lack of consistent striatal D_1 receptor findings in schizophrenia case-control studies, there were no significant *ZNF804A* genotype effects on striatal D_1 receptor availability. These data suggest that *ZNF804A* is not simply associated with a generalized effect on striatal dopamine receptors, but, rather, with a $D_{2/3}$ subtype-specific effect.

The aforementioned preclinical and postmortem data align well with the possibility that these findings are attributable to overall protein levels. However, it is also conceivable that endogenous dopamine levels may play a role in our study results. While [^{11}C]NNC112 has not shown increased binding after dopamine depletion (67), suggesting that baseline scanning with this tracer is unlikely affected by endogenous dopamine levels, data are mixed for [^{18}F]fallypride binding, which has been found to increase following dopamine depletion in one study (68), although not in others (69, 70). If endogenous dopamine receptor occupancy is a meaningful component of baseline BP_{ND} for [^{18}F]fallypride, but not [^{11}C]NNC-112, one might speculate that the selective reduction in $D_{2/3}$ receptor availability associated with the risk-allele (T) may reflect a genetic predisposition to elevated synaptic dopamine, leading to competition for $D_{2/3}$, but not D_1, radioligand binding sites. This interpretation would also converge with findings of elevated dopamine function in the associative striatum of patients with schizophrenia (for review see (60)). However, additional work directly exploring the relationship between the *ZNF804A* SNP and endogenous dopamine in healthy individuals and patients with schizophrenia is necessary to support this interpretation.

Frontotemporal circuit dysfunction has been proposed as a critical neurobiological deficit in schizophrenia (71–73), and the risk allele has previously been associated with altered hippocampal-PFC connectivity in healthy individuals (22, 23). Along with prior work showing that reduced D_2 receptor availability in the hippocampus may predict variations in frontal lobe functioning (44, 45), our discovery of less hippocampal $D_{2/3}$ availability, in possible concert with greater PFC D_1 availability, in risk allele carriers provides one

potential mechanism for how *ZNF804A* could be important for frontotemporal circuit functioning and cognition. Additionally, exploration of extrastriatal regions in our voxelwise analysis linked risk allele homozygotes (TT) with lower $D_{2/3}$ receptor availability in the thalamus, a preliminary finding that aligns with reduced thalamic $D_{2/3}$ availability previously reported in patients with schizophrenia, but requires further investigation.

Our findings should be interpreted with consideration of several limitations. First, the [^{18}F]fallypride ligand is not purely specific for D_2 receptors, and, thus, we cannot disentangle the effects of binding potential specifically associated with D_2 receptors from those associated with D_3 receptors. Second, as discussed above, our exploratory voxel-wise analyses employed a relatively liberal threshold; thus, any uncorrected voxelwise findings should be considered preliminary and require replication. Third, because data clarifying the effect size of the *ZNF804A* genotype on dopaminergic measures in humans are not available, it is possible that this study, although large for PET investigations, was not sufficiently powered, and findings may not be comprehensive. Additionally, although all subjects were of reported European ancestry, the results are not immune from stratification effects. Further work is needed to understand how these findings extend to other populations. Also, we cannot rule out the possibility that noise in BP_{ND} estimates obscured a true difference in our D_1 analyses. Replication studies, including those using arterial sampling to permit two-tissue compartmental modeling in addition to simplified reference tissue modeling (51), could enhance confidence in our negative findings. Finally, our study only examines healthy individuals, and, given some evidence for disparate effects of this genotype within groups of patients with schizophrenia, a study in patients with schizophrenia is necessary to fully elucidate the nature of the association between *ZNF804A* and illness-relevant dopaminergic phenotypes.

Despite these limitations, the present investigation is the first to directly assess the relationship between *ZNF804A* and *in vivo* dopamine receptor availability. By evaluating both $D_{2/3}$ and D_1 receptor availability, we provide a more extensive evaluation of how variation in *ZNF804A* genotype may affect dopaminergic phenotypes than previously reported. Conceivably, these rs1344706-associated variations in dopamine receptor availability may be a downstream consequence of ZNF804A-mediated disruptions in synaptic structure and function. Although our findings cannot directly address the role of *ZNF804A* in the risk for schizophrenia, they do provide support for further investigation of the potential dopaminergic-related mechanisms underlying this gene's clinical associations.

In conclusion, our results suggest that *ZNF804A* rs1344706 is associated with dopamine receptor availability in the associative striatum of healthy controls. Specifically, risk allele homozygotes (TT) exhibited lower $D_{2/3}$ availability compared to non-risk allele carriers. Future studies based upon this evidence may enable the identification of new mechanisms through which *ZNF804A* affects the dopamine system, and possibly, risk for schizophrenia.

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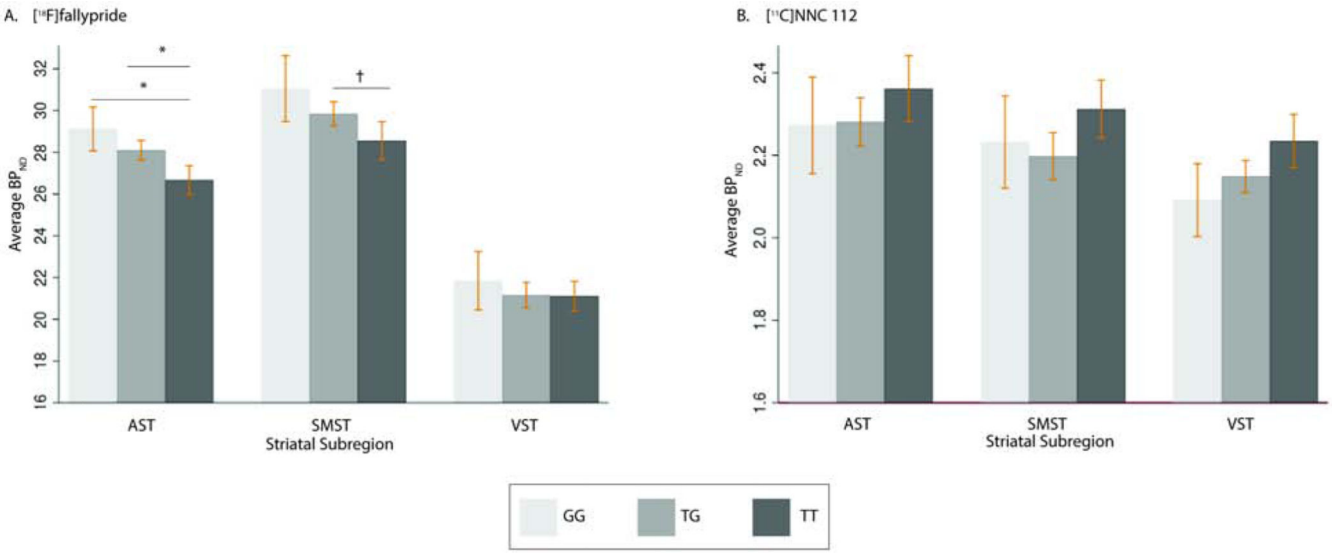

Figure 1.

ROI Average Striatal Values

Average values by individual genotype (T = risk allele) obtained from ROI analyses for A) [^{18}F]fallypride and B) [^{11}C]NNC-112 data. Significant results from post-hoc, pairwise t-tests are indicated as follows: * $p < 0.05$, † $p < 0.10$. Abbreviations : AST = Associative Striatum, SMST = Sensorimotor Striatum, VST = Ventral Striatum, BP_{ND} = Binding Potential.

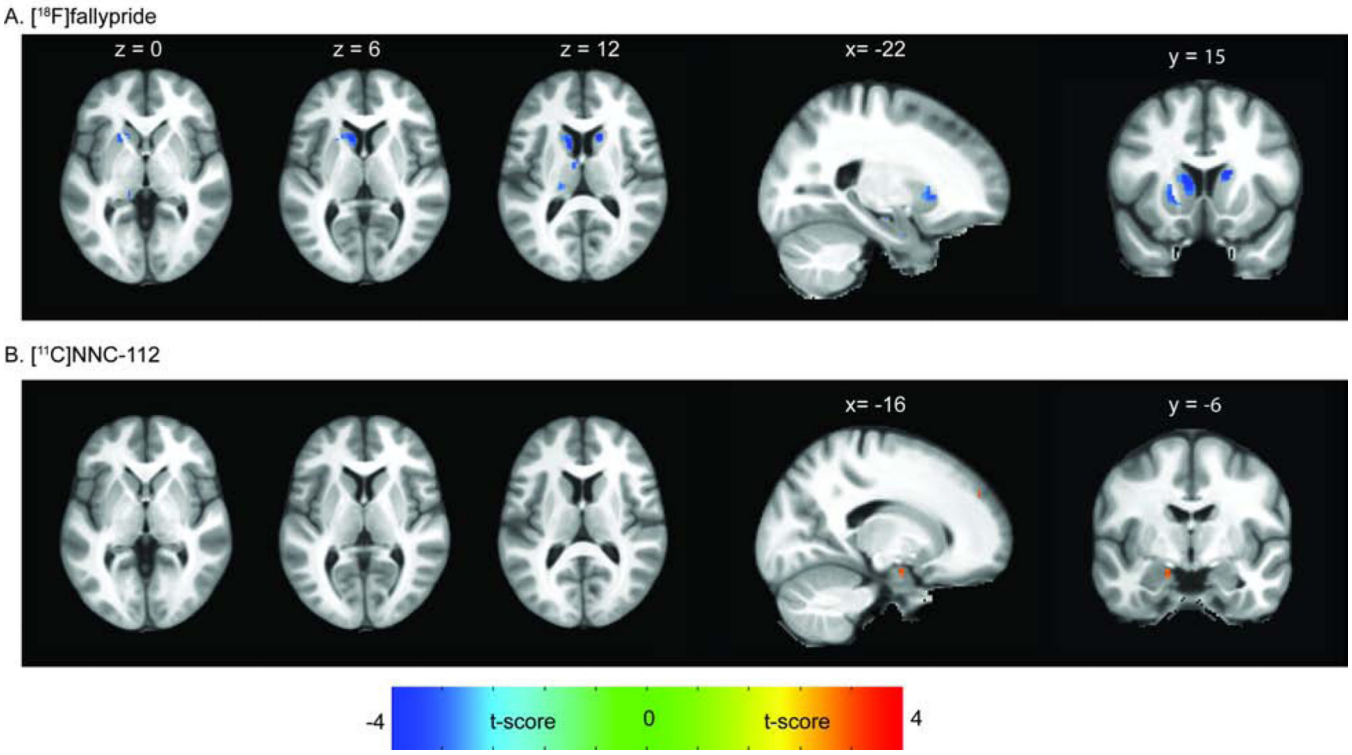

Figure 2.

Voxelwise Between-Group Results

Axial slices showing the contrast of risk-allele homozygotes (TT) minus non-risk allele carrier group (GG & TG, combined) for A) [^{18}F]fallypride Binding Potential (BP_{ND}) and B) [^{11}C]NNC-112 BP_{ND}. Negative t-score values (blue) indicate regions in which risk-allele homozygotes exhibited lower values than non-risk carriers. Color bar applies to all images, which are masked with striatal and extrastriatal regions of interest, and shown at a threshold of $p < 0.005$, uncorrected, for display purposes (Left = Left).

Table 1.

Demographic Information

	GG (n=12)	TG (n=32)	TT (n=28)	Statistics
Female (%)	8 (67%)	11 (34%)	11(39%)	χ^2 (2)=3.85, p=0.146
Age (yrs. ± SD)[1]	37.01±10.73	40.82±10.83	36.58±11.62	F(2,69)=1.22, p=0.31
Edinburgh Handedness[2]	93.64±12.06	74.62±50.38	77.86±44.59	F(2,62)=0.755, p=0.474
[^{18}F]fallypride ($D_{2/3}$)				
Dose (mCi)	5.13±0.09	5.09±0.16	5.06±0.29	F(2,69)=0.53, p=0.591
Mass (μg)	0.68±0.15	0.72±0.32	0.80±0.33	F(2,69)=0.88, p=0.421
Specific Activity (mCi/mmol)	2905±678	3088±1584	2721±1245	F(2,69)=0.55, p=0.577
[^{11}C]NNC 112 (D_1)				
Dose (mCi)	19.18±1.34	19.59±0.39	19.61±0.31	F(2,69)=2.26, p=0.112
Mass (μg)	2.16±1.60	2.39±1.51	2.32±1.33	F(2,69)=0.11, p=0.894
Specific Activity (mCi/mmol)	47125±3528	3844±2149	3691±1373	F(2,69)=0.96, p=0.399

Abbreviations: yrs=years, SD=standard deviation.

[1]Age for each individual was calculate as the average of ages at [^{18} F]Fallypride and [^{11} C]NNC-112 scans.

[2]Handedness was not available for eight individuals.

Table 2.

Whole Brain Voxelwise Analysis: Effect of *ZNF804A* Genotype on Receptor Parameters

Modality	Con	Neuroanatomy			MNI Coordinates			Statistics		
		Brain Region	Hem	k	x	y	z	Z	p[a]	q[b]
[^{18}F]fallypride ($D_{2/3}$)	G > TT	AST	R	294	15	15	12	4.15	4.87×10^{-5}	0.014
		AST	L	1803	−10	14	8	3.75	8.83×10^{-5}	0.014
		Thalamus	L	46	−15	−33	−2	3.5	4.21×10^{-4}	
		Hippocampus	L	42	−22	−20	−16	3.52	2.91×10^{-4}	
[^{11}C]NNC-112 (D_1)	TT > G	Amygdala	L	35	−16	−6	−26	3.27	0.001	
		DLPFC	L	14	−16	51	33	3.16	0.001	
		DLPFC	R	24	46	27	40	3.14	0.001	

Whole-brain voxelwise results comparing risk-allele homozygotes (TT) to non-risk carriers (G = GG & TG, combined). A small volume correction was applied for *a priori* striatal regions, which were thresholded at $q < 0.05$. A threshold of $p < 0.005$, uncorrected, with a minimum cluster size of 10 voxels was given to exploratory non-striatal regions. Abbreviations: Hem = hemisphere, k = cluster size (voxels), MNI = Montreal Neurological Institute, SVC = small volume correction, AST = associative Striatum, DLPFC = dorsolateral prefrontal cortex, SMST = Sensorimotor Striatum, L = Left, R = Right.

[a] Uncorrected peak voxel p-value

[b] False Discovery Rate (FDR) significance after small volume correction for striatum.