Eur Arch Psychiatry Clin Neurosci (2009) 259:459–465
DOI 10.1007/s00406-009-0010-8

ORIGINAL PAPER

The effect of the COMT val^{158}met polymorphism on neural correlates of semantic verbal fluency

Axel Krug · Valentin Markov · Abigail Sheldrick · Sören Krach · Andreas Jansen · Klaus Zerres · Thomas Eggermann · Tony Stöcker · N. Jon Shah · Tilo Kircher

Received: 23 September 2008 / Accepted: 31 March 2009 / Published online: 21 April 2009
© Springer-Verlag 2009

Abstract Variation in the val^{158}met polymorphism of the COMT gene has been found to be associated with cognitive performance. In functional neuroimaging studies, this dysfunction has been linked to signal changes in prefrontal areas. Given the complex modulation and functional heterogeneity of frontal lobe systems, further specification of COMT gene-related phenotypes differing in prefrontally mediated cognitive performance are of major interest. Eighty healthy individuals (54 men, 26 women; mean age 23.3 years) performed an overt semantic verbal fluency task while brain activation was measured with functional magnetic resonance imaging (fMRI). COMT val^{158}met genotype was determined and correlated with brain activation measured with fMRI during the task. Although there were no differences in performance, brain activation in the left inferior frontal gyrus [Brodmann area 10] was positively correlated with the number of val alleles in the COMT gene. COMT val^{158}met status modulates brain activation during the language production on a semantic level in an area related to executive functions.

Keywords COMT · fMRI · Verbal fluency · Inferior frontal gyrus · BA 10

A. Krug (✉) · S. Krach · A. Jansen · T. Kircher
Department of Psychiatry and Psychotherapy,
Philipps-University Marburg, Rudolf-Bultmann-Str. 8,
35039 Marburg, Germany
e-mail: kruga@med.uni-marburg.de

V. Markov · A. Sheldrick
Department of Psychiatry and Psychotherapy,
RWTH Aachen University, Pauwelsstr. 30,
52074 Aachen, Germany

K. Zerres · T. Eggermann
Institute of Human Genetics, RWTH Aachen University,
Pauwelsstr. 30, 52074 Aachen, Germany

T. Stöcker · N. J. Shah
Institute of Neuroscience and Biophysics 3, Medicine, Research Center Jülich, Jülich, Germany

N. J. Shah
Central Service Facility "Functional Imaging"
at the ICCR-BIOMAT, RWTH Aachen University,
Pauwelsstr. 30, 52074 Aachen, Germany

N. J. Shah
Institute of Physics, University of Dortmund,
Dortmund, Germany

Introduction

A functional polymorphism in the human catechol-O-methyltransferase gene (COMT, located at 22q11.1-q11.2) has a significant influence on cognition [43, 45]. This polymorphism (G–A) at codon 158 results in a substitution of methionine to valine. Owing to the higher enzymatic activity caused by the val allele, lower levels of extracellular dopamine are found, while the opposite is true for the met allele. Because the alleles are codominant, heterozygous carriers have intermediate levels of COMT activity. High COMT activity leads to a hypodopaminergic state; low COMT activity has the opposite effect.

A number of studies have shown that the met allele is beneficial in cognitive tasks that rely on prefrontal cortical activity (e.g. [43, 45]). In addition, it has been found that this specific single nucleotide polymorphism (SNP) has a significant influence on brain activation during a number of different tasks, such as memory encoding [5], perceptual processing of faces [13] and sentence completion [29]. The met/met genotype has further been associated with the

better performance in the N-Back Task [16] as well as in the Wisconsin Card Sorting Test (WCST) [27, 38]. Further effects have been reported on executive functioning and personality traits [41]. Effects of the COMT val^{158}met polymorphism have also been found for functional connectivity in a memory processing task [5] in healthy individuals and brain volume in relatives of patients with schizophrenia [29]. Functional connectivity between the hippocampal formation and the ventrolateral prefrontal cortex decreases with the number of met alleles [5] resulting in better performance for met/met allele carriers and with decreased levels of gray matter density with increasing number of val alleles [29]. Several studies imply that increasing (pre)frontal levels of dopamine could lead to better performance in working memory tasks (e.g. [4, 28]), and healthy homozygous val allele carriers could benefit from amphetamine [28].

Recent studies suggest that the val allele contributes to poorer cognitive function in healthy individuals [1] as well as in schizophrenia spectrum disorders [14, 32]. Because of its association with cognitive function in these groups, COMT has been suggested as playing a role in the etiology of schizophrenia (e.g. [15, 26, 50]); however, recent studies have questioned this association [33, 39, 49].

Given the complex modulation and functional heterogeneity of frontal lobe systems, further specification of COMT gene-related phenotypes differing in prefrontally mediated cognitive performance are of major interest. So far, little is known about the exact dopaminergic modulation of the processes during semantic verbal fluency tasks. It seems that COMT genotype has no influence on a behavioral level (for a meta-analysis see [2]) even though it could be shown that this domain relies on prefrontal brain areas (e.g. [3, 10, 17, 48]). These areas are also activated differentially in patients with schizophrenia when compared with healthy subjects (e.g. [40]). However, while several studies on the effect of COMT genotype on neural correlates of working memory have emerged [5, 29–31], no studies have been conducted with regard to semantic verbal fluency. Thus, it is of interest to study effects of COMT genotype on neural activation during semantic verbal fluency.

In this study, the effect of COMT genotype on performance in a verbal fluency task and its neural correlates was investigated. As a first step, healthy individuals were studied to establish results unbiased from psychopathology usually found in patients. Based on the previous findings that the COMT val^{158}met genotype has an impact on prefrontal cortical dopamine signaling, we hypothesized that carriers of the homozygous val allele have increased prefrontal activation in order to compensate for slightly impaired performance.

Materials and methods

Subjects

This sample is a subsample of [41]. Subjects were recruited at RWTH Aachen University; the majority of them (90%) were students. Eighty-five subjects were enrolled into the study. However, five subjects had to be excluded due to reasons given below. Resulting subjects were 80 individuals (54 men, 26 women). The inclusion criteria were age 18–55 years and no psychiatric disorder according to ICD-10 past or present. The subjects had a mean age of 23.3 years (SD = 3.0), were all right handed (as tested with the Edinburgh Laterality Scale [34]) and had 15.7 (2.6) years of education. The German MWT-B multiple choice vocabulary test [24] was used as assessment as an estimate for verbal intelligence. All subjects were of German descent and native German speakers. After a complete description of the procedure subjects provided written informed consent to participate in the study. The protocol was approved by the local ethics committee according to the declaration of Helsinki. After participants provided consent, the cognitive tests and fMRI were assessed. Subjects for fMRI scanning were randomly selected on availability, eligibility for the scanning procedure and to have enough subjects in each cell. This is the reason why genotype distribution is not in HWE in this subsample. Characteristics of this sample are given in Table 1.

Genotyping

Genomic DNA was isolated from peripheral lymphocytes by a simple salting-out procedure. COMT val^{158}met genotypes were determined using restriction-fragment length polymorphism as previously described [27]. A 109-base pair polymerase chain reaction (PCR) product was generated in 40 cycles with an annealing temperature of 50°C by using primers Comt1 nt 1881 5′-CTCATCAC CATCGAGAGATCAA-3′ and Comt2 nt 1989 5′-CCAG GTCTGACAACGGGTCA-3′[22]. The val^{158} and met^{158} alleles were discriminated by digesting the PCR product with *Nla*III at 37°C for 4 h, followed by a native 10% polyacrylamide gel electrophoresis. The val^{158} homozygotes (86 and 23 base pairs), met^{158} homozygotes (68 and 18 base pairs) and val^{158}met heterozygotes (86, 68, 23 and 18 base pairs) were visualized by silver staining.

fMRI task

Task and stimuli

Stimuli were presented with Presentation software package (Neurobehavioral Systems Inc., San Francisco, CA). This

Table 1 Sociodemographic data, standard deviations in parentheses ($n = 80$)

Variable	COMT genotype				
	met/met ($n = 31$)	val/met ($n = 26$)	val/val ($n = 23$)	F	P
Sex ratio (men/women)	24/7	14/12	16/7	$\chi = 3.64$	0.22
Age	23.7 (3.6)	22.4 (2.4)	23.7 (2.6)	1.8	0.16
Education	16.0 (3.0)	15.1 (1.8)	16.0 (2.7)	1.0	0.32
Estimated verbal IQ	110.9 (13.2)	115.1 (10.7)	109.8 (13.2)	1.3	0.27

semantic verbal fluency task used a block design with two alternating conditions: subjects had to read aloud single German nouns presented to them (high-level baseline condition) or, in response to a German noun, they had to name one member of the category this noun represented (e.g. say "dog" when the word "animal" was presented; semantic verbal fluency condition). There were four blocks for each condition. At the beginning of each block, an instruction slide was shown for 2,000 ms (semantic verbal fluency: "generate a category member"; baseline: "read the word"). Then, a fixation cross appeared in the center of the screen for 500 ms that was followed by the stimulus word for 3,000 ms. Subjects were required to respond within this time frame. Each block consisted of 10 stimuli with duration of 34 s each. In sum, subjects had to generate 40 words. The appearance of the #-symbol for 6,000 ms indicated the end of each block. Words were presented in white color on a black background and recorded for later analysis. The task has been used previously in other studies of ours successfully [19, 48].

Data acquisition

Imaging was performed on a 3-T Tim Trio MR scanner (Siemens Medical Systems) in the Institute of Neuroscience and Biophysics, Medicine, Research Centre Jülich. Functional images were collected with echo-planar imaging (EPI) sensitive to BOLD contrast (T2*, 64 × 64 matrix, FoV 200 × 200 mm, 36 slices, 3 mm thickness, TR = 2.25 s, TE = 30 ms, flipangle = 90°). Slices covered the whole brain and were positioned trans-axially parallel to the anterior–posterior commissural line (AC–PC). One hundred and fifty-seven functional images were collected, and the initial three images excluded from further analysis in order to remove the influence of T1 stabilization effects.

Data analyses

Because there were sufficient data in all three groups, statistical analyses of genotype effects in the behavioral as well as fMRI data were performed in accordance with a codominant model (regression analysis), thus checking if the number of val alleles influences brain activation. Recorded speech of all subjects was analyzed. This procedure was used to assure correct task adherence and to have a behavioral index of performance. Five subjects had to be excluded from further analyses for not following instructions correctly. They did not name category members but freely associated about the word stimuli, thus potentially having a different neural activation pattern due to performing a different task [19, 48].

fMRI data analysis

FMRI data analyses were calculated using SPM5 (www.fil.ion.ucl.ac.uk/spm/). After realignment, unwarping and stereotaxic normalization (2 × 2 × 2 mm), a 6 mm full-width-at-half-maximum (FWHM) Gaussian smoothing kernel was applied to increase the signal-to-noise ratio and compensate for inter-subject anatomic variation. The volume of interest was restricted to gray matter voxels by the use of an inclusive mask created from the segmentation of the standard brain template (SPM2).

Semantic verbal fluency related brain activation was analyzed for each subject contrasting the semantic verbal fluency condition with high-level baseline. In a first step, a one sample t test was calculated for the whole sample ($n = 80$) to investigate general semantic verbal fluency activation. To investigate genotype effects, resulting contrasts were entered in a multiple regression using genotype as a covariate. The multiple regressions were calculated both ways in order to detect increasing brain activation depending on increasing number of val alleles or met alleles. In order to correct for multiple comparisons within a search volume, we applied a cluster extent threshold determined by Monte Carlo simulations [42]. For a threshold at the voxel level at $P = 0.005$ and spatial properties as present in this study, 10,000 simulations resulted in an extent threshold of 33 resampled voxels. This procedure prevented a false-positive rate above 5% due to multiple testing. Brain activations were plotted on the anatomical SPM template.

Results

Genetic analysis

Distribution of COMT val^{158}met genotypes was 31 with met/met genotype (24 male), 26 with val/met genotype (14 male) and 23 with val/val genotype (16 male). The resulting groups and variables are displayed in Table 1.

Behavioral data

Data were analyzed and checked for errors in the semantic verbal fluency task. Mean error rates for the three groups were 3.5 (SD = 2.2) for met/met status, 3.9 (2.9) for val/met status and 3.8 (2.9) for val/val status. There was no significant influence of genotype on errors ($F_{2,77} = 0.13$, $P = 0.87$).

fMRI data

Because we used an overt semantic fluency task that could lead to head movement, realignment parameters were checked for each subject. All subjects had tolerable head movement smaller than one voxel size, similar to previous reports [19].

The fMRI group analysis ($n = 80$) of the contrast "semantic verbal fluency" > "reading aloud" revealed activations in the left inferior frontal gyrus (BA 47), left middle temporal gyrus (BA19), and the cingulate gyrus (BA 24). Activated regions are listed in Table 2.

Regression analyses revealed a linear effect of val alleles in the left inferior frontal gyrus (Brodmann Area 10) for the contrast "semantic verbal fluency" > "reading aloud" (see Fig. 1). The peak voxel was located at $x = -46$, $y = 45$, $z = -2$ (Talairach and Tournoux atlas space [44], $t = 4.28$, $p = 0.001$, $R^2 = 0.133$). The corresponding cluster consisted of 45 voxels.

In order to test for the opposite linear effects (increase in activation), regression analyses were calculated using the number of met alleles as covariate. No increasing brain activation with respect to an increasing number of met alleles was observed.

Discussion

In the present study, we investigated the effect of COMT on the neural correlates of semantic verbal fluency in a large sample of healthy subjects. We found an increase in brain activity in the left inferior frontal gyrus (IFG, BA 10) with the number of val alleles.

BA 10 has consistently been shown to be involved in working memory tasks such as the Continuous Performance Test (CPT) [23, 25, 35, 37, 47]) and other tasks such as explicit processing of internal states (for a comprehensive review, see [11]), some aspects of memory retrieval [46], branching and reallocation of attention [7, 20, 21], prospective memory [8, 9] and relational integration [12, 22], as reviewed for example by Ramnani and Owen [36]. This region is involved when tasks require more than one specific cognitive process. Our semantic fluency task is an example of such a situation since in order to successfully perform this task it is necessary to understand the category that is being presented, find candidate members of this category and monitor for possible errors while selecting an appropriate response while at the same time, the category

Table 2 Brain activation for the contrast "semantic verbal fluency" > "reading aloud" for the whole fMRI sample ($n = 80$), $P = 0.05$ corr., cluster extend 20 voxels

Region	Side	BA	x	y	z	k_E	Max. SPM (T)
Middle temporal gyrus	L	19	−30	−56	14	63	7.20
Parahippocampal gyrus	L	37	−36	−39	−1	55	6.85
Hypothalamus	R	–	4	−6	−5	21	6.58
Inferior frontal gyrus	L	47	−28	21	−4	23	5.54
Cingulate gyrus	L	24	−8	21	41	32	5.34
"Reading aloud" > "semantic verbal fluency"							
Putamen	L	–	−14	9	−11	428	15.98
Anterior cingulate	R	25	6	13	−7	341	15.76
Transverse temporal gyrus	L	42	−57	−13	12	1,293	13.39
Transverse temporal gyrus	R	42	59	−13	8	300	12.39
Inferior temporal gyrus	L	37	−45	−66	0	38	11.89
Middle temporal gyrus	R	39	46	−74	28	62	11.26

Coordinates are listed in Talairach and Tournoux atlas space [44]

BA the Brodmann area nearest to the coordinate and should be considered approximate

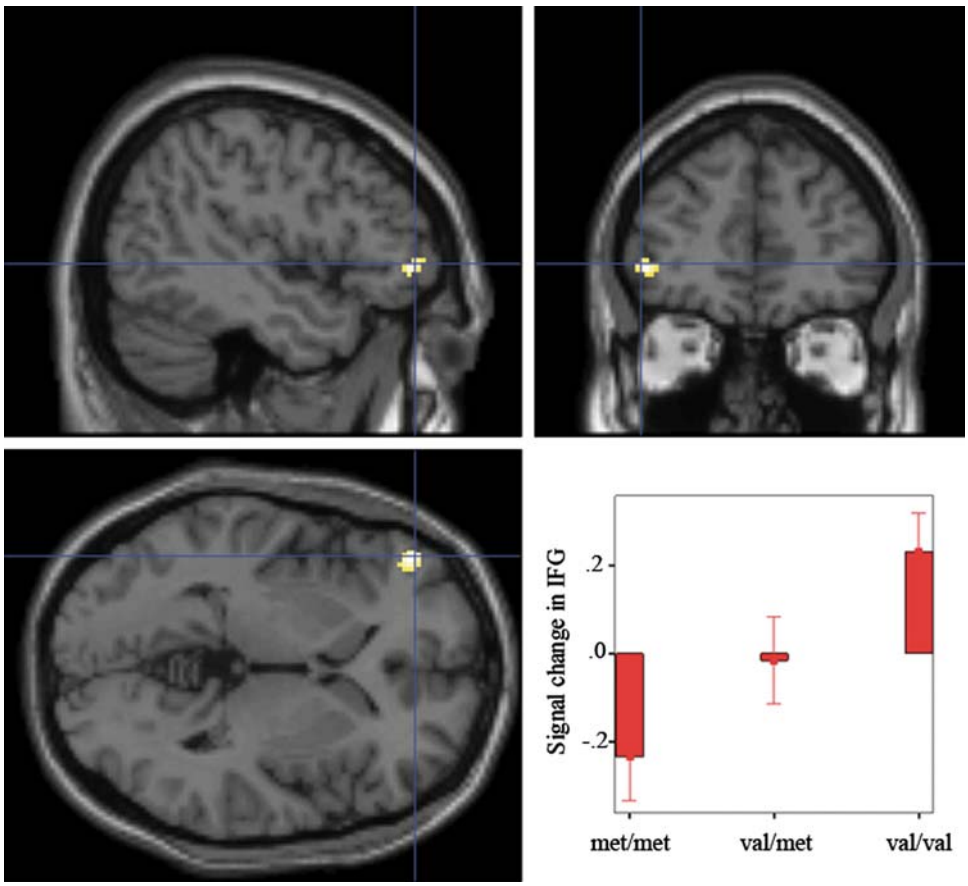

Fig. 1 Regression analysis of BOLD response (COMT met/met < val/met < val/val) for "semantic verbal fluency" > "reading aloud". During semantic verbal fluency versus reading BOLD response increased with the number of val alleles of the COMT gene in a linear fashion ($P < 0.005$, corrected by Monte Carlo simulations; cluster extend = 33 voxels). Cluster size = 45 voxels. *Bottom right* shows the parameter estimates, *error bars* represent standard mean error

has to be kept in working memory. This interpretation is supported by a number of previous functional imaging semantic verbal fluency studies, showing the involvement of this region in the task [3, 17, 48].

The influence of the val alleles on neural hyperactivations especially in frontal and prefrontal areas has been found in several studies (e.g. [18, 29, 45]). The increased activation that correlates with the increasing number of val alleles has been linked to the effects of changes in dopamine levels on the selectivity of information processing within the prefrontal cortex [6].

The linear activation increase in BA 10 with increasing number of val alleles suggests that performance in this verbal fluency task may at least in part depend on a brain area related to working memory, although (pre)frontal areas such as BA 10 have been found to be involved in verbal fluency tasks that might depend less on working memory. Our study shows implications of COMT for frontal activation in tasks other than just working memory tasks, and thus it seems that COMT influences a variety of cognitive processes that are related to the frontal lobe. As a hypothetical clinical implication, these findings might imply that patients with homozygous val alleles might benefit from pharmacologically enhanced prefrontal dopamine levels.

As these results were obtained in healthy individuals, semantic verbal fluency seems to be modulated by prefrontal levels of dopamine. This finding expands on earlier results (focusing on working memory [5, 16, 29–31]). A limitation is that our sample mainly consisted of university students. This makes generalizations on a population level more difficult, so they should be confirmed in independent samples. On the other hand, the sample is very homogenous in terms of general cognitive abilities and age.

Conclusion

In summary, we found a linear effect of COMT on brain activation during a semantic verbal fluency task in the left inferior frontal gyrus (BA 10) in a large group of healthy volunteers. The increase in BOLD response was correlated with the number of val alleles. The data point to an influence of COMT onto brain activation during semantic verbal fluency in a region that reflects executive function

and/or working memory processes during this task even though differences in activation do not necessarily surface on the behavioral level.

Acknowledgments This work was supported by the Federal Ministry of Education and Research (Brain Imaging Centre West, 01GO0204). SK and AJ are supported by The Federal Ministry of Education and Research (01GW0751).

Conflict of interest statement All authors report no conflict of interest.

References

1. Aguilera M, Barrantes-Vidal N, Arias B, Moya J, Villa H, Ibanez MI, Ruiperez MA, Ortet G, Fananas L (2008) Putative role of the COMT gene polymorphism (Val158Met) on verbal working memory functioning in a healthy population. Am J Med Genet B Neuropsychiatr Genet 147B:898–902
2. Barnett JH, Scoriels L, Munafo MR (2008) Meta-analysis of the cognitive effects of the catechol-*O*-methyltransferase gene Val158/108Met polymorphism. Biol Psychiatry 64:137–144
3. Basho S, Palmer ED, Rubio MA, Wulfeck B, Muller RA (2007) Effects of generation mode in fMRI adaptations of semantic fluency: paced production and overt speech. Neuropsychologia 45:1697–1706
4. Bertolino A, Caforio G, Blasi G, De Candia M, Latorre V, Petruzzella V, Altamura M, Nappi G, Papa S, Callicott JH, Mattay VS, Bellomo A, Scarabino T, Weinberger DR, Nardini M (2004) Interaction of COMT (Val(108/158)Met) genotype and olanzapine treatment on prefrontal cortical function in patients with schizophrenia. Am J Psychiatry 161:1798–1805
5. Bertolino A, Rubino V, Sambataro F, Blasi G, Latorre V, Fazio L, Caforio G, Petruzzella V, Kolachana B, Hariri A, Meyer-Lindenberg A, Nardini M, Weinberger DR, Scarabino T (2006) Prefrontal-hippocampal coupling during memory processing is modulated by COMT val158met genotype. Biol Psychiatry 60:1250–1258
6. Blasi G, Mattay VS, Bertolino A, Elvevag B, Callicott JH, Das S, Kolachana BS, Egan MF, Goldberg TE, Weinberger DR (2005) Effect of catechol-O-methyltransferase val158met genotype on attentional control. J Neurosci 25:5038–5045
7. Braver TS, Bongiolatti SR (2002) The role of frontopolar cortex in subgoal processing during working memory. Neuroimage 15:523–536
8. Burgess PW, Veitch E, y Costello A, Shallice T (2000) The cognitive and neuroanatomical correlates of multitasking. Neuropsychologia 38:848–863
9. Burgess PW, Quayle A, Frith CD (2001) Brain regions involved in prospective memory as determined by positron emission tomography. Neuropsychologia 39:545–555
10. Cabeza R, Nyberg L (2000) Imaging cognition II: an empirical review of 275 PET and fMRI studies. J Cogn Neurosci 12:1–47
11. Christoff K, Gabrieli JDE (2000) The frontopolar cortex and human cognition: evidence for a rostrocaudal hierarchical organization within the human prefrontal cortex. Psychobiology 28:168–186
12. Christoff K, Prabhakaran V, Dorfman J, Zhao Z, Kroger JK, Holyoak KJ, Gabrieli JD (2001) Rostrolateral prefrontal cortex involvement in relational integration during reasoning. Neuroimage 14:1136–1149
13. Drabant EM, Hariri AR, Meyer-Lindenberg A, Munoz KE, Mattay VS, Kolachana BS, Egan MF, Weinberger DR (2006) Catechol *O*-methyltransferase val158met genotype and neural mechanisms related to affective arousal and regulation. Arch Gen Psychiatry 63:1396–1406
14. Ehlis AC, Reif A, Herrmann MJ, Lesch KP, Fallgatter AJ (2007) Impact of catechol-*O*-methyltransferase on prefrontal brain functioning in schizophrenia spectrum disorders. Neuropsychopharmacology 32:162–170
15. Glatt SJ, Faraone SV, Tsuang MT (2003) Association between a functional catechol *O*-methyltransferase gene polymorphism and schizophrenia: meta-analysis of case–control and family-based studies. Am J Psychiatry 160:469–476
16. Goldberg TE, Egan MF, Gscheidle T, Coppola R, Weickert T, Kolachana BS, Goldman D, Weinberger DR (2003) Executive subprocesses in working memory: relationship to catechol-O-methyltransferase Val158Met genotype and schizophrenia. Arch Gen Psychiatry 60:889–896
17. Hirshorn EA, Thompson-Schill SL (2006) Role of the left inferior frontal gyrus in covert word retrieval: neural correlates of switching during verbal fluency. Neuropsychologia 44:2547–2557
18. Ho BC, Wassink TH, O'Leary DS, Sheffield VC, Andreasen NC (2005) Catechol-O-methyl transferase Val158Met gene polymorphism in schizophrenia: working memory, frontal lobe MRI morphology and frontal cerebral blood flow. Mol Psychiatry 10(229):287–298
19. Kircher T, Whitney C, Krings T, Huber W, Weis S (2008) Hippocampal dysfunction during free word association in male patients with schizophrenia. Schizophr Res 101:242–255
20. Koechlin E, Basso G, Pietrini P, Panzer S, Grafman J (1999) The role of the anterior prefrontal cortex in human cognition. Nature 399:148–151
21. Koechlin E, Corrado G, Pietrini P, Grafman J (2000) Dissociating the role of the medial and lateral anterior prefrontal cortex in human planning. Proc Natl Acad Sci USA 97:7651–7656
22. Kroger JK, Sabb FW, Fales CL, Bookheimer SY, Cohen MS, Holyoak KJ (2002) Recruitment of anterior dorsolateral prefrontal cortex in human reasoning: a parametric study of relational complexity. Cereb Cortex 12:477–485
23. Krug A, Markov V, Eggermann T, Krach S, Zerres K, Stocker T, Shah NJ, Schneider F, Nothen MM, Treutlein J, Rietschel M, Kircher T (2008) Genetic variation in the schizophrenia-risk gene neuregulin1 correlates with differences in frontal brain activation in a working memory task in healthy individuals. Neuroimage 42:1569–1576
24. Lehrl S, Triebig G, Fischer B (1995) Multiple choice vocabulary test MWT as a valid and short test to estimate premorbid intelligence. Acta Neurol Scand 91:335–345
25. Leung HC, Gore JC, Goldman-Rakic PS (2005) Differential anterior prefrontal activation during the recognition stage of a spatial working memory task. Cereb Cortex 15:1742–1749
26. Maier W, Hofgen B, Zobel A, Rietschel M (2005) Genetic models of schizophrenia and bipolar disorder: overlapping inheritance or discrete genotypes? Eur Arch Psychiatry Clin Neurosci 255:159–166
27. Malhotra AK, Kestler LJ, Mazzanti C, Bates JA, Goldberg T, Goldman D (2002) A functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. Am J Psychiatry 159:652–654
28. Mattay VS, Goldberg TE, Fera F, Hariri AR, Tessitore A, Egan MF, Kolachana B, Callicott JH, Weinberger DR (2003) Catechol *O*-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. Proc Natl Acad Sci USA 100:6186–6191

29. McIntosh AM, Baig BJ, Hall J, Job D, Whalley HC, Lymer GK, Moorhead TW, Owens DG, Miller P, Porteous D, Lawrie SM, Johnstone EC (2007) Relationship of catechol-*O*-methyltransferase variants to brain structure and function in a population at high risk of psychosis. Biol Psychiatry 61:1127–1134
30. Meyer-Lindenberg A, Kohn PD, Kolachana B, Kippenhan S, McInerney-Leo A, Nussbaum R, Weinberger DR, Berman KF (2005) Midbrain dopamine and prefrontal function in humans: interaction and modulation by COMT genotype. Nat Neurosci 8:594–596
31. Meyer-Lindenberg A, Nichols T, Callicott JH, Ding J, Kolachana B, Buckholtz J, Mattay VS, Egan M, Weinberger DR (2006) Impact of complex genetic variation in COMT on human brain function. Mol Psychiatry 11:867–877, 797
32. Minzenberg MJ, Xu K, Mitropoulou V, Harvey PD, Finch T, Flory JD, New AS, Goldman D, Siever LJ (2006) Catechol-*O*-methyltransferase Val158Met genotype variation is associated with prefrontal-dependent task performance in schizotypal personality disorder patients and comparison groups. Psychiatr Genet 16:117–124
33. Nunokawa A, Watanabe Y, Muratake T, Kaneko N, Koizumi M, Someya T (2007) No associations exist between five functional polymorphisms in the catechol-*O*-methyltransferase gene and schizophrenia in a Japanese population. Neurosci Res 58:291–296
34. Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9:97–113
35. Owen AM, McMillan KM, Laird AR, Bullmore E (2005) N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. Hum Brain Mapp 25:46–59
36. Ramnani N, Owen AM (2004) Anterior prefrontal cortex: insights into function from anatomy and neuroimaging. Nat Rev Neurosci 5:184–194
37. Rasser PE, Johnston P, Lagopoulos J, Ward PB, Schall U, Thienel R, Bender S, Toga AW, Thompson PM (2005) Functional MRI BOLD response to Tower of London performance of first-episode schizophrenia patients using cortical pattern matching. Neuroimage 26:941–951
38. Rosa A, Peralta V, Cuesta MJ, Zarzuela A, Serrano F, Martinez-Larrea A, Fananas L (2004) New evidence of association between COMT gene and prefrontal neurocognitive function in healthy individuals from sibling pairs discordant for psychosis. Am J Psychiatry 161:1110–1112
39. Sanders AR, Duan J, Levinson DF, Shi J, He D, Hou C, Burrell GJ, Rice JP, Nertney DA, Olincy A, Rozic P, Vinogradov S, Buccola NG, Mowry BJ, Freedman R, Amin F, Black DW, Silverman JM, Byerley WF, Crowe RR, Cloninger CR, Martinez M, Gejman PV (2008) No significant association of 14 candidate genes with schizophrenia in a large European ancestry sample: implications for psychiatric genetics. Am J Psychiatry 165:497–506
40. Schneider F, Habel U, Reske M, Kellermann T, Stocker T, Shah NJ, Zilles K, Braus DF, Schmitt A, Schlosser R, Wagner M, Frommann I, Kircher T, Rapp A, Meisenzahl E, Ufer S, Ruhrmann S, Thienel R, Sauer H, Henn FA, Gaebel W (2007) Neural correlates of working memory dysfunction in first-episode schizophrenia patients: an fMRI multi-center study. Schizophr Res 89:198–210
41. Sheldrick AJ, Krug A, Markov V, Leube D, Michel TM, Zerres K, Eggermann T, Kircher T (2008) Effect of COMT val158met genotype on cognition and personality. Eur Psychiatry 23:385–389
42. Slotnick SD, Moo LR, Segal JB, Hart J Jr (2003) Distinct prefrontal cortex activity associated with item memory and source memory for visual shapes. Brain Res Cogn Brain Res 17:75–82
43. Stefanis NC, van Os J, Avramopoulos D, Smyrnis N, Evdokimidis I, Stefanis CN (2005) Effect of COMT Val158Met polymorphism on the continuous performance test, identical pairs version: tuning rather than improving performance. Am J Psychiatry 162:1752–1754
44. Talairach J, Tournoux P (1988) Co-planar stereotaxic atlas of the human brain. Thieme, New York
45. Tan HY, Chen Q, Goldberg TE, Mattay VS, Meyer-Lindenberg A, Weinberger DR, Callicott JH (2007) Catechol-*O*-methyltransferase Val158Met modulation of prefrontal-parietal-striatal brain systems during arithmetic and temporal transformations in working memory. J Neurosci 27:13393–13401
46. Wagner AD, Desmond JE, Glover GH, Gabrieli JD (1998) Prefrontal cortex and recognition memory. Functional-MRI evidence for context-dependent retrieval processes. Brain 121 (Pt 10): 1985–2002
47. Walter H, Vasic N, Hose A, Spitzer M, Wolf RC (2007) Working memory dysfunction in schizophrenia compared to healthy controls and patients with depression: evidence from event-related fMRI. Neuroimage 35:1551–1561
48. Whitney C, Weis S, Krings T, Huber W, Kircher T (2009) Task-dependent Modulations of prefrontal and hippocampal activity during intrinsic word production. J Cogn Neurosci 4:697–712
49. Williams HJ, Glaser B, Williams NM, Norton N, Zammit S, MacGregor S, Kirov GK, Owen MJ, O'Donovan MC (2005) No association between schizophrenia and polymorphisms in COMT in two large samples. Am J Psychiatry 162:1736–1738
50. Wonodi I, Stine OC, Mitchell BD, Buchanan RW, Thaker GK (2003) Association between Val108/158 Met polymorphism of the COMT gene and schizophrenia. Am J Med Genet B Neuropsychiatr Genet 120B:47–50