Effect of D-Amino Acid Oxidase Activator (DAOA; G72) on Brain Function During Verbal Fluency

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Abstract: *Background.* The D-Amino acid oxidase activator (G72 or DAOA) is believed to play a key role in the regulation of central glutamatergic transmission which is seen to be altered in psychosis. It is thought to regulate D-amino acid oxidase (DAO), which metabolizes D-serine, a co-agonist of NMDA-type glutamate receptors and to be involved in dendritic arborization. Linkage, genetic association and expression studies have implicated the G72 gene in both schizophrenia and bipolar disorder. *Aims.* To examine the influence of G72 variation on brain function in the healthy population. *Method.* Fifty healthy volunteers were assessed using functional magnetic resonance imaging while performing a verbal fluency task. Regional brain activation and task-dependent functional connectivity during word generation was compared between different rs746187 genotypes. *Results.* G72 rs746187 genotype had a significant effect on activation in the left postcentral and supramarginal gyri (FWE $P < 0.05$), and on the task-dependent functional coupling of this region with the retrosplenial cingulate gyrus (FWE $P < 0.05$). *Conclusions.* Our results may reflect an effect of G72 on glutamatergic transmission, mediated by an influence on D-amino acid oxidase activity, on brain areas particularly relevant to the hypoglutamatergic model of psychosis. *Hum Brain Mapp 33:143–153, 2012.* © 2011 Wiley Periodicals, Inc.

Key words: schizophrenia; psychosis; glutamate; DAOA/G72; verbal fluency; fMRI

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INTRODUCTION

The D-Amino acid oxidase activator (DAOA or G72) is thought to play a key role in the regulation of central glutamatergic transmission by activating D-amino acid oxidase (DAO) and thus modulating the metabolism of D-amino acids like D-serine. D-serine is a co-agonist with glutamate at NMDA glutamatergic receptors [Boks et al., 2007; Schell et al., 1995]. G72 is a primate-specific protein, expressed in mitochondria [Kvajo et al., 2007] and is also implicated in dendritic arborization [Kvajo et al., 2007]. Within the brain, its expression is maximal in the amygdala, caudate nucleus, and the dorsolateral prefrontal cortex [Chumakov et al., 2002; Korostishevsky et al., 2004] although one study has not found signicant levels [Benzel et al., 2008]. These brain regions show abnormal function in schizophrenia [Boks et al., 2007] and G72 expression in the dorsolateral prefrontal cortex is higher in schizophrenia patients compared to healthy controls [Korostishevsky et al., 2004]. In-vitro experiments provide evidence of both physical and functional interactions between G72 and DAO [Chumakov et al., 2002] although not in the same direction [Sacchi et al., 2008] and one study has failed to reproduce any effect [Kvajo et al., 2007]. Significant allelic association of these genes with schizophrenia has also been shown [Chumakov et al., 2002]. Consistent with the above, evidence of statistical epistasis between DAO and G72 loci and disease risk has been reported [Corvin et al., 2007]. In fact, G72 is situated in a chromosomal region, 13q22-q34, that had previously been linked to schizophrenia [Owen et al., 2004]. Following this, several studies have reported positive associations between both G72 and DAO, with schizophrenia and bipolar disorder [Addington et al., 2004; Bass et al., 2009; Chumakov et al., 2002; Detera-Wadleigh et al., 2006; Hall et al., 2004; Korostishevsky et al., 2006; Prata et al., 2008; Schumacher et al., 2004; Shinkai, 2007; Wang et al., 2004; Zou et al., 2005]. Glutamate is the most abundant excitatory neurotransmitter in the mammalian nervous system, and the principal neurotransmitter of cortical efferents [Zahr et al., 2008]. NMDA receptor activation by glutamate is critical for normal memory functions [Villarreal et al., 2002]. In humans, glutamatergic antagonists (e.g., ketamine) impair performance on tests of verbal [Parwani et al., 2005] and nonverbal declarative memory [Newcomer et al., 1999], verbal fluency, and problem solving [Krystal et al., 1999], and can provoke psychotic symptoms [Krystal et al., 1994]. Glutamate hypofunction is thus implicated in psychosis [Stone et al., 2009]. Glutamate receptor agonists may have therapeutic potential in psychotic disorders [Patil et al., 2007] and agents that directly or indirectly activate the D-serine modulatory site on the NMDA receptor may reduce psychotic symptoms and cognitive impairments in schizophrenia [Heresco-Levy, 2005; Heresco-Levy et al., 2005; Lane et al., 2005]. Evidence that altered glutamate transmission contributes to the pathophysiology of psychosis is consistent with data suggesting that variation in the gene for G72 influences the risk of psychotic disorders [Chumakov et al., 2002; Hall et al., 2004; Prata et al., 2008; Shinkai, 2007].

The aim of the present study was to examine the impact of G72 variation on activation across the brain during a verbal fluency task in healthy volunteers. The G72 rs746187 single nucleotide polymorphism (SNP) was chosen, as this has been associated, in haplotype and/or individual form, with schizophrenia through case–control and transmission disequilibrium test designs [Chumakov et al., 2002; Hall et al., 2004; Shinkai, 2007] and bipolar disorder in a case-control investigation [Prata et al., 2008]. The phonological verbal fluency task normally engages the frontal, cingulate, temporal and partietal cortex, the striatum and thalamus [Curtis et al., 1998; Friedman et al., 1998; Fu et al., 2002; Hutchinson et al., 1999; Lurito et al., 2000; Phelps et al., 1997; Schlosser et al., 1998; Yetkin et al., 1995; Yurgelun-Todd et al., 1996] and is associated with impaired performance [Allen et al., 1993; Howanitz et al., 2000] and altered cortical activation [Artiges et al., 2000; Curtis et al., 1998; Fletcher et al., 1996; Frith et al., 1995; Fu et al., 2005; Yurgelun-Todd et al., 1996] in schizophrenia and bipolar disorder [Broome et al., 2009; Gur et al., 2007]. We predicted that variation in G72 rs746187 would significantly influence cerebral cortical responses during verbal fluency. In specific, we predicted that the risk allele for psychosis (the G-allele) would be associated with a relatively less efficient form of regional activation, i.e. greater activation compared to the nonrisk allele given the same level of task performance. Relatively greater blood oxygen level-dependent regional activation has been interpreted as a proxy of neuronal inefficiency in several previous studies on the basis that compensatory resources have to be recruited to achieve the same performance output [Winterer et al., 2004].

METHODS

Subjects

All 50 participants were native English speakers and gave written informed consent after Local or Multi Centre Research Ethics Committee approval. Subjects were recruited through local media advertisement or from a volunteer register and had no personal or first-degree family history of psychiatric illness as assessed using the Family Interview for Genetic Studies (FIGS). Exclusion criteria were: a history of neurological illness or of systemic illness with known neurological complication; a history of head injury with loss of consciousness of more than 1 minute; and a substance misuse or dependence disorder (as defined by DSM-IV).

All subjects were genotyped for G72 rs746187 yielding 24 A homozygotes; 16 heterogygotes and 10 G homozygotes. Demographic and performance data according to genotype are summarized in Table I and calculated using Statistical Package for Social Sciences (SPSS) (version 15.0).

TABLE I. Demographics and performance according to G7 genotype subgrups

Genotype for *G72 rs746187*	A/A	A/G	G/G
N	24	16	10
Age [mean (SD)]	33.4 (9.4)	36.3 (12.6)	33.2 (10.4)
IQ [mean (SD)]	116.5 (13.5)	118.0 (11.3)	120.8 (8.4)
Years of education [mean (SD)]	15.4 (3.0)	14.3 (3.1)	15.8 (3.4)
Handedness (R/L)	24/0	15/1	8/2
Gender (M/F)	12/12	8/8	5/5
Ethnicity (Caucasian/other)	23/1	16/0	9/1
Easy task [mean Nr errors (SD)]	3.5 (2.6)	3.8 (4.7)	2 (1.3)
Hard task [mean Nr errors (SD)]	6.1 (3.3)	5.9 (5.4)	6.1 (3.9)

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 WAIS-III correlates highly both with WAIS-R (93.9%) [Wechsler, 1997] and with WASI-FSIQ (492%) [Wechsler, 1999]. The Quick Test has also been shown to yield comparable results to WAIS (Quick Test, 78 ± 7 and WAIS, 83 ± 6 in schizophrenia) [Frith et al., 1991]). The proportion of subjects assessed with each method was matched between genotype groups. Given the different tools used, IQ scores were standardized for the analysis of variance.

Chi-square/Fisher's tests (for categorical variables) and ANOVA (for continuous variables) were used to describe demographic group differences. The effect of task load and of genotype 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 × 2 ANOVA, with genotype as between-subject factor and task load as a within-subject factor. There were no significant differences between genotypic groups on any demographic variable. There was also no significant (at $P < 0.05$) effect of genotype, nor of a genotype by task load interaction on task performance.

Genotyping

DNA was extracted from blood or cheek swabs using standard methods. Genotyping of the rs746187 (a.k.a G72's M-7) [Shinkai, 2007] was performed blind to status under contract by KBioscience (Herts, UK; available at: http://www.kbioscience.co.uk/) using a competitive allele specific PCR system (CASP). Quality control procedures included negative control (water) wells and duplicate wells. A-primer was 5′GAAGGTGACCAAGTTCATGCTAAGGAGTGGCA GTCAACCGACT3′; G-Primer: 5′GAAGGTCGGAGTCAA CGGATTGGAGTGGCAGTCAACCGACC3′, and common primer: 5′AGTGTGAGGCATGTATTGAGAATGTTCAA3′. The genotyping frequencies of the sample from which the scanned subjects were originated did not significantly deviate from Hardy-Weinberg equilibrium ($X^2 = 0.3$, $P = 0.34$).

Verbal Fluency Task

During a "generation" condition subjects were visually presented with a series of letters and were required to overtly articulate a word beginning with each letter. This was contrasted with a "repetition" (baseline) condition in which subjects were presented with the word "rest" and were required to say "rest" out loud. A blocked design was used, with letter and "rest" cues presented in blocks of seven events. The demands of the task were manipulated by presenting two different sets of letter cues, "easy" and "hard" [Fu et al., 2002]. These had previously been shown to be associated with a significant difference in behavioural performance in healthy volunteers [Fu et al., 2002]. The "easy" condition involved the presentation of letters that are normally associated with relatively large numbers of correct responses and relatively few errors (e.g. T, B, S), whereas the "hard' condition involved letters associated with the generation of fewer correct words and relatively more errors (e.g. N, E, G). Five blocks of "rest" trials alternated with five blocks of "easy" letters or "hard" letters, resulting in a total of 70 generation and 70 repetition trials. Verbal responses were recorded permitting the identification of "incorrect" trials in which the subject did not generate any response, or generated repetitions, derivatives or grammatical variations of a earlier word.

Image Acquisition

T_2^*-weighted gradient-echo single-shot echo-planar images were acquired on a 1.5-T, neuro-optimized IGE LX System (General Electric, Milwaukee) at the Maudsley Hospital, London, UK. Twelve noncontiguous axial planes (7 mm thickness, 1 mm slice skip, 3.75 × 3.75 mm voxel size in plane and 64 × 64 mm matrix size in plane) parallel to the anterior commissure-posterior commissure line were collected over 1,100 ms in a "clustered" acquisition (TE = 40 ms, flip angle = 70°) which permitted articulatory responses to be made when images were not being acquired, minimising the effects of head movement on the BOLD signal [Fu et al., 2002]. Immediately after each acquisition a letter was presented (remaining visible for 750 ms, height: 7 cm, subtending a 0.4° field of view), and a single overt verbal response was made during the silent

portion (duration = 2,900 ms) of each repetition (TR = 4,000 ms), with an image acquired over 1,100 ms. Head movement was minimized by a forehead strap. To ensure that subjects heard their responses clearly, their speech was amplified by a computer sound card and then relayed back through an acoustic MRI sound system and noise-insulated headphones.

Neuroimaging Analysis

Analysis was performed using SPM5 software (available at: http//www.fil.ion.ucl.ac.uk/spm) [Friston, 2003], running under Matlab 6.5 (Mathworks Inc. Sherbon, MA). In order to minimize movement-related artifacts, all volumes from each subject were realigned and unwarped (using the first as reference re-sliced with sinc interpolation), normalized to a standard MNI-305 template and spatially smoothed with an 8 mm FWHM 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 haemodynamic response function. 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, the subject-specific contrast images were entered into a full-factorial 3 × 2 ANOVA, with genotype and task load as factors (the latter being a repeated measurement), to permit inferences at the population level [Penny et al., 2003]. This allowed us to characterize the impact of the experimental task on brain activation in "easy" and "hard" separately within each of the three experimental groups (AA, AG, and GG genotype groups), and test for the effects of genotype. We modeled task load in order to minimize error variance but report results for the hard and easy conditions combined. The *t*-images for each contrast at the second level were transformed into statistical parametric maps of the *Z* statistic.

To establish putative alterations in functional integration that were responsible for regional responses showing a significant effect of genotype, we used the psychophysiological interaction (PPI) method [Friston et al., 1997]. PPI is a multiple regression based-method that allows the investigation of the functional coupling between regions (i.e. functional connectivity) as a function of one or more experimental manipulations of interest. For each region of interest (defined as a sphere with a 6-mm radius around the voxel(s) which showed significant effects of genotype in the standard analysis of regional responses) the time series was extracted from each participant using the "VOI extraction" tool in SPM. This time series was then multiplied by a vector which contrasted easy and hard task performance against rest. For each participant, this resulted in a "PPI vector" which encoded the interaction between the activation of a region of interest and the experimental context (easy and hard verbal fluency vs. rest). A correlation analysis was then performed between this PPI vector and the rest of the brain, in a subject specific fashion; finally, the subject-specific contrast images were entered into an ANOVA in order to make inferences at the group level. We report findings that are significant at $P < 0.05$ after a voxel-wise family wise error (FWE) correction for multiple comparisons across the whole brain with a cluster size greater than 10 voxels.

RESULTS

Main Effect of Task

Word generation was associated with activation in a distributed network that included, bilaterally, the inferior frontal and middle temporal cortex and insula, the left middle frontal and precentral gyri, left thalamus, and right caudate (FWE $P < 0.05$). Conversely, word repetition was associated with activation in the precuneus, and the anterior and posterior cingulate, supramarginal and angular gyri bilaterally (Supp. Info., Fig. 1).

Effect of G72 Genotype on Regional Activation

There was a significant effect (FWE $P < 0.05$) of genotype on activation in the left postcentral/supramarginal gyrus (peak at −56, −14, 20), where the GG genotype was associated with greater activation than the AA genotype (irrespective of task difficulty; i.e. when hard and easy versions were combined; Fig. 1). Plotting of the parameter estimates at this site revealed that the heterozygous group showed an intermediate level of activation relative to the AA and GG groups, suggesting an allele-wise linear load-effect (Fig. 1). There was no interaction between genotype and task difficulty in this region, indicating that the effect of genotype did not differ for easy and hard conditions; as confirmed by the plotting of the parameter estimates.

Effect of G72 Genotype on Functional Connectivity With the Left Postcentral/ Supramarginal Gyrus

We then examined the effect of genotype on task-dependent functional integration between the left postcentral/ supramarginal gyrus and other brain regions. A homozygotes showed stronger functional connectivity between the left postcentral/supramarginal gyrus and

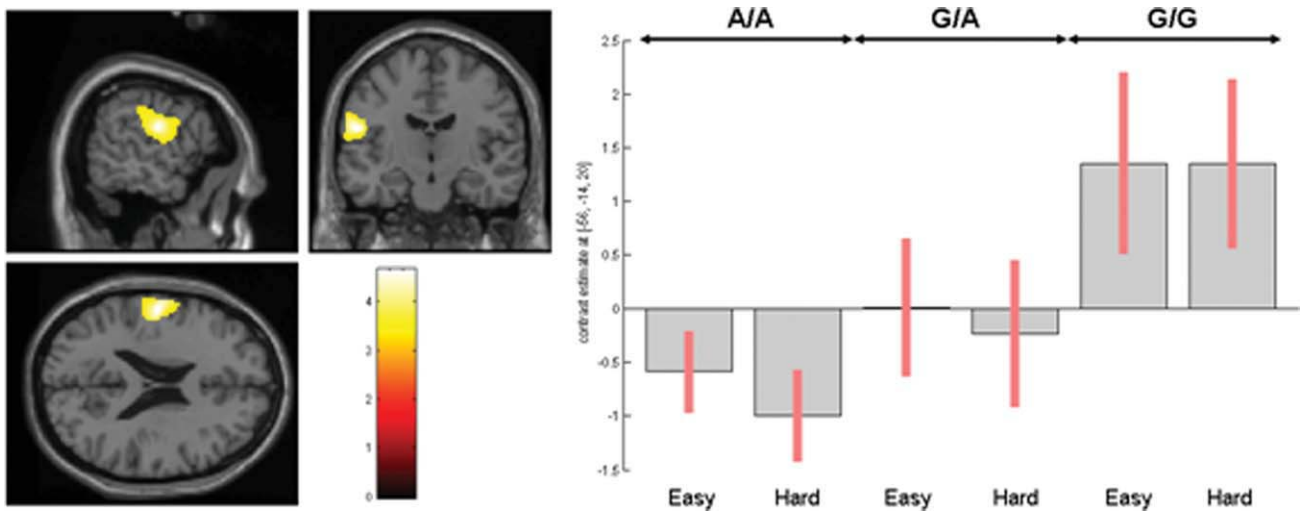

Figure 1.

Effect of G72 genotype on activation during word generation relative to repetition. G homozygotes showed more activation than A homozygotes in the left postcentral/supramarginal gyrus, with an intermediate level of activation in heterozygotes. (A threshold of $P < 0.001$, uncorrected, was used in this image for display purposes only.). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

the retrosplenial part of the posterior cingulate gyrus (peak at 0 −44 16) than G homozygotes (FWE $P < 0.05$; Fig. 2). This indicates that the greater activation in the G homozygotes in the left postcentral/supramarginal gyrus was associated with weaker task-dependent functional connectivity between this region and the retrosplenial cingulate gyrus. Plotting of the parameter estimates revealed that this functional connectivity in the heterozygous group was intermediate relative to the AA and GG groups, suggesting an allele-wise linear load-effect (Fig. 2).

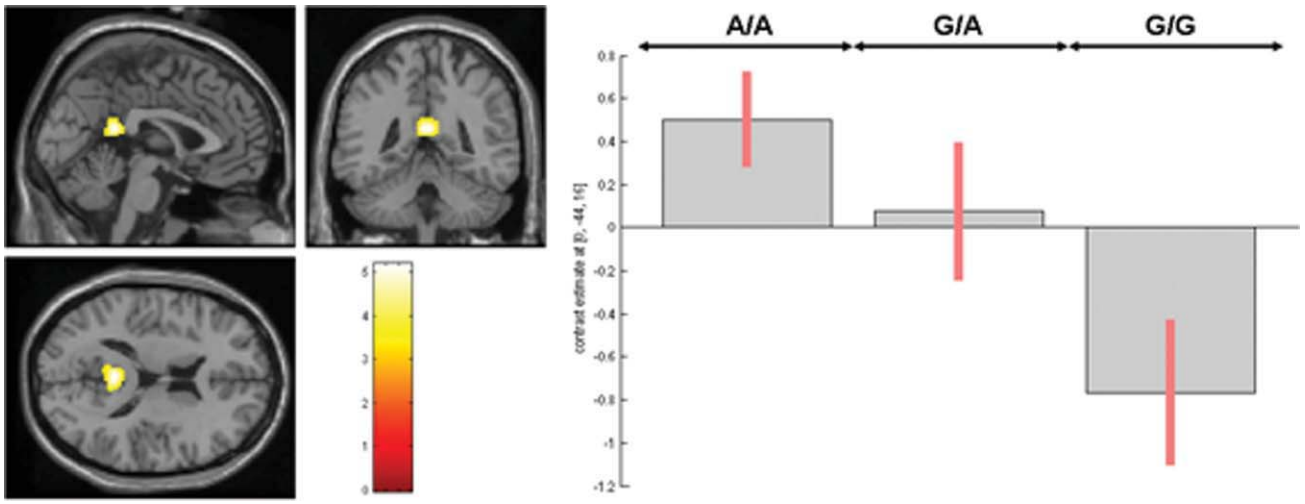

Figure 2.

Effect of G72 on task-dependent functional connectivity with the left postcentral/supramarginal gyrus. A homozygotes showed stronger functional connectivity between the left postcentral/supramarginal gyrus and the retrosplenial cingulate gyrus than G homozygotes, with connectivity in heterozygotes at an intermediate level. (A threshold of $P < 0.001$, uncorrected, was used in this image for display purposes only.). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

DISCUSSION

The network of areas engaged by the verbal fluency task was consistent with previous reports using this paradigm [Curtis et al., 1998; Fletcher et al., 1996; Fu et al., 2002; Yurgelun-Todd et al., 1996]. The focus of the present study was to examine if variation in the G72 gene (the rs746187 polymorphism) was associated with differences in brain activation during a verbal fluency task, as measured with fMRI. We found this to be the case in the left postcentral/supramarginal gyrus, an effect which was significant after correction for multiple comparisons across the whole brain. As we predicted, the risk allele (G) was associated with relatively greater (i.e. putatively less efficient) activation in an allele-load fashion, compared to the opposite allele. The differences in activation were not attributable to an effect of genotype on task performance, as there was no difference in the number of erroneous responses between genotype groups (Table I), and the analysis was restricted to images associated with correct responses. The postcentral gyrus is known to have a prominent role in somatosensory processing, however it has also been reported to be significantly activated during verbal fluency in several previous studies although not in the present one [Baldo et al., 2006; Heim et al., 2008; Hirshorn et al., 2006; Lim et al., 2008; Mensebach et al., 2009; Peters et al., 2009]. Likewise, the supramarginal gyrus is thought to be 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 also plays a role in semantic representation [Xiao et al., 2005], and in decision making under conditions of uncertainty [Vickery et al., 2009].

The impact of variation in G72 rs746187 genotype on brain activation may reflect an effect on glutamate transmission. Exactly how G72 influences brain function at the biochemical level is still not well understood. However, G72 is a regulator of DAAO [Chumakov et al., 2002; Korostishevsky et al., 2004; Sacchi et al., 2008] especially in the cerebral cortex were NMDA receptors are present throughout [Geyer et al., 1997; Passani et al., 1997], including the postcentral and supramarginal gyri. Subjects with two copies of the risk-allele for this SNP, G, might thus have higher activation of DAO, and therefore lower availability of the NMDA-glutamante receptor co-agonist, D-serine, lowering cortical glutamatergic tone. Nevertheless, 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 point to the G allele as being the risk variant associated with psychosis [Detera-Wadleigh et al., 2006]. The latter may be because of phenotypic heterogeneity and/or allelic heterogeneity (e.g. different markers in different ethnicities being associated with the same disease) which are commonly observed in complex and multifactorial diseases. To date, there are no functional variations identified in the G72 gene, and we cannot exclude the possibility that the association found in the present study may be due to an unknown functional variation in strong linkage disequilibrium with the present SNP.

Previous fMRI studies on G72 variation have reported its effect on activation of the hippocampus and parahippocampus during verbal working memory tasks [Goldberg et al., 2006; Hall et al., 2008; Jansen et al., 2009]. Jansen et al. [2009] found, surprisingly, that psychosis-risk alleles of the rs3918342 and rs1421292 SNPs were associated with better performance and stronger deactivation in these areas. These performance results were consistent with another study that previously found a risk haplotype to be associated with better performance in semantic fluency [Opgen-Rhein et al., 2008]. To explain this, these authors suggested that psychosis-risk alleles conferred some advantage in the healthy population, which accounted for their high prevalence and that of psychosis. Hall et al. [2008] found the same deactivating effect of rs3918342 on medial temporal activation in subjects at high familial risk for schizophrenia and, with increasing task difficulty, the opposite effect in the right inferior frontal gyrus. Goldberg et al. [2006] reported that rs1421292 was associated with altered hippocampal and parahippocampal activation in healthy subjects during episodic memory. The present study adds to these findings by demonstrating that the impact of G72 is not confined to medial temporal or inferior frontal regions in the context of memory processing, but extends to the parietal cortex when subjects engage executive functions. In fact, recently, Krug et al. [2010] have found G72 risk alleles (of rs3918342 and rs1421292) to be associated with increased activation in the right middle temporal gyrus and the parietal cortex (specifically, the right precuneus). Moreover, the present study is the first to report an effect of variation in this gene that was significant at voxel level after correction for multiple comparisons across the whole brain; in contrast previous studies either used small volume correction [Goldberg et al., 2006; Jansen et al., 2009; Krug et al., 2010] or whole brain correction at cluster level [Hall et al., 2008; Krug et al., 2010].

Another novel aspect of our investigation was the use of the psycho-physiological interaction method to better understand the impact of the G72 variation on brain function. Whole brain analysis revealed that the increased postcentral/supramarginal activation in G homozygotes was associated with decreased task-dependent functional connectivity between this region and the retrosplenial cingulate cortex. One possible explanation for this pattern of results is that the increased regional activation detected with the standard analysis might reflect a compensatory mechanism following poor functional integration. The posterior cingulate cortex (that includes the restrosplenial cortex) is thought to play a fundamental role in memory processing and retrieval [Düzel et al., 1999; Fink et al.,

1996; Krause et al., 1999; Maddock et al., 2001; Maguire et al., 1999] and spatial orientation [Sutherland et al., 1988; Vogt et al., 1992] and has also been found to be engaged during a range of cognitive tasks [Chang et al., 2009; Ries et al., 2006], including verbal fluency [Fletcher et al., 1996; Fu et al., 2005]. Nevertheless, our data show increased activation of this area during word repetition compared to word generation rather than the opposite. This area is densely and reciprocally connected with the hippocampus consistent with the observation that they are both implicated in memory processes [Sutherland et al., 1988; Vogt et al., 1992]. In fact, it is interesting to note that although we have searched the whole brain, we have found an effect of G72 on the functional coupling of an area highly anatomically and functionally interconnected with the hippocampus, which is where an effect of this gene has been mostly reported in the past (see previous paragraph). There is extensive evidence for structural and functional alterations in the posterior cingulate in schizophrenia [Franck et al., 2002; Haznedar et al., 1997; Holcomb et al., 2000; Hulshoff Pol et al., 2001; Kiehl et al., 2001; Leonard et al., 1999; Miller et al., 2001; Tendolkar et al., 2004; Wheeler et al., 2007] namely reduction of BOLD activation and volume. Interestingly, NMDA receptor hypofunction, which has been hypothesized to be implicated in psychosis, has been shown to affect mainly the restrosplenial/posterior cingulate [Olney et al., 1995]. This area also appears to be most susceptible to neurodegeneration by the disinhibitory effects induced by NMDA receptor hypofunction [Olney et al., 1995]. In accordance with this, a special role of the restrosplenial/posterior cingulate in the pathophysiology of psychotic symptoms has been proposed [Olney et al., 1995]. This was subsequently supported by an fMRI study that found ketamine administration (a NMDA-antagonist which induces psychosis-like symptoms) to reduce posterior cingulate activation in humans during episodic memory [Northoff et al., 2005]. It is therefore possible that normal variation in G72 may affect NMDA signalling in the restrosplenial/posterior cingulate, thus impacting on its connectivity to cortical areas. This may influence susceptibility to psychosis according to the above model by Olney and Farber [Olney et al., 1995]. Although, in the present study, we cannot discern the direction of the functional connectivity between these areas, we have found an association between the G allele and lower connectivity between the restrosplenial/posterior cingulate and the parietal cortex which is consistent with the association of this allele with susceptibility to psychosis [Hall et al., 2004; Prata et al., 2008; Shinkai, 2007].

Glutamate acts as a neurotransmitter throughout the brain and D-serine and NMDR-receptors are highly coexpressed in the gray matter of the cerebral cortex, hippocampus, anterior olfactory nucleus, olfactory tubercle, and amygdale, their presence being inversely correlated to that of D-amino acid oxidase [Wolosker et al., 2008]. Thus it is unclear why the effects of variation in G72 genotype in the present study should be particularly evident in the parietal cortex. However, we note that we previously found an interaction between the effects of two genes that influence central dopamine transmission (DAT and COMT) on activation in a similar postcentral/supramarginal area (with peak at −60, −16, 34) during verbal fluency in the same subjects [Prata et al., 2009]. This suggests activation in this region may be particularly sensitive to neurochemical modulation in the context of executive processing. Functional and structural abnormalities in the parietal cortex have been reported in schizophrenia. This region has been shown to be underactivated during motor discrimination [Wang et al., 2010] and verbal and nonverbal working memory tasks [Barch et al., 2007] in schizophrenia. It has also been repeatedly found to be larger in the right hemisphere and smaller in the left hemisphere in schizophrenia relative to controls [Buchanan et al., 2004; Frederikse et al., 2000; Niznikiewicz et al., 2000].

The observation of altered functional integration in individuals with the variant of the G72 gene associated with psychosis is consistent with the notion that abnormal interactions within a distributed network of regions is a key pathophysiological feature of psychotic disorders [Meda et al., 2009]. Moreover, the greater postcentral/supramarginal activation associated with the G allele (which decreased with the decrease in G allele load) in the context of equal task performance can be interpreted as a manifestation of less efficient cortical function, with more activation required to achieve the same behavioral output [Winterer et al., 2004]. This is consistent with previous association of this allele with an increased risk for schizophrenia [Hall et al., 2004; Shinkai, 2007] and bipolar disorder [Prata et al., 2008]. Further investigation of the effect of this variation on brain function in schizophrenia and bipolar patient samples, their unaffected relatives and individuals at high risk for these illnesses is warranted in order to further characterize its implication in psychosis.

We conclude that a common variation in the psychosis candidate risk-gene G72 has an effect on postcentral/supramarginal activation and its functional connectivity with the posterior cingulate cortex during verbal fluency. This may reflect differences in glutamatergic tone in these regions.

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