Published in final edited form as:

Behav Neurosci. 2012 February ; 126(1): 209–215. doi:10.1037/a0026466.

Effects of the Val(158)Met catechol-O-methyltransferase gene polymorphism on olfactory processing in schizophrenia

Vidyulata Kamath^{a,b,*}, Paul J. Moberg^{a,b}, Raquel E. Gur^{a,c}, Richard L. Doty^b, and Bruce I. Turetsky^{a,b}

^aNeuropsychiatry Division, Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

^bSmell and Taste Center, Department of Otorhinolaryngology: Head & Neck Surgery, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

^cDepartment of Radiology, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Abstract

The catechol-O-methyltransferase (*COMT*) val158met polymorphism has received attention in schizophrenia due to its role in prefrontal dopamine catabolism. Given the rich dopaminergic innervations of the olfactory bulb and the influence of dopamine on the transmission of olfactory signals, we examined the influence of *COMT* genotype status on the olfactory processing impairment observed in schizophrenia. The University of Pennsylvania Smell Identification Test was administered unilaterally to individuals with schizophrenia ($n = 42$) and a demographically-matched sample of healthy controls ($n = 30$). Individuals were genotyped for the *COMT* val158met polymorphism. A statistically significant interaction of diagnosis and *COMT* genotype was observed, such that schizophrenia heterozygotes and Met homozygotes showed impaired odor identification accuracy relative to Val158 homozygotes. These findings could not be explained by factors such as antipsychotic medication status, clinical symptomatology, or demographic and illness characteristics. Notably, the schizophrenia Val158 homozygotes' odor identification performance was comparable to that of the control group. These data indicate that odor identification impairments observed in schizophrenia are influenced by the *COMT* val158met polymorphism. This relationship is consistent with specific dopaminergic modulation of primary olfactory sensory afferents, rather than a broader effect on cognitive processes. Future studies examining the olfactory processing deficit in schizophrenia with respect to other olfactory measures and *COMT* haplotypes is warranted.

Keywords

dopamine; olfaction; smell; *COMT*; genetics

*Correspondence to: Vidya Kamath, Ph.D., Neuropsychiatry Section, Department of Psychiatry, University of Pennsylvania Medical Center, 3400 Spruce Street, 10th Floor – Gates Building, Philadelphia, PA 19104. Telephone: 011.1.215.839.9193 Fax: 011.1.215.662.7903 kamathv@upenn.edu.

Publisher's Disclaimer: The following manuscript is the final accepted manuscript. It has not been subjected to the final copyediting, fact-checking, and proofreading required for formal publication. It is not the definitive, publisher-authenticated version. The American Psychological Association and its Council of Editors disclaim any responsibility or liabilities for errors or omissions of this manuscript version, any version derived from this manuscript by NIH, or other third parties. The published version is available at www.apa.org/pubs/journals/bne

1. Introduction

Disruptions in prefrontal circuitry and dopamine (DA) neurotransmission are often regarded as central to the neuropathophysiology and cognitive dysfunction observed in schizophrenia (Tan, Callicott, & Weinberger, 2007). Olfactory brain regions, medially located within the prefrontal cortex, are significantly affected by genetically-mediated neurodevelopmental processes (Anholt & Mackay, 2010; Rawson et al., 2010), and evidence from the extant human and animal literature has indicated an extensive role for DA in olfactory processing. Dopaminergic neurons are abundant within the olfactory bulb (OB), with greater density observed in the glomerular, mitral and granular cell layers of the OB than in the midbrain substantia nigra and ventral tegmentum combined (McLean & Shipley, 1988; Skagerberg, Lindvall, & Bjorklund, 1984). DA neurotransmission is thought to play a central role in olfactory neurogenesis and olfactory bulb development (Feron, Vincent, & Mackay-Sim, 1999). The synaptic organization, neural circuitry, and biochemistry of the olfactory system may, therefore, provide a unique model with which to investigate the effects of altered DA-mediated processes in schizophrenia.

Catechol-O-methyltransferase (*COMT*) located on chromosome 22q11.2 is one candidate gene for schizophrenia that has received widespread attention due to its role in prefrontal dopamine degradation. A relatively common deletion at chromosome 22q11.2, encompassing the entire *COMT* gene, is responsible for DiGeorge Syndrome (also known as velocardiofacial syndrome or VCFS), which manifests in adults with a high prevalence of a schizophrenia-like psychosis (Murphy, 2002). Consistent with this, genome-wide scans of rare copy number variants (CNVs) have revealed that microdeletions at chromosome 22q11.2 confer significant risk for schizophrenia (Karayiorgou et al., 1995; Levinson et al., 2011; Vacic et al., 2011). A common functional polymorphism of the *COMT* gene consists of a guanine to adenine transition at codon 158 in the membrane-bound isoform of the enzyme and at codon 108 in the short soluble form, which results in a valine (Val) to methionine (Met) amino acid mutation. The higher thermostability of the Val allele results in a four-fold increase in the rate of dopamine catabolism and significantly lower synaptic dopamine levels, compared to the thermolabile Met allele (Lachman et al., 1996). Mounting evidence from neuropsychological, structural and functional imaging studies have indicated that this biallelic single nucleotide polymorphism influences the cognitive and emotional disturbances seen in the illness. Though the nature of these impairments have been debated, there is general consensus that the Val allele is associated with greater working memory dysfunction, while the Met allele is associated with increased treatment resistance and limbic dysfunction (for a review, see: Bilder, Volavka, Lachman, & Grace, 2004).

Schizophrenia patients have marked olfactory deficits which are pervasive, observed across the lifespan and are independent of antipsychotic medication effects (Brewer et al., 2001; Moberg, Roalf, Gur, & Turetsky, 2004). Furthermore, olfactory impairment is often associated with increased negative symptomatology (Ishizuka et al., 2010) and is prevalent in individuals with deficit-syndrome schizophrenia (Malaspina et al., 2002). Thus, it is reasonable to consider whether the olfactory abnormalities observed in schizophrenia might also be related to abnormalities in the genetic mediation of dopamine catabolism. Prior studies have shown that individuals with 22q deletion syndrome are impaired on measures of odor identification, odor discrimination and olfactory sensitivity compared to healthy controls (Romanos et al., 2011; Sobin et al., 2006). Bassett and colleagues (2007) similarly examined birhinal odor identification performance in Met and Val hemizygotes with 22q deletion syndrome. Met hemizygotes had more pronounced odor identification impairment compared to Val hemizygotes. Based on these findings, it is likely that variations in the *COMT* genotype might similarly influence the olfactory processing deficits observed in patients with schizophrenia. However, this question has not been addressed previously.

2. Methods

2.1 Participants

Schizophrenia patients ($n = 42$) and healthy adults ($n = 30$) were recruited to the Schizophrenia Research Center at the University of Pennsylvania Medical Center. Following a full explanation of study procedures, written informed consent was obtained in compliance with guidelines established by the University of Pennsylvania Institutional Review Board and in accordance with The Code of Ethics of the World Medical Association (1964 Declaration of Helsinki). Patients were administered the Diagnostic Interview for Genetic Studies (DIGS; Nurnberger et al., 1994) or the Structured Clinical Interview for DSM-IV - Patient Edition (SCID; First, Spitzer, Gibbon, & Williams, 1996) and consensus DSM-IV-TR (American Psychiatric Association, 2000) diagnoses for schizophrenia were established. Healthy individuals were screened for Axis I Disorders using the SCID – Nonpatient Edition (First, Spitzer, Gibbon, & Williams, 1995). Controls were excluded for any history of Axis I psychiatric illness, Axis II diagnosis of schizotypal, schizoid or paranoid personality disorder, or a positive family history of schizophrenia or schizophrenia-spectrum disorder. Additional exclusion criteria for all groups included lack of English proficiency, a history of central nervous disease or head trauma with loss of consciousness, past substance dependence, current substance abuse within the preceding six months, or medical conditions affecting cerebral or olfactory functioning (e.g., sinusitis, nasal fracture/surgery, deviated septum, common cold).

In patients, clinical status was assessed using the Brief Psychiatric Rating Scale (BPRS; Rhoades & Overall, 1988) and the Scales for the Assessment of Negative Symptoms (SANS; Andreasen, 1984a) and Positive Symptoms (SAPS; Andreasen, 1984b). Medication status of schizophrenia patients was as follows: 1 was unmedicated, 9 were taking first generation antipsychotic medication, 23 were taking second generation antipsychotic medication (of which 1 individual was also on a mood-stabilizer), and 8 were not on an antipsychotic medication but were taking another psychotropic or anticholinergic agent at the time of testing. Medication data for 1 individual was unavailable. Sample characteristics are presented in Table 1.

2.2 COMT Genotyping

Genotyping was performed at the Molecular Diagnosis and Genotyping Core of the Hospital of the University of Pennsylvania. Participants were genotyped for the *COMT* val158met polymorphism (rs4680) using TaqMan® based assays-on-demand (Assay ID: C__25746809_50) from Applied Biosystems Inc., Foster City, CA, USA.

2.3 Olfactory assessment

Odor identification ability was assessed with the University of Pennsylvania Smell Identification Test (UPSIT; Doty, Shaman, & Dann, 1984). The UPSIT is a standardized, four-alternative, forced-choice test of olfactory identification comprised of four booklets containing 40 stimuli embedded in “scratch and sniff” microcapsules fixed and positioned on strips at the bottom of each page. The specific stimuli and the reliability and sensitivity of this test have been described in detail elsewhere (Doty, Frye, & Agrawal, 1989; Doty, et al., 1984). The UPSIT was administered to each participant unilaterally (each naris separately) with the contralateral naris occluded using a piece of Durapore™ tape (3M Corporation, Minneapolis, MN) fitted tightly over the edges of the naris. This procedure is employed in order to isolate the naris being examined and limits retronasal airflow (Bromley & Doty, 1995). A trained technician released the microencapsulated stimuli, placed them under the participant’s unoccluded nare, and recorded the answer following the subject’s response. Two booklets of 20 items were presented to the right naris and the remaining two booklets

were presented to the left naris. Booklet order and naris presentation were systematically counterbalanced to avoid position effects.

Following UPSIT administration, participants were given the Picture Identification Test (PIT; Vollmecke, 1985). The PIT is identical to the UPSIT in item composition and response characteristics except that line drawings are presented instead of odors. This test was designed as a companion to the UPSIT to screen for individuals with gross cognitive deficits that might confound UPSIT scores.

2.4 Statistical Analysis

An analysis of variance (ANOVA) was conducted to examine group differences in age, education, parental education, PIT scores, and smoking pack-days within and between schizophrenia and control groups. Pearson chi-square tests were conducted to examine differences in sex and racial distribution. In patients, additional ANOVAs were performed to examine differences in schizophrenia symptomatology and illness characteristics. Overall group differences in picture and odor identification performance were assessed using an ANOVA, with group (patient, control) and *COMT* genotype (Val/Val, Val/Met, Met/Met) as between-group factors. Naris (right, left) was included as the within-group factor for olfactory analysis.

3. Results

3.1 Demographic characteristics and genotype frequency

Patient and controls did not differ significantly with respect to age ($F_{1,70} = 2.85, p = .10$), sex composition ($\chi^2(1) = 0.20, p = .66$), or racial distribution ($\chi^2(2) = 3.64, p = .16$). As expected, controls had a significantly higher level of educational attainment compared to patients ($F_{1,70} = 15.82, p < .001$), though groups did not differ with regard to parental educational (Wilks' $F_{2,62} = 0.06, p = .94$). Patients and controls did not differ with respect to smoking burden (as quantified by pack-days) ($F_{1,65} = 1.01, p = .32$).

The distribution of genotypes was consistent with Hardy-Weinberg equilibrium expectations in both patients ($\chi^2(1) = 1.22, p = .27$) and controls ($\chi^2(1) = 1.16, p = .28$) and did not differ between groups ($\chi^2(2) = 1.47, p = .48$). Within the patient cohort, the Val/Val, Val/Met, and Met/Met groups did not differ with respect to age ($F_{2,39} = 0.21, p = .81$), race ($\chi^2(2) = 3.52, p = .17$), education ($F_{2,39} = 0.52, p = .60$), pack-days ($F_{2,39} = 0.68, p = .51$), antipsychotic medication dosage ($F_{2,38} = 0.59, p = .56$), age of onset ($F_{2,38} = 0.20, p = .82$), illness duration ($F_{2,38} = 1.71, p = .19$), general psychiatric symptoms ($F_{2,37} = 0.67, p = .52$), negative symptoms ($F_{2,39} = 0.60, p = .55$), or positive symptoms ($F_{2,39} = 0.53, p = .59$). Groups did differ with respect to sex composition ($\chi^2(2) = 7.39, p = .02$); a higher proportion of males were represented in the Val/Met group (81.3%) compared to the Met/Met (42.9%) and Val/Val group (36.8%). Within controls, the Val/Val, Val/Met, and Met/Met groups did not differ with respect to age ($F_{2,27} = 0.63, p = .54$), sex ($\chi^2(2) = 2.33, p = .31$), race ($\chi^2(2) = 1.26, p = .53$), education ($F_{2,27} = 1.47, p = .25$), or pack-days ($F_{2,22} = 1.88, p = .18$).

3.2 Picture Identification Performance by *COMT* Genotype

There was no statistically significant group difference ($F_{1,60} = 0.21, p = .65$) or interaction of *COMT* genotype by group ($F_{2,60} = .16, p = .85$; see Figure 1) on picture identification scores. Within the patient group, the main effect of *COMT* status was not statistically significant ($F_{2,36} = .16, p = .85$); inclusion of sex as a covariate did not alter these findings ($F_{2,35} = .05, p = .95$).

3.3 Odor Identification Performance by COMT Genotype

Consistent with previous findings, there was a highly significant main effect of diagnosis on olfactory identification performance ($F_{1,66} = 23.76, p < .00001$), with patients performing worse than controls. However, a statistically significant interaction of *COMT* genotype and group was also observed ($F_{2,66} = 5.20, p < .01$). Notably, schizophrenia Val¹⁵⁸ homozygotes were indistinguishable from Val¹⁵⁸ homozygote controls ($F_{1,66} = 0.12, p = .73$) at identifying odors. Val¹⁵⁸Met heterozygote patients ($F_{1,66} = 17.46, p < .0001$) and Met¹⁵⁸ homozygote patients ($F_{1,66} = 14.00, p < .001$) were significantly impaired at identifying odors relative to their control counterparts (see Figure 1). There were no significant main or interaction effects of naris (all p 's $> .32$). Inclusion of sex and smoking burden as covariates did not alter the significant effects observed. Exclusion of the 8 patients not actively taking antipsychotic medications also did not alter the observed effects.

Post-hoc paired comparisons of odor identification scores by *COMT* genotype within the patient group revealed that Val¹⁵⁸ homozygote schizophrenia patients made significantly fewer errors across both nares compared to both Met¹⁵⁸ homozygote ($F_{1,39} = 7.07, p = .01$) and Val¹⁵⁸Met heterozygote patients ($F_{1,39} = 14.81, p < .001$). These results remained statistically significant after including sex and antipsychotic medication dosage as covariates in the analysis. Odor identification scores in the control group did not differ significantly by *COMT* genotype (all p 's $> .26$).

4. Discussion

The results of our investigation replicate the well-documented observation of odor identification impairment in schizophrenia, and further suggest that this deficit is influenced by *COMT* genotype status. Notably, we found that schizophrenia patients with a Met allele were impaired at identifying odors relative to both Val¹⁵⁸ homozygote patients and controls regardless of genotype. Val¹⁵⁸ homozygote patients' performance was comparable to healthy controls. This performance dissociation observed across patient subgroups could not be explained by factors such as antipsychotic medication status, clinical symptomatology, or demographic and illness characteristics. As the Met allele is associated with decreased dopamine catabolism, and therefore higher PFC dopamine levels, these findings raise the possibility that lower *COMT* activity contributes to increased olfactory impairment in schizophrenia.

COMT has been investigated extensively in schizophrenia due to its location on chromosome 22q, where a deletion encompassing the *COMT* gene results in the development of VCFS, a disorder associated with a high prevalence of schizophrenia-like psychotic symptoms (Murphy, 2002). VCFS is characterized by cardiovascular and craniofacial dysmorphology, as well as olfactory impairment (Romanos, et al., 2011). Individuals with schizophrenia have similarly shown minor midline physical anomalies (e.g., increased palate height, cleft palate; O'Callaghan, Larkin, Kinsella, & Waddington, 1991), as well as abnormalities on structural and functional olfactory indices (Moberg et al., 2006; Moberg, et al., 2004; Turetsky, Crutchley, Walker, Gur, & Moberg, 2009; Turetsky et al., 2007; Turetsky et al., 2000). Notably, the face, olfactory structures, and forebrain develop embryologically in close association with each other (Carstens, 2002; Diewert, Lozanoff, & Choy, 1993), and these early morphogenetic processes are affected in a dose-related fashion to diminished 22q11 genes (Meechan, Maynard, Tucker, & LaMantia, 2011; Meechan, Tucker, Maynard, & LaMantia, 2009). Thus, it is plausible that genetic disruption influences neurogenesis and, in turn, contributes to the observed abnormalities in the structure and function of olfactory regions observed in both schizophrenia and VCFS.

Alternatively, dopaminergic transmission in the prefrontal cortex may influence olfactory signal transduction. Olfactory receptor neurons (ORN) embedded in the nasal epithelium transduce and relay odor signals to the olfactory bulb (OB). Within the OB, the ORNs arborize within the glomeruli and terminate on mitral and tufted cell dendrites. It is here that the first point of olfactory information integration is initiated (for a review, see: Wachowiak & Shipley, 2006). In the glomerular layer, dopamine D2 receptors are highly expressed in juxtaglomerular neurons, which are involved in lateral inhibitory interactions within and between glomeruli. Though it is not entirely clear how dopamine influences transmission of olfactory signals, evidence from the extant animal literature indicates that dopamine suppresses the transmission of olfactory signals at the level of the OB via presynaptic action on ORN terminals (Berkowicz & Trombley, 2000; Ennis et al., 2001). Dopamine receptor agonists disrupt odor-induced metabolic activity in the OB glomeruli (Sallaz & Jourdan, 1992), reduce ORN to mitral cell synaptic transmission (Hsia, Vincent, & Lledo, 1999), and impair odor detection ability (Doty & Risser, 1989). These disruptive effects appear to be mediated specifically through D2 receptors, as they can be blocked by pre-treatment with selective D2 antagonists (Doty & Risser, 1989). In humans, the indirect dopamine receptor agonist, methylphenidate, has been shown to negatively affect olfactory performance. Children with attention-deficit/hyperactivity disorder (ADHD) exhibit enhanced abilities to detect and discriminate between odors, relative to healthy children, but this is attenuated following treatment with methylphenidate (Romanos et al., 2008; Schecklmann et al., 2011). Also, post-mortem studies of patients with Parkinson's disease show a 100% increase in dopaminergic neurons in the olfactory bulb (Huisman, Uylings, & Hoogland, 2004). This dopaminergic increase was theorized to explain the olfactory impairment well-described in the illness.

In the current study, Val¹⁵⁸ homozygote schizophrenia patients, who presumably have reduced levels of available dopamine, were significantly better at identifying odors compared to Met homozygotes. This is consistent with findings in VCFS patients (Bassett, et al., 2007) and with available research on the role of dopamine in olfactory processing. However, several studies examining correlates of the *COMT* val158met polymorphism in schizophrenia have found that the Val/Val genotype is generally associated with poorer performance on cognitive tasks reflecting prefrontal cortical activity (for a review, see: Kurnianingsih et al., 2011). Since accurate odor identification involves accessing the necessary verbal information from semantic stores, the task is thought to rely partly on verbal and executive functions (Hedner, Larsson, Arnold, Zucco, & Hummel, 2010) and we might therefore expect the Val¹⁵⁸ homozygote patients to perform worse, rather than better. That this was not the case suggests that decreased prefrontal dopamine levels do not interfere with the verbal and executive components of odor identification performance in patients. This hypothesis is further supported by the finding that picture identification scores did not differ by group or *COMT* genotype status. Rather, it strongly suggests that the effect of the val158met polymorphism is a direct reflection of altered dopamine levels within the afferent olfactory neurocircuitry. It also implies that olfactory impairment in schizophrenia is not a byproduct of antipsychotic medications. Based on these findings, treatment with antipsychotic medications might actually enhance olfactory performance.

It is important to also note that the effect of the val158met polymorphism on olfactory performance was not observed in our healthy control sample. The reason for this is unclear. It may be that healthy subjects have sufficient olfactory reserve capacity, such that the lower dopamine levels associated with Val¹⁵⁸ homozygote status does not result in impaired performance. Alternatively, the impact of the polymorphism may only manifest itself in the broader context of appropriate gene-gene or gene-environment interactions that exert a greater effect on olfactory function (Wishart et al., 2011). So, for example, altered dopaminergic modulation coupled with altered excitatory glutamate transmission could

result in an observable deficit (e.g., Vorstman et al., 2009). Addressing the question of such interactions, however, requires much larger samples than those available for this study.

Several other limitations must be noted. The current study only employed one behavioral measure of olfactory processing. Odor identification tasks, like the one used here, are considered the most highly standardized and reliable of psychophysical olfactory processing measures in humans. Other olfactory measures, such as odor detection threshold and odor discrimination, typically load on one broad olfactory domain with odor identification (Doty, Smith, McKeown, & Raj, 1994). Nevertheless, studies like the aforementioned investigations by Romanos et al. (2008) and Schecklmann et al. (2011) have shown that methylphenidate differentially affects some aspects of olfactory performance, but not others. Thus, certain olfactory measures may be more sensitive to the influence of dopamine on odor processing despite sharing a common source of variance in the overall olfactory domain. Use of a broader olfactory battery would therefore be of interest in future studies. It would also be useful to examine the extent to which other structural and functional olfactory measures shown to be abnormal in schizophrenia (e.g., posterior nasal volume, olfactory sulcus depth, olfactory bulb volume, and olfactory event-related potentials) are influenced by *COMT* genotype status. Finally, as noted above, multiple gene interactions across multiple neural networks are tied to dopamine and olfactory processing in schizophrenia. While the current findings provide strong inferential support, replication and inclusion of additional functional *COMT* haplotypes and the examination of other candidate schizophrenia genes will be necessary to determine the extent to which the current findings are unique to the *COMT* val158met polymorphism.

Few studies have examined how olfactory deficits relate to current neurochemical or genetic theories of schizophrenia. The results of the current study suggest that odor identification impairment may be influenced, in part, by functional dopaminergic activity. Neuroimaging, genetic, neuropsychological, and animal studies converge in suggesting an important role of dopamine in olfactory processing. This finding is consistent with prior studies in individuals with VCFS and provides the impetus for future studies examining the role of genetic polymorphisms on olfactory performance in schizophrenia and other neuropsychiatric illnesses.

Acknowledgments

This study was funded in part by National Institutes of Health Grants MH63381 to Dr. Moberg, MH59852 to Dr. Turetsky, and an Independent Investigator Award from the Brain Behavior Research Foundation (awarding NARSAD grants) to Dr. Moberg. The funding source had no role in the study design, collection, analysis, or interpretation of this data or writing of this manuscript. The authors thank Stephen J. Kanes, M.D., Ph.D. for facilitating acquisition of the genotyping data and the Hoffman Trust for their support of this research through NARSAD.

References

- American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4. Washington, DC: Author; 2000. text revision
- Andreasen, NC. The Scale for the Assessment of Negative Symptoms (SANS). Iowa City, IA: The University of Iowa; 1984a.
- Andreasen, NC. The Scale for the Assessment of Positive Symptoms (SAPS). Iowa City, IA: The University of Iowa; 1984b.
- Anholt, RRH.; Mackay, TFC. Principles of behavioral genetics. Amsterdam: Academic; 2010. Genetics of Olfaction and Taste; p. 207-230.
- Bassett AS, Caluseriu O, Weksberg R, Young DA, Chow EW. Catechol-O-methyl transferase and expression of schizophrenia in 73 adults with 22q11 deletion syndrome. *Biol Psychiatry*. 2007; 61(10):1135–1140. [PubMed: 17217925]

- Berkowicz DA, Trombley PQ. Dopaminergic modulation at the olfactory nerve synapse. *Brain Res.* 2000; 855(1):90–99. [PubMed: 10650134]
- Bilder RM, Volavka J, Lachman HM, Grace AA. The catechol-O-methyltransferase polymorphism: Relations to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes. *Neuropsychopharmacology.* 2004; 29(11):1943–1961. [PubMed: 15305167]
- Brewer WJ, Pantelis C, Anderson V, Velakoulis D, Singh B, Copolov D, et al. Stability of olfactory identification deficits in neuroleptic-naïve patients with first-episode psychosis. *Am J Psychiatry.* 2001; 158:107–115. [PubMed: 11136641]
- Bromley SM, Doty RL. Odor recognition memory is better under bilateral than unilateral test conditions. *Cortex.* 1995; 31(1):25–40. [PubMed: 7781318]
- Carstens MH. Development of the facial midline. *J Craniofac Surg.* 2002; 13(1):129–187. [PubMed: 11887012]
- Diewert VM, Lozanoff S, Choy V. Computer reconstructions of human embryonic craniofacial morphology showing changes in relations between the face and brain during primary palate formation. *J Craniofac Genet Dev Biol.* 1993; 13(3):193–201. [PubMed: 8227291]
- Doty RL, Frye RE, Agrawal U. Internal consistency reliability of the fractionated and whole University of Pennsylvania Smell Identification Test. *Percept Psychophys.* 1989; 45(5):381–384. [PubMed: 2726398]
- Doty RL, Risser JM. Influence of the D-2 dopamine receptor agonist quinpirole on the odor detection performance of rats before and after spiperone administration. *Psychopharmacology (Berl).* 1989; 98(3):310–315. [PubMed: 2568654]
- Doty RL, Shaman P, Dann M. Development of the University of Pennsylvania Smell Identification Test: A standardized microencapsulated test of olfactory function. *Physiol Behav.* 1984; 32(3):489–502. [PubMed: 6463130]
- Doty RL, Smith R, McKeown DA, Raj J. Tests of human olfactory function: Principal components analysis suggests that most measure a common source of variance. *Percept Psychophys.* 1994; 56(6):701–707. [PubMed: 7816540]
- Ennis M, Zhou FM, Ciombor KJ, Aroniadou-Anderjaska V, Hayar A, Borrelli E, et al. Dopamine D2 receptor-mediated presynaptic inhibition of olfactory nerve terminals. *J Neurophysiol.* 2001; 86(6):2986–2997. [PubMed: 11731555]
- Feron F, Vincent A, Mackay-Sim A. Dopamine promotes differentiation of olfactory neuron in vitro. *Brain Res.* 1999; 845(2):252–259. [PubMed: 10536207]
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM-IV - Nonpatient Edition (SCID-NP, Version 2.0). New York: New York State Psychiatric Institute; 1995.
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM-IV - Patient Edition (SCID-P, Version 2.0). New York: New York State Psychiatric Institute; 1996.
- Hedner M, Larsson M, Arnold N, Zucco GM, Hummel T. Cognitive factors in odor detection, odor discrimination, and odor identification tasks. *J Clin Exp Neuropsychol.* 2010; 32(10):1062–1067. [PubMed: 20437286]
- Hsia AY, Vincent JD, Lledo PM. Dopamine depresses synaptic inputs into the olfactory bulb. *J Neurophysiol.* 1999; 82(2):1082–1085. [PubMed: 10444702]
- Huisman E, Uylings HB, Hoogland PV. A 100% increase of dopaminergic cells in the olfactory bulb may explain hyposmia in Parkinson's disease. *Mov Disord.* 2004; 19(6):687–692. [PubMed: 15197709]
- Ishizuka K, Tajinda K, Colantuoni C, Morita M, Winicki J, Le C, et al. Negative symptoms of schizophrenia correlate with impairment on the University of Pennsylvania smell identification test. *Neurosci Res.* 2010; 66(1):106–110. [PubMed: 19819272]
- Karayorgou M, Morris MA, Morrow B, Shprintzen RJ, Goldberg R, Borrow J, et al. Schizophrenia susceptibility associated with interstitial deletions of chromosome 22q11. *Proc Natl Acad Sci U S A.* 1995; 92(17):7612–7616. [PubMed: 7644464]
- Kurnianingsih YA, Kuswanto CN, McIntyre RS, Qiu A, Ho BC, Sim K. Neurocognitive-genetic and neuroimaging-genetic research paradigms in schizophrenia and bipolar disorder. *J Neural Transm.* 2011

- Lachman HM, Papolos DF, Saito T, Yu YM, Szumlanski CL, Weinshilboum RM. Human catechol-O-methyltransferase pharmacogenetics: Description of a functional polymorphism and its potential application to neuropsychiatric disorders. *Pharmacogenetics*. 1996; 6(3):243–250. [PubMed: 8807664]
- Levinson DF, Duan J, Oh S, Wang K, Sanders AR, Shi J, et al. Copy number variants in schizophrenia: Confirmation of five previous findings and new evidence for 3q29 microdeletions and VIPR2 duplications. *Am J Psychiatry*. 2011; 168(3):302–316. [PubMed: 21285140]
- Malaspina D, Coleman E, Goetz RR, Harkavy-Friedman J, Corcoran C, Amador X, et al. Odor identification, eye tracking and deficit syndrome schizophrenia. *Biol Psychiatry*. 2002; 51(10):809–815. [PubMed: 12007455]
- McLean JH, Shipley MT. Postmitotic, postmigrational expression of tyrosine hydroxylase in olfactory bulb dopaminergic neurons. *J Neurosci*. 1988; 8(10):3658–3669. [PubMed: 2461434]
- Meechan DW, Maynard TM, Tucker ES, LaMantia AS. Three phases of DiGeorge/22q11 deletion syndrome pathogenesis during brain development: patterning, proliferation, and mitochondrial functions of 22q11 genes. *Int J Dev Neurosci*. 2011; 29(3):283–294. [PubMed: 20833244]
- Meechan DW, Tucker ES, Maynard TM, LaMantia AS. Diminished dosage of 22q11 genes disrupts neurogenesis and cortical development in a mouse model of 22q11 deletion/DiGeorge syndrome. *Proc Natl Acad Sci U S A*. 2009; 106(38):16434–16445. [PubMed: 19805316]
- Moberg PJ, Arnold SE, Doty RL, Gur RE, Balderston CC, Roalf DR, et al. Olfactory functioning in schizophrenia: Relationship to clinical, neuropsychological, and volumetric MRI measures. *J Clin Exp Neuropsychol*. 2006; 28(8):1444–1461. [PubMed: 17050269]
- Moberg PJ, Roalf DR, Gur RE, Turetsky BI. Smaller nasal volumes as stigmata of aberrant neurodevelopment in schizophrenia. *Am J Psychiatry*. 2004; 161(12):2314–2316. [PubMed: 15569907]
- Murphy KC. Schizophrenia and velo-cardio-facial syndrome. *Lancet*. 2002; 359(9304):426–430. [PubMed: 11844533]
- Nurnberger JI Jr, Blehar MC, Kaufmann CA, York-Cooler C, Simpson SG, Harkavy-Friedman J, et al. Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative. *Arch Gen Psychiatry*. 1994; 51(11):849–859. discussion 863–844. [PubMed: 7944874]
- O'Callaghan E, Larkin C, Kinsella A, Waddington JL. Familial, obstetric, and other clinical correlates of minor physical anomalies in schizophrenia. *Am J Psychiatry*. 1991; 148(4):479–483. [PubMed: 2006694]
- Rawson NE, Lischka FW, Yee KK, Peters AZ, Tucker ES, Meechan DW, et al. Specific mesenchymal/epithelial induction of olfactory receptor, vomeronasal, and gonadotropin-releasing hormone (GnRH) neurons. *Dev Dyn*. 2010; 239(6):1723–1738. [PubMed: 20503368]
- Rhoades HM, Overall JE. The semistructured BPRS interview and rating guide. *Psychopharmacol Bull*. 1988; 24(1):101–104. [PubMed: 3290934]
- Romanos M, Renner TJ, Schecklmann M, Hummel B, Roos M, von Mering C, et al. Improved odor sensitivity in attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2008; 64(11):938–940. [PubMed: 18814862]
- Romanos M, Schecklmann M, Kraus K, Fallgatter AJ, Warnke A, Lesch KP, et al. Olfactory deficits in deletion syndrome 22q11.2. *Schizophr Res*. 2011; 129:220–221. [PubMed: 21282042]
- Sallaz M, Jourdan F. Apomorphine disrupts odour-induced patterns of glomerular activation in the olfactory bulb. *Neuroreport*. 1992; 3(10):833–836. [PubMed: 1421083]
- Schecklmann M, Schaldecker M, Aucktor S, Brast J, Kirchgassner K, Muhlberger A, et al. Effects of methylphenidate on olfaction and frontal and temporal brain oxygenation in children with ADHD. *J Psychiatr Res*. 2011
- Skagerberg G, Lindvall O, Bjorklund A. Origin, course and termination of the mesohabenular dopamine pathway in the rat. *Brain Res*. 1984; 307(1-2):99–108. [PubMed: 6087992]
- Sobin C, Kiley-Brabeck K, Dale K, Monk SH, Khuri J, Karayiorgou M. Olfactory disorder in children with 22q11 deletion syndrome. *Pediatrics*. 2006; 118(3):e697–703. [PubMed: 16908619]
- Tan HY, Callicott JH, Weinberger DR. Dysfunctional and compensatory prefrontal cortical systems, genes and the pathogenesis of schizophrenia. *Cereb Cortex*. 2007; 17(Suppl 1):i171–181. [PubMed: 17726000]

- Turetsky BI, Crutchley P, Walker J, Gur RE, Moberg PJ. Depth of the olfactory sulcus: A marker of early embryonic disruption in schizophrenia? *Schizophr Res.* 2009; 115(1):8–11. [PubMed: 19767178]
- Turetsky BI, Glass CA, Abbazia J, Kohler CG, Gur RE, Moberg PJ. Reduced posterior nasal cavity volume: A gender-specific neurodevelopmental abnormality in schizophrenia. *Schizophr Res.* 2007
- Turetsky BI, Moberg PJ, Yousem DM, Doty RL, Arnold SE, Gur RE. Reduced olfactory bulb volume in patients with schizophrenia. *Am J Psychiatry.* 2000; 157(5):828–830. [PubMed: 10784482]
- Vacic V, McCarthy S, Malhotra D, Murray F, Chou HH, Peoples A, et al. Duplications of the neuropeptide receptor gene VIPR2 confer significant risk for schizophrenia. *Nature.* 2011; 471(7339):499–503. [PubMed: 21346763]
- Vollmecke T, Doty RL. Development of the Picture Identification Test (PIT): A research companion to the University of Pennsylvania Smell Identification Test. *Chem Senses.* 1985; 10:413–414.
- Vorstman JA, Turetsky BI, Sijmens-Morcus ME, de Sain MG, Dorland B, Sprong M, et al. Proline affects brain function in 22q11DS children with the low activity COMT 158 allele. *Neuropsychopharmacology.* 2009; 34(3):739–746. [PubMed: 18769474]
- Wachowiak M, Shipley MT. Coding and synaptic processing of sensory information in the glomerular layer of the olfactory bulb. *Semin Cell Dev Biol.* 2006; 17(4):411–423. [PubMed: 16765614]
- Wishart HA, Roth RM, Saykin AJ, Rhodes CH, Tsongalis GJ, Pattin KA, et al. COMT val158met genotype and individual differences in executive function in healthy adults. *J Int Neuropsychol Soc.* 2011; 17(1):174–180. [PubMed: 21144101]

Figure 1.
Picture and odor identification performance by *COMT* genotype in schizophrenia patients and controls

Table 1

Demographic and Clinical Characteristics

	Schizophrenia Patients (<i>n</i> = 42)	Healthy Controls (<i>n</i> = 30)
Age (years)	35.43 (10.82)	30.83 (12.14)
Sex (Males:Females)	23:19	18:12
Education level ^a (years)	13.05 (2.46)	15.33 (2.32)
Mother's Education (years)	12.23 (2.90)	12.64 (3.05)
Father's Education (years)	12.34 (3.62)	12.61 (3.47)
Pack-days	0.27 (0.44)	0.16 (0.40)
<i>COMT</i> Genotype		
Val/Val:Val/Met:Met/Met	19:16:7	10:12:8
BPRS ^b Total Score	29.33 (9.14)	-
SANS ^c Total Score	26.12 (17.11)	-
SAPS ^d Total Score	14.83 (15.58)	-
Chlorpromazine Equivalents	279.16 (310.42)	-

Means and standard deviations are presented unless otherwise noted

^aSignificant group difference ($p < 0.05$)

^bBrief Psychiatric Rating Scale (Rhoades & Overall, 1988)

^cScale for the Assessment of Negative Symptoms (Andreasen, 1984a)

^dScale for the Assessment of Positive Symptoms (Andreasen, 1984b)