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Interaction Between Effects of Genes Coding for Dopamine and Glutamate Transmission on Striatal and Parahippocampal Function

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Abstract: The genes for the dopamine transporter (DAT) and the D-Amino acid oxidase activator (DAOA or G72) have been independently implicated in the risk for schizophrenia and in bipolar disorder and/or their related intermediate phenotypes. DAT and G72 respectively modulate central dopamine and glutamate transmission, the two systems most robustly implicated in these disorders. Contemporary studies have demonstrated that elevated dopamine function is associated with glutamatergic dysfunction in psychotic disorders. Using functional magnetic resonance imaging we examined whether there was an interaction between the effects of genes that influence dopamine and glutamate transmission (DAT and G72) on regional brain activation during verbal fluency, which is known to be abnormal in psychosis, in 80 healthy volunteers. Significant interactions between the effects of G72 and DAT polymorphisms on activation were evident in the striatum, parahippocampal gyrus, and supramarginal/angular gyri bilaterally, the right insula, in the right pre-/postcentral and the left posterior

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cingulate/retrosplenial gyri ($P < 0.05$, FDR-corrected across the whole brain). This provides evidence that interactions between the dopamine and the glutamate system, thought to be altered in psychosis, have an impact in executive processing which can be modulated by common genetic variation. *Hum Brain Mapp 34:2244–2258, 2013.*

Key words: schizophrenia; psychosis, DAOA/G72; DAT; epistasis; imaging genetics; verbal fluency

INTRODUCTION

The dopamine hypothesis of schizophrenia proposes that dysfunction of central dopamine transmission is fundamental to the pathophysiology of the disorder [Tost et al., 2010]. Dopamine receptor agonists can induce positive psychotic symptoms in healthy individuals, and dopamine receptor antagonists reduce the severity of positive psychotic symptoms [Janowsky and Risch, 1979; Seeman and Lee, 1975]. Furthermore, schizophrenia is associated with an increase in dopamine synthesis capacity and dopamine release in the striatum [Abi-Dargham et al., 2009; McGowan et al., 2004]. Nevertheless, it is unclear whether dopamine dysfunction alone underlies all features of schizophrenia, and there is an independent body of research that implicates the glutamate system [Stone et al., 2007]. Glutamate receptor antagonists are shown to provoke psychotic symptoms and cognitive impairments in healthy subjects [Krystal et al., 2005; Stone and Pilowsky, 2006], and its agonists to have therapeutic potential in psychotic disorders [Patil et al., 2007]. Also, NMDA-receptor modulators may reduce negative, positive and cognitive symptoms in schizophrenia [Heresco-Levy, 2005].

Psychosis may thus involve changes in both dopaminergic and glutamatergic function, and contemporary models propose that it results from an interaction between these two systems [Carlsson and Carlsson, 1990; Lisman et al., 2008; Olney and Farber, 1995]. Specifically, it is thought that elevated dopamine activity in the striatum may be driven by glutamatergic inputs from a dysfunctional medial temporal cortex [Lisman et al., 2008]. In line with this, animal models [Lodge and Grace, 2006, 2008, 2009] and human neuroimaging studies [Stone et al., 2010] point to an altered relationship between medial temporal glutamate levels and striatal dopamine function in psychosis [Stone et al., 2010]. The posterior cingulate [Aalto et al., 2005; Olney and Farber, 1995; Olney et al., 1989] and the prefrontal cortex [Castner and Williams, 2007; Nixon et al., 2011; Rios Valentim et al., 2009; Yang and Chen, 2005] also seem to be critical sites where dopamine-glutamate interactions underlie the development of psychosis.

In the striatum, a pivotal site of dopaminergic-glutamatergic interactions and of especial interest to the aetiology of psychosis, the amplitude of phasic dopamine release is modulated by the tonic dopamine level, which in turn is regulated by a cortical and medial temporal (i.e. amygdala and hippocampus) afferent feedback [Chesselet, 1990; Grace, 1991]. While phasic stimulation of postsynaptic receptors is terminated by immediate uptake by presynaptic transporters [Grace, 1991], such as the dopamine transporter (DAT), tonic stimulation is regulated by afferent cortical glutamatergic presynaptic stimulation [Grace, 1991] which the D-Amino acid oxidase activator (DAOA, G72) modulates. Reciprocally, through cortico-striato-thalamic-cortical loops [Newman and Grace, 1999], striatal DAT can also regulate cortical and medial temporal function whereby the dopamine released in the basal ganglia modulates a network of (G72-regulated) glutamatergic pathways that connect several areas in the brain [Alm, 2004; Tisch et al., 2004].

The presynaptic dopamine transporter regulates dopamine availability in the dopaminergic synapse by uptaking dopamine from the synaptic cleft [Masson et al., 1999]. The DAT gene is highly expressed in the striatum, substantia nigra, and ventral tegmentum [Lewis et al., 2001], and in the posterior cingulate, motor, and insular cortices [Lewis et al., 2001; Wang et al., 1995], exclusively in dopaminergic neurons [Lorang et al., 1994]. Its expression is lower in prefrontal, anterior cingulate and occipital cortices [Lewis et al., 2001; Wang et al., 1995], where catechol O-methyltransferase (COMT) plays a relatively greater role in dopamine regulation. Dopamine inactivation is crucial for determining neuronal signal-to-noise ratios during cognitive task performance [Bertolino et al., 2008; Caldu et al., 2007; Prata et al., 2009b; Yacubian et al., 2007]. Although these findings would point to DAT being a susceptibility gene for schizophrenia, the evidence from genetic association studies is not supportive of that [Gamma et al., 2005]. Nevertheless, it may mediate or moderate the cognitive impairments present in the disorder. The DAT gene displays a polymorphic 40-base pair variable number of tandem repeats (VNTR) in the 3′ untranslated region (DAT 3′UTR VNTR), which yields common, 9- and 10-repeat alleles [Vandenbergh et al., 1992]. The 10-repeat allele has been associated with increased gene expression compared with the 9-repeat allele [Fuke et al., 2001; Heinz et al., 2000; Mill et al., 2002; VanNess et al., 2005], although not in all studies [Martinez et al., 2001; van Dyck et al., 2005]. The 9-repeat allele has been associated with over-activation (i.e., putatively less efficient) in the frontal cortex during working memory [Bertolino et al., 2006], verbal fluency as a trend [Prata et al., 2009c] and reward delivery [Dreher et al., 2009] and in the ventral striatum [Dreher et al., 2009; Forbes et al., 2009] and caudate nucleus [Dreher et al., 2009] during a reward task. In addition, the 10-repeat allele has been associated with heightened activation in the

caudate nucleus and insula during verbal fluency [Prata et al., 2009c]. Further studies have shown epistatic (i.e. gene-gene) interactions between COMT and DAT during cognitive tasks [Bertolino et al., 2008; Caldu et al., 2007; Prata et al., 2009b; Yacubian et al., 2007].

G72 regulates glutamatergic transmission, by activating D-amino acid oxidase (DAAO), which modulates the metabolism of D-amino acids like D-serine, a coagonist for the NMDA glutamate receptor [Boks et al., 2007]. The G72 gene has been consistently implicated in the susceptibility to psychotic disorders [Chumakov et al., 2002; Detera-Wadleigh and McMahon, 2006; Kvajo et al., 2008; Shinkai et al., 2007]. It is highly expressed in the striatum, medial temporal lobe, and dorsolateral prefrontal cortex [Chumakov et al., 2002; Korostishevsky et al., 2004], areas which show abnormal function in schizophrenia [Boks et al., 2007]. Schizophrenia patients also show increased G72 expression in the dorsolateral prefrontal cortex compared to healthy controls [Korostishevsky et al., 2004]. G72 variations have shown effects both on task performance [Jansen et al., 2009; Opgen-Rhein et al., 2008] and activation of the hippocampus, parahippocampus, parietal cortex and right middle temporal gyrus [Goldberg et al., 2006; Hall et al., 2008; Jansen et al., 2009; Krug et al., 2010]. In particular, the rs746187 single nucleotide polymorphism (SNP) in the G72 gene has been associated with both schizophrenia and bipolar disorder [Chumakov et al., 2002; Shinkai et al., 2007], and we have recently found that the risk allele (G) is associated with over-activation (i.e., putatively less efficient) in the left postcentral and supramarginal gyri during verbal fluency [Prata et al., 2012].

The aim of this study was to examine for the first time an epistasis (i.e., gene–gene interaction) between DAT and G72 on human brain function, on the basis that striatal dopaminergic activity (which DAT regulates) modulates and is modulated by cortical and medial temporal glutamatergic activity (which G72 regulates). These pathways, genes and brain regions have been implicated in psychosis. We used functional Magnetic Resonance Imaging (fMRI) to assess genotype effects on regional activation during a verbal fluency task in 80 healthy volunteers because both performance and activation during this executive task is abnormal in psychotic disorders [Allen et al., 1993; Artiges et al., 2000; Frith et al., 1995; Fu et al., 2005; Howanitz et al., 2000] and it taps to both subcortical and cortical areas widely implicated in the dopaminergic and glutamatergic systems and in these disorders [Curtis et al., 1998; Fu et al., 2002; Hutchinson et al., 1999; Lurito et al., 2000; Schlosser et al., 1998; Yetkin et al., 1995; Yurgelun-Todd et al., 1996]. We investigated the whole brain, while expecting that interactions would be particularly evident in the areas most robustly implicated in verbal fluency and psychosis, such as the striatum, hippocampus and fronto-temporal cortex. More specifically, we predicted we would detect areas where dopamine–glutamate interactions have been associated with psychosis on human neuroimaging and animal studies [Aalto et al., 2005; Carlsson and Carlsson 1990; Lisman et al., 2008; Rabiner 2007; Rios Valentim et al., 2009], such as the striatum [Lodge and Grace, 2006, 2008, 2009; Stone et al., 2010], the medial temporal [Lodge and Grace, 2006, 2008, 2009; Stone et al., 2010], the posterior cingulated [Aalto et al., 2005; Olney and Farber 1995; Olney et al., 1989] and the prefrontal cortex [Castner and Williams 2007; Nixon et al., 2011; Rios Valentim et al., 2009; Yang and Chen, 2005]. Furthermore, also using an imaging genetics design, Nixon et al. [2011] have recently detected a functional gene-gene interaction between G72 and COMT in the dorsolateral prefrontal cortex.

MATERIALS AND METHODS

A maximum of 50% of the subjects examined in the present investigation have been included in seven previous studies that investigated the impact of other candidate genes [Mechelli et al., 2008; Papagni et al., 2011; Prata et al., 2008, 2009a,b,c, 2012] and in 3 previous studies that investigated brain dysfunction in psychosis [Costafreda et al., 2009, 2011; Fu et al., 2005].

Participants

A total of 80 healthy volunteers participated. All were native-English speakers and gave written informed consent in accordance to protocols approved by the Local or Multi Centre Research Ethics Committee. Subjects were recruited through local media advertisement and had no history of mental illness and no first-degree relatives with a psychiatric disorder, as assessed using the FIGS (Family Interview for Genetic Studies). Exclusion criteria were history of head injury with loss of consciousness of more than one minute; and a substance misuse or dependence disorder (as defined by DSM-IV) within the last six months. All subjects were genotyped for the SNP rs746187 in *G72* and for the VNTR in the 3′UTR of *DAT*. The subjects comprised the following groups: there were 34 A G72 homozygotes (of which were 14 9-repeat carriers and 20 10-repeat homozygotes for the DAT 3′UTR VNTR), 31 G72 heterozygotes (13 9-repeat carriers, 18 10-repeat homozygotes for the DAT 3′UTR VNTR) and 15 G G72 homozygotes (11 9-repeat carriers, 4 10-repeat homozygotes for the DAT 3′UTR VNTR).

Demographics

Demographic and performance data according to genotypes are summarized in Table I. Chi-square/Fisher's tests (for categorical variables) and ANOVA (for continuous variables) were used to describe group differences and their interactions. Statistical test were performed using SPSS (Statistical Package for Social Sciences—version 17.0). There were no significant differences between genotypic groups on any demographic variable except for age ($F =$

TABLE I. Demographics and performance according to genotype subgroups

		Main effect of DAT		Main effect of G72		
	Whole sample ($n = 80$)	9-repeat carriers ($n = 38$)	10/10-repeat homozygotes ($n = 42$)	G72 A/A ($n = 34$)	G72 A/G ($n = 31$)	G72 G/G ($n = 15$)
Age, mean (SD)	38.22 (12.86)	43.14 (13.85)	34.68 (10.64)[a]	36.13 (12.57)	41.53 (13.16)	38.85 (12.97)
IQ [z-scores (SD)][b]	0.01 (0.94)	0.18 (0.93)	−0.15 (0.98)	−0.11 (0.98)	−0.01 (0.98)	0.32 (0.89)
IQ, mean (SD)[c]	115.69 (11.24)	117.39 (10.54)	114.08 (11.78)	113.84 (11.95)	115.71 (11.78)	119.86 (7.34)
Years of education; mean (SD)	15.16 (2.82)	14.89 (2.61)	15.42 (3.02)	15.55 (2.68)	14.50 (2.90)	15.77 (2.71)
Handedness (R/L/M)	74/5/1	35/2/1	39/3/0	33/1/0	29/2/0	12/2/1
Gender (M/F)	36/44	15/23	21/21	15/19	12/19	9/6
Ethnicity (Caucasian/black-Caribbean/ black-African/mixed)	78/0/1/1	37/0/1/0	41/0/0/1	33/0/0/1	31/0/0/0	14/0/1/0
VF easy errors, mean (SD)	3.47 (3.63)	3.37 (3.65)	3.57 (3.65)	3.24 (2.96)	4.52 (4.68)	1.87 (1.25)
VF hard errors, mean (SD)	6.11 (4.73)	6.26 (5.04)	5.98 (4.49)	5.59 (3.61)	6.77 (6.21)	5.93 (3.37)

SD, standard deviation; R, right; L, left; M, male; F, female; VF, verbal fluency.
[a]Significant differences (at $P < 0.05$) in demographic features: $F = 9.713$, $P = 0.003$.
[b]IQ was assessed using the WAIS-III (Wechsler Adult Intelligence Scale-III) [Wechsler, 1997], WAIS-R (Wechsler Adult Intelligence Scale-Revised) [Wechsler, 1981], the WASI-FSIQ-4 (Wechsler Abbreviated Scale of Intelligence—Full Scale IQ) [Wechsler, 1999] or the Quick Test [Ammons et al., 1962]. The proportion of subjects assessed with each tool was matched between genotype groups and ANOVA was performed with standardized scores (z-score) based on the mean and standard deviation of the controls group for each tool.
[c]Mean and standard deviation of nonstandardized IQ data shown for easier interpretation.

9.713; $P = 0.003$). No demographic variables showed a significant genotype x genotype interaction.

Genotyping

Genomic DNA was extracted from blood or cheek swabs using standard methods [Freeman et al., 2003]. Genotyping of G72 rs746187 SNP (a.k.a G72's M-7) [Shinkai et al., 2007] and the DAT 3′UTR VNTR was performed blind to status under contract by KBioscience (Herts, UK; http://www.kbioscience.co.uk/) using a competitive allele specific PCR system (CASP). The following primers for the amplification of the G72 rs746187 polymorphism were used: A-primer 5′GAAGGTGACCAAGTTCATGCTAAGG AGTGGCAGTCAACCGACT3′; G-Primer: 5′GAAGGTCGG AGTCAACGGATTGGAGTGGCAGTCAACCGACC3′ and common primer: 5′AGTGTGAGGCATGTATTGAGAATGT TCAA3′. Quality control procedures included negative control (water) wells and duplicate wells. G72 genotyping frequencies did not significantly deviate from Hardy-Weinberg equilibrium ($X^2 = 2.55$, $P = 0.11$).

Amplification of the DAT 3′UTR VNTR region was performed using the forward primer 5′TGGCACGCACCTG AGAG3′ and the reverse primer 5′GGCATTGGAGGA TGGGG3′. Its products were then separated under UV light after electrophoresis on a 3.5% agarose gel containing ethidium bromide. DAT 3′UTR VNTR genotype frequencies did not significantly deviate from Hardy-Weinberg equilibrium ($X^2 = 0.20$, $P = 0.66$). Genotypes carrying alleles other than the 9-repeat and the 10-repeat allele for the DAT 3′ UTR VNTR were not included in the 80-subject sample that was further analyzed, to reduce allelic heterogeneity.

Verbal Fluency Task and Image Acquisition

The task and image acquisition was performed as described earlier [Fu et al., 2002, 2005], see SI for further details. Briefly, during a "generation condition", subjects were visually presented with a series of letters and required to overtly articulate a word that started with that letter. This condition was contrasted with a "repetition condition", in which subjects were presented with the word "REST" and were required to read it out loud. Task difficulty was manipulated by presenting separate sets of "easy" and "hard" letters. Verbal responses were recorded allowing the identification of "incorrect" trials, in which the subject did not generate any response or generated repetitions, derivates, or grammatical variations of a previous word.

Behavioral Data Analysis

The effect of task load and of genotypes and their interaction on the level of accuracy of verbal responses (measured by the number of incorrect responses during scanning) were assessed using a multivariate $3 \times 2 \times 2$ ANOVA, with both genotypes as between-subjects factors and task load as a within-subject factor. The effect of task difficulty was assessed using a paired t-test.

Image Analysis

Analysis was performed using SPM5 software (http://www.fil.ion.ucl.ac.uk/spm) [Friston, 2003], running under Matlab 7.6 (Mathworks, Sherbon, MA). To minimize movement-related artifacts, all volumes from each subject were realigned and unwarped, using the first as reference resliced with sinc interpolation. After normalization to a standard MNI-305 template, the volumes were spatially smoothed with an 8-mm full width at half maximum isotropic Gaussian kernel.

First, the statistical analysis of regional responses was performed in a subject-specific fashion by convolving each onset time with a synthetic hemodynamic response function (HRF). To minimize performance confounds, we modeled correct and incorrect trials separately using an event-related model, yielding four experimental conditions: (i) easy generation, (ii) hard generation, (iii) repetition, and (iv) incorrect responses. The latter was excluded from the group analysis to control for effects of group differences in task performance. Correct responses among the generation events (35 events in the hard and 35 in the easy version) were contrasted with 70 repetition events. To remove low-frequency drifts, data were high-pass filtered using a set of discrete cosine basis functions with a cut-off period of 128 s. Parameter estimates were calculated for all brain voxels using the general linear model, and contrast images for "easy generation > repetition" and "hard generation > repetition" were computed in a subject-specific fashion.

Second, to permit inferences at the population level [Friston, 2003], the subject-specific contrast images were entered into a full-factorial ANOVA. We avoided using a $3 \times 2 \times 2$ ANOVA with G72 genotype and DAT genotype as factors, as this would have resulted in one cell containing only four subjects. Instead, we used an ANCOVA model in which G72 genotype (AA, AG, GG) was modeled as a between-subject factor, task load (easy, hard) as a within-subject factor to minimize error variance, and DAT genotype (9-repeat carriers, 10-repeat homozygotes) was modeled as an interactive covariate. Modelling DAT genotype as an interactive covariate involved entering 6 regressors made of -1 (for individuals who were 9-repeat carriers) and 1 (for 10-repeat homozygotes), one for each of the 6 experimental groups resulting from modeling task version and G72 genotype as factors. This statistical model, which has previously been used to examine three-way interactions [Prata et al., 2009b], allowed us to test for the main effect of the task, the main effects of G72 and DAT genotypes, and any nonadditive interactions between the two genes. Estimation of the model included correction for nonsphericity to account for possible unequal variance between experimental groups [Kiebel et al., 2003].

We used a standard threshold of $P < 0.05$ after voxel-wise false discovery rate (FDR) correction for multiple comparisons across the whole brain with a cluster size greater than 10 voxels. To assess how much of the interindividual variance in activation was explained by the genetic variation, we calculated the η_p^2 and η^2 measure of effect size (η^2 Between-Groups Sum of Squares/Total Sum of Squares) [Pierce et al., 2004] after extracting the subjects' beta-measure at the voxel of peak activation from SPM5 into an ANOVA in SPSS v17. Because age was significantly different between the genotype groups, we included age as a covariate of no interest in our analyses and also performed a whole-brain regression analysis with age as a covariate.

RESULTS

Behavioral Data

As expected, there was a significant main effect of task demand on the number of incorrect responses ($T = -6.037$; $P < 0.0001$). However, neither the main effect of genotype, or the genotype by task load interaction on task performance were significant. Finally, there was no significant interaction between the effects of G72 and DAT on number of incorrect responses (at $P < 0.05$).

fMRI Data

Main effect of task

Word generation relative to repetition (irrespective of task difficulty or genotype) was associated with activation in a distributed network that included, bilaterally, the inferior frontal and cingulate gyri, the striatum and thalamus, as well the left middle frontal, superior temporal and supramarginal gyri (FDR $P < 0.05$). Conversely, word repetition relative to word generation was associated with bilateral activation in the precuneus and posterior cingulate gyrus, the medial frontal and the parieto-temporal cortex, and the insula (FDR $P < 0.05$). There were no differences in the localization of the network comparing the activation while performing the hard and the easy task. The network of areas engaged by the VF task was consistent with that reported in previous studies [Curtis et al., 1998; Fu et al., 2002; Hutchinson et al., 1999; Lurito et al., 2000; Schlosser et al., 1998; Yetkin et al., 1995].

Main effects of DAT and of G72 genotype

DAT genotype had a significant effect on activation in the right postcentral gyrus ($Z = 4.75$; $P < 0.02$ after FDR correction; cluster size = 63), with 10-repeat homozygotes activating more than 9-repeat carriers while performing the hard version of the verbal fluency task only (details in Supporting Information Fig. SII). G72 genotype had more widespread effects on activation during the hard version of the task, with significant effects in precentral, supramarginal/angular, cingulate, superior temporal, middle occipital gyrus and hippocampus bilaterally, and in the right insula, right medial superior frontal, right postcentral, and the left inferior parietal gyrus ($P < 0.05$, after FDR

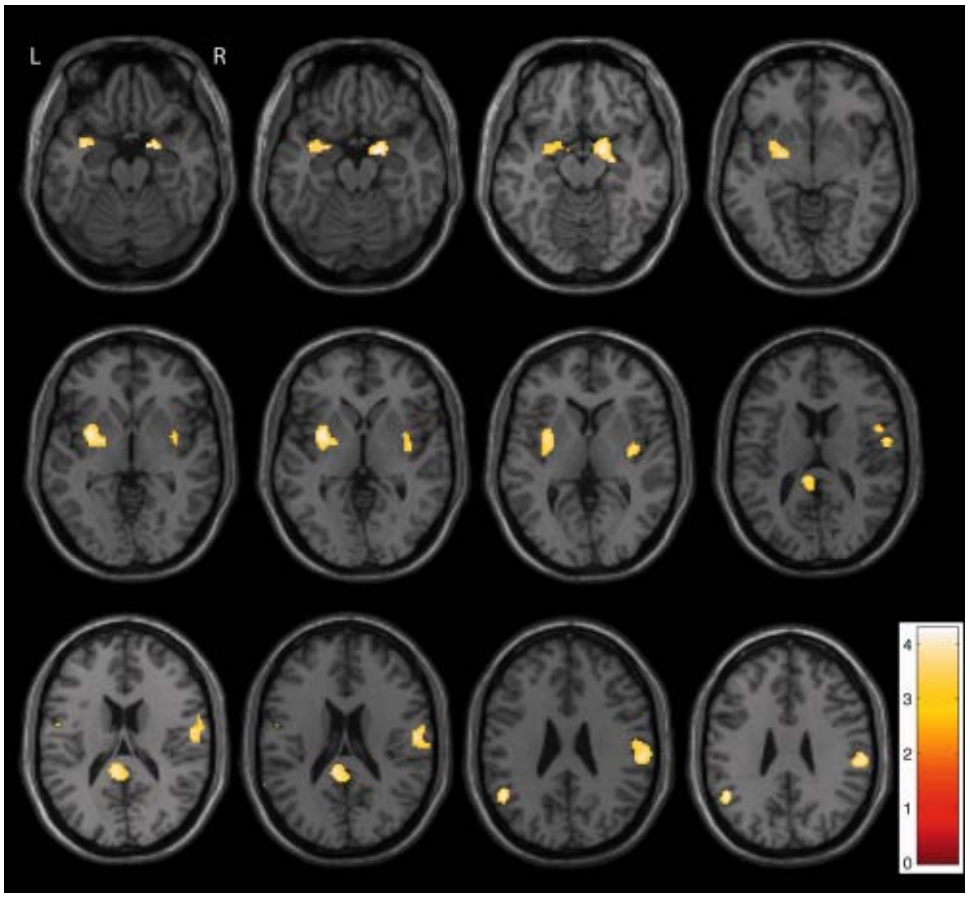

Figure 1.

Interaction between the effects of G72 and DAT genotype on activation during verbal fluency when task demands were high ("hard" version) ($P < 0.05$, FDR corrected). The epistasis was evident in the hippocampus, putamen and supramarginal/angular gyri bilaterally, and in the left posterior cingulate gyrus, in the right insula, and the right post- and precentral gyri. Color scale indicates the *Z*-score. The left side of the brain is shown on the left side of the images. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

correction) (details in Supporting Information Table and Figure SIII). In these regions, individuals with the G72 GG genotype activated more than subjects with the G72 AA genotype while the opposite was not detected anywhere. There were no significant single gene effects on activation while performing the easy version of the task.

DAT x G72 interaction

There was an interaction between the effects of DAT and G72 genotypes on activation during the hard version of the task in several regions ($P < 0.05$, FDR corrected). The strongest interactions were in a bilateral distribution in homologous parts of the hippocampus and putamen in each hemisphere. Additional interactions were evident in the supramarginal/angular gyrus bilaterally, the right insula, the retrosplenial part of the left posterior cingulate gyrus, and the right post- and precentral gyri (Fig. 1, Table II). Exploration of the parameter estimates indicated that in all these regions, within the G72 GG group, DAT 10/10-repeat subjects activated more than 9-repeat carriers, whereas the opposite applied in G72 AA subjects, with 9-repeat carriers activating more than 10/10-repeat subjects (Fig. 2). G72 heterozygotes showed an intermediate effect of DAT genotype on activation between G72 homozygote groups. The interaction accounted for 10.1%–19.9% of the variance in activation in these areas. There was a trend ($P < 0.001$, uncorrected) for the same interaction during the easy version of the task.

Effects of potentially confounding factors on activation

Whole brain analysis did not show a significant effect of age in any brain region ($P < 0.001$, uncorrected). Nevertheless, all results listed above include age as a covariate of

TABLE II. Areas where there was a significant interaction between the effects of DAT and G72 genotype on activation during the hard version of the verbal fluency task (DAT × G72 interaction)

Cerebral region	Hemisphere	MNI coordinates	Voxel-wise FDR *P*-value	*Z*-value	η_p^2 (DAT)	η_p^2 (G72)	η^2 (DAT&G72)	Cluster size
Parahippocampal Gyrus/ Hippocampal Head/Amygdala	R	20, −2, −18	0.034	4.14	3.9%	2.4%	18.3%	246
Parahippocampal Gyrus/ Hippocampus	R	24, −12, −14	0.034	3.90	6.8%	1.4%	17.6%	
Putamen	L	−32, 0, 0	0.034	4.14	5.0%	6.2%	15.4%	531
Parahippocampal Gyrus/ Hippocampus	L	−26, −8, −16	0.034	3.75	4.7%	5.1%	17.6%	
Globus Pallidus	L	−22, −4, −6	0.034	3.75	5.2%	0.9%	19.9%	
Superior Temporal Gyrus	L	−36, 2, −20	0.034	3.74	3.6%	2.1%	12.0%	
Supramarginal/Angular Gyrus	L	−50, −56, 26	0.034	3.96	5.0%	12.1%	13.7%	155
Posterior Cingulate Gyrus	L	−6, −40, 18	0.034	3.89	2.7%	3.5%	16.1%	163
Supramarginal Gyrus	R	60, −26, 28	0.034	3.88	8.8%	13.7%	12.2%	347
Postcentral Gyrus	R	58, −14, 20	0.034	3.77	18.4%	14.9%	12.6%	
Precentral Gyrus	R	64, 0, 18	0.037	3.32	7.1%	10.6%	11.2%	
Insula	R	38, −12, 4	0.034	3.57	1.5%	8.8%	10.5%	87
Putamen	R	36, −2, −2	0.038	3.24	1.8%	9.1%	10.1%	
Precentral Gyrus	R	52, 4, 14	0.037	3.26	9.5%	11.2%	10.4%	17

All inferences significant at FDR $P < 0.05$ are reported and their *Z*-score and effect size added (partial eta-squared for the main effects and eta squared for the interaction).
R, right; L, left; η_p^2, partial eta-squared; η^2, eta-squared.

no interest. As the group of DAT 10/10-repeat homozygotes with G72 GG genotype comprised only four subjects, we also performed additional analyses combining the G72 GG and AG groups to increase the group size. This did not alter the *Z*-scores for the majority of the areas we report: right hippocampus, left putamen, right supramarginal/angular gyrus, left posterior cingulate gyrus, right insula, and the right postcentral gyrus. To rule out confounding effects of population stratification in our results, we performed an additional analysis excluding the two non-Caucasian subjects. A small number of regions no longer survived the corrected significance voxel-wise threshold ($P < 0.05$, FDR): the right putamen and precentral gyri (for the G72 × DAT interaction), the right postcentral gyrus (for the DAT main effect) and the right insula, bilateral hippocampus and the left middle occipital and cingulate gyri (for the G72 main effect). However, the *Z*-scores did not substantially change (maximum change seen was of 0.6) nor did the foci of peak differential activation. This indicates that the few differences in corrected statistical significance were most probably due to a slight decrease in power with the subjects' exclusion. Furthermore, we also did not find additional areas when we excluded non-Caucasians, which indicates we had not missed any areas due to ethnic admixture.

DISCUSSION

To our knowledge, DAT by G72 epistasis on regional brain activation has not been investigated before. This is also the first study to demonstrate a nonadditive interaction on brain function between genes that respectively influence glutamatergic and dopaminergic neurotransmission that was significant at voxel level after correction for multiple comparisons ($P < 0.05$, FDR-corrected) across the whole brain; in contrast, the only previous study used small volume correction [Nixon et al., 2011]. We avoided using regional gene-related analyses restricted only to those areas delineated by the main effect of the task, as there may be significant genetic effects in areas that, when all individuals are averaged, are not significantly more activated during word generation relative to word repetition. We also did not use a region-of-interest approach in view of the lack of previous studies of nonadditive interactive effects of these genotypes on activation during verbal fluency. Thus, the statistical threshold we used was relatively more conservative.

A significant task load-dependent nonadditive interaction between G72 and DAT genotype effects was found in the putamen and the parahippocampal gyri bilaterally, as well as in the supramarginal/angular gyri bilaterally, and in the right insula, the left posterior cingulate/retrosplenial gyri and the right pre-/postcentral gyri. All these areas have been implicated in the task at hand, verbal fluency [Curtis et al., 1998; Fu et al., 2002; Hutchinson et al., 1999; Lurito et al., 2000; Pihlajamaki et al., 2000; Rosen et al., 2000; Spence et al., 2000; Yetkin et al., 1995] and encompass prominent glutamatergic and dopaminergic transmission. Most noticeably the striatum and the parahippocampus, have been extensively implicated in both the dopaminergic and the glutamatergic models of

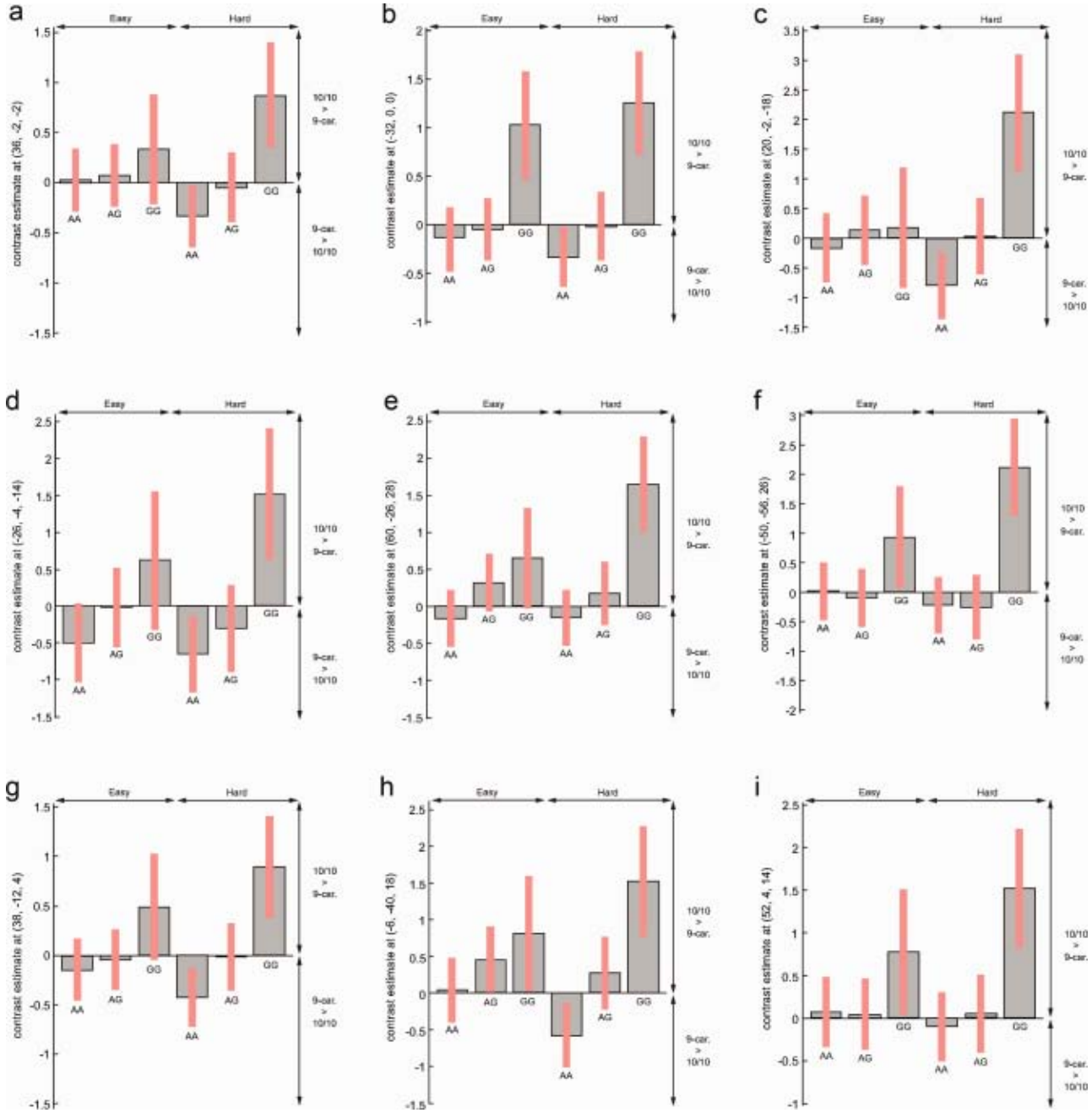

Figure 2.

Plots of interaction between the effects of G72 and DAT genotype on activation during the "hard" version of verbal fluency in (**a**) the right putamen, (**b**) the left putamen, (**c**) the right hippocampus, (**d**) the left hippocampus, (**e**) the right supramarginal/angular gyrus, (**f**) the left supramarginal/angular gyrus, (**g**) the right insula, (**h**) left posterior cingulate gyrus, and (**i**) the right precentral gyrus. Positive bars represent activation of 10/10-repeat subjects being greater than that of 9-repeat carriers while negative bars represent the reverse. In subjects with the G72 GG genotype, those who had the DAT 10/10-repeat activated more than 9-repeat carriers, whereas the opposite applied in subjects with the G72 AA genotype. The effect of DAT genotype on activation in G72 heterozygotes (AG) was intermediate between that in the G72 homozygotes (GG and AA). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

psychosis. In all regions, the 10-repeat homozygotes showed more activation than the 9-repeat carriers, which was more pronounced in individuals with the GG genotype for G72 than in those with the genotype AA. On the same order, GG activated more than AA if they were 10-repeat homozygotes and the opposite was true if they were 9-repeat carriers. G72 heterozygotes showed an intermediate effect of DAT genotype on activation between the G72 homozygote groups, which suggests a codominant model for this polymorphism. This epistatic effect on activation was not attributable to an effect of any genotype (or their interaction) on task performance, as there was no difference in the number of errors between the genotype groups (Table I), and the analysis was restricted to images associated with correct responses. Given this premise, we have interpreted our results of relatively greater blood oxygen level-dependent activation in cortical areas as a proxy of neuronal inefficiency on the basis that compensatory resources have to be recruited to achieve the same performance output [Winterer and Weinberger, 2004]. The fact that significant effects were limited to the hard version of the task suggests that the impact of the epistasis is modulated by cognitive load, as the hard condition is more demanding than the easy condition. This is consistent with a role of these genes in neurocognitive processing [Caldu et al., 2007; Prata et al., 2009c; Prata et al., 2012]. Below, we refer to each area in particular.

Putamen

Our finding in the putamen is consistent with it being, together with the caudate nucleus (both making up the striatum), the brain area with the highest expression of both DAT [Wang et al., 1995] and G72 [Chumakov et al., 2002; Korostishevsky et al., 2004]. The striatum is a major termination site of both dopaminergic projections from the brainstem [Lindvall and Bjorklund, 1978] and extensive glutamatergic projections from cortical regions, including the hippocampus [Lodge and Grace, 2006]. Increased release of striatal dopamine in vivo has been reported following administration of the NMDA-antagonist ketamine in humans, in support for interaction effects in this area, although not consistently [Rabiner, 2007]. Furthermore, our finding is consistent with the well-documented involvement of the striatum in schizophrenia aetiology, especially concerning positive symptoms (delusion and hallucination), whereby psychotic patients show increased striatal dopamine availability and synaptic release [Abi-Dargham et al., 2009; McGowan et al., 2004].

Parahippocampal gyrus

The parahippocampal gyrus has been extensively implicated in memory function [Sutherland et al., 1988; Vogt et al., 1992] and is a site where G72 expression is the highest in the brain [Chumakov et al., 2002; Korostishevsky et al., 2004]. The interaction effect we found on its bilateral activation is consistent with contemporary animal models of schizophrenia [Lodge and Grace, 2006, 2008, 2009)] proposing that parahippocampal dysfunction drives the striatal hyperdopaminergia classically associated with the disorder. Loss of hippocampal GABAergic tone in schizophrenia, either due to intrinsic GABAergic interneuron deficits or to dysfunction of NMDA receptors [Law and Deakin, 2001; Pilowsky et al., 2006], may lead to disinhibition of local glutamate efferents, which in turn increases the number of spontaneously active dopamine neurons and the amount of dopamine release in the striatum [Lisman et al., 2008; Lodge and Grace, 2006; Stone et al., 2007].

Postcentral/supramarginal gyrus

The postcentral/supramarginal gyrus has a prominent role in somatosensory processing and although it was not relatively more activated during verbal fluency than in the word repetition (rest) task in the present study, this has been reported in previous studies [Baldo et al., 2006; Heim et al., 2008]. It is involved in the integration of somatosensory, auditory, and visual input [Clower et al., 2001], in the phonological and articulatory processing of words [Celsis et al., 1999] and semantic representation [Xiao et al., 2005]. In an overlapping sample, this area has also shown an interaction between the effects of the DAT 3′UTR VNTR and the COMT Val158Met polymorphisms [Prata et al., 2009b] as well as a main effect of the G72 rs746187 SNP [Prata et al., 2012] on activation during the same task. The addition of the present finding suggests that this region is highly susceptible to the epistatic effect of both dopaminergic and glutamatergic genetic variants in the context of verbal fluency. In schizophrenic patients, this region seems to be less activated during motor discrimination [Wang et al., 2009] and verbal and nonverbal working memory tasks [Barch and Csernansky, 2007] and larger in the right hemisphere and smaller in the left hemisphere compared with healthy controls [Niznikiewicz et al., 2000].

Insula

The present interaction in the right insula is consistent with its prominent role in verbal fluency and other language-related tasks [Curtis et al., 1998; Fu et al., 2002; Yurgelun-Todd et al., 1996] and its relatively elevated expression of DAT [Wang et al., 1995]. A main effect of the DAT gene on activation during the same task in the left anterior insula [Prata et al., 2009c] using an overlapping sample, as well as a trend for a G72 main effect [Goldberg et al., 2006] during a working memory task in the right insula have also been reported. Other insular-related functions, such as processing of auditory and visual emotional information, pain and neuronal representations of the self as well a insular gray-matter volume, cortical thickness and cellular structure are altered in schizophrenia [Wylie and Tregellas, 2010].

Posterior cingulate cortex (restrosplenial)

The retrosplenial part of the posterior cingulate cortex (PCC) is densely connected to the hypothalamus and plays an important role in memory processing and retrieval [Duzel et al., 1999; Maddock et al., 2001], and spatial orientation [Vann and Aggleton 2002; Vogt et al., 1992]. During verbal fluency, the PCC is typically more engaged during word generation than repetition [Fu et al., 2005], although not in the present study. The PCC is less activated during semantic processing [Tendolkar et al., 2004], auditory oddball and recognition tasks [Holcomb et al., 2000; Kiehl and Liddle, 2001] and shows reduced resting glucose metabolism [Haznedar et al., 2004], gray-matter volume and gyrification [Hulshoff Pol et al., 2001; Wheeler and Harper, 2007] in schizophrenic patients compared with healthy controls. In the PCC, NMDA-antagonists induce morphological changes [Olney et al., 1989], reduced activation during episodic memory [Northoff et al., 2005] and increased dopamine release [Aalto et al., 2005]. Hence the area is suggested a key site where glutamate interacts with the dopamine system, which concurs with our finding [Olney and Farber 1995; Olney et al., 1999].

Precentral gyrus

Reduced gray matter thickness in the precentral gyrus has been associated with schizophrenia [Jung et al., 2011; Tanskanen et al., 2010]. It is also a region commonly recruited in verbal fluency [Curtis et al., 1998; Yetkin et al., 1995] and its increased activation has been associated with formal thought disorder and auditory verbal hallucination in schizophrenia [Jardri et al., 2011; Kircher et al., 2001]. In this area, additive effects of COMT and DAT on activation bilaterally have previously been reported [Bertolino et al., 2006], as well as a main effect of G72 in the left precentral gyrus [Goldberg et al., 2006].

We did not find any significant G72 × DAT interactions affecting prefrontal cortical activation, despite previous evidence that the dopamine and glutamate systems interact in this area [Castner and Williams, 2007; Lorrain et al., 2003; Nixon et al., 2011; Rios Valentim et al., 2009] and that it is a region of interest in the aetiology of schizophrenia. One possibility is that our analysis is not sufficiently powered, i.e., a larger sample or a less conservative statistical approach would be required in order to detect such interaction. It is also possible the effect of this interaction on the prefrontal activation becomes larger when additionally influenced by other polymorphisms in the DAT and G72 genes or even in other genes relevant to the same systems.

In addition, we found separate main effects of G72 rs746187 and of DAT 3′ UTR VNTR. This occurred in regions overlapping with the ones where we found an interactive effect. The main effect of DAT 3′ UTR VNTR in the right postcentral gyrus showed the same foci of maximal significance as we found for the interactive effect. Most of the areas where G72 rs746187 showed a main effect coincided with the ones where we found an interactive effect: parahippocampal (main foci more dorsal/superior) and supramarginal/angular gyri bilaterally, the right insula (main foci more frontal) and the right pre-/postcentral gyrus. In regions where we found an epistasis, this accounted for 10.1–19.9% of the variance in activation, while the eta-squared values in these areas for either gene alone were, in general, lower (Table II). This indicates that the individual variability in activation in these areas was better explained by an interaction model than by a main effect model for each polymorphism, i.e., that, in these areas, the effect of having a given genotype (e.g., GG compared with AA) was much stronger when the individual also had a specific genotype of the other gene (e.g., 10-repeat/10-repeat) than when it was measured irrespective of the other gene.

Both dopamine and glutamate levels modulate the local signal-to-noise ratio [Goldman-Rakic et al., 2000], and the efficiency of regional brain function [Winterer and Weinberger, 2004]. The effects of the G72 rs746187 and DAT 3′ UTR VNTR genotype on brain activation may reflect the influence of G72 and DAT on glutamate and dopamine transmission, respectively. However, the allelic directions of the interactive effects we detected remain unexplained, due to the lack of previous studies predicting interaction effects at the synaptic and genotypic level and of the functional role of the G72 SNP to begin with. Nevertheless, functional effects of the DAT VNTR both at the cellular level [Fuke et al., 2001; Heinz et al., 2000; Mill et al., 2002; VanNess et al., 2005] and in the brain have been more frequently researched [Bertolino et al., 2006; Dreher et al., 2009; Forbes et al., 2009; Prata et al., 2009c]. Subjects who are 10-repeat carriers, and thus according to previous evidence [Fuke et al., 2001; Heinz et al., 2000; Mill et al., 2002; VanNess et al., 2005] have higher DAT activity than 9-repeat carriers, would presumably remove dopamine from the synapse more rapidly. At least during cognitive tasks and in cortical areas where DAT's expression is high, its effects could directly impact on the signal-to-noise ratio which is dependent on cortical dopaminergic tone [see U curve model in [Goldman-Rakic et al., 2000]. The over-activation of the postcentral gyrus (which has been shown in monkeys to have high DAT levels [Lewis et al., 2001]) in 10-repeat allele homozygotes that we found may thus reflect suboptimal cortical dopamine levels which lead to inefficient activation [Winterer and Weinberger, 2004]. By contrast, reward studies have showed higher activation in the basal ganglia in 9-repeat carriers [Dreher et al., 2009; Forbes et al., 2009]; however the different nature of the task limits a valid comparison. In areas where DAT's expression is reduced (i.e., prefrontal cortex), the impact of DAT genotype may have its main origin in the striatum via the cortico-striato-thalamo-cortical loop, whereby an inhibitory effect to the thalamus causes the end effect in the cortex to be reversed [Bertolino et al., 2006; Prata et al., 2009c]. How variation in G72 rs746187 may influence brain function is still poorly understood. Subjects with two copies of the risk-allele (G) for the SNP G72 rs746187 may

have greater activation of DAAO, and thus lower availability of the NMDA-glutamate receptor coagonist, D-serine, lowering cortical glutamatergic tone, also possibly reducing efficiency and leading to increased local (compensatory) activation. Consistently, this was the main effect of G72 genotype in a wide network of brain regions; however, again, this has to remain a tentative explanation. Furthermore, a recent in vitro study has opened the debate on whether G72 activates or inactivates DAO [Sacchi et al., 2008] and, on the other hand, not all genetic association studies indicate that the G allele is the risk variant for psychosis [Detera-Wadleigh and McMahon, 2006].

It is important to note, that other genes relevant to the dopamine and glutamate systems might have a possible moderating role on the observed G72 × DAT interactions. The tonic-phasic dopamine model [Bilder et al., 2004; Grace, 1991] proposes that the amplitude of phasic striatal dopamine release is modulated by the tonic dopamine level which in turn is regulated by an interaction of glutamatergic presynaptic stimulation and COMT metabolism. COMT modulates striatal dopamine levels via (1) removing dopamine from the extrasynaptic space and (2) by regulating dopamine in the PFC that in the other hand stimulates glutamatergic pyramidal neurons that control tonic dopamine release within striatal regions. There are several genetic neuroimaging studies showing an epistatic effect between COMT and DAT [Bertolino et al., 2008; Caldu et al., 2007; Prata et al., 2009b; Yacubian et al., 2007], and recently Nixon et al. [2011] have detected an interaction between COMT and G72 in the dorsolateral prefrontal cortex.

In conclusion, these data suggest that genes that regulate glutamate and dopamine transmission interact to affect the function of the striatum, the medial temporal, insular, precentral, cingulated, and parietal cortex. They also support the central involvement of the striatum and the parahippocampus in the dopaminergic and glutamatergic models of schizophrenia. It remains to be established whether these epistatic effects lie on the pathway between genes and clinical phenotype [Owen, 2010]: neuroimaging intermediate phenotypes such as verbal fluency may mediate or moderate the increased risk conferred by genes, but could also reflect gene effects which do not necessarily result in increased risk, consistent with the notion of pleiotropy [Owen, 2010]. It is also unclear whether the effects identified in healthy participants are expressed similarly in individuals with psychotic disorders. Because patients with these disorders are likely to carry the risk variants of several other genes, the effect of a DAT and G72 epistasis on brain function may differ as a result of an altered genetic and neurochemical context [Weinberger, 2010]. Future studies involving a clinical sample should address these issues.

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