Published in final edited form as:

Schizophr Res. 2018 December ; 202: 113–119. doi:10.1016/j.schres.2018.07.012.

Olfactory Deficits and Psychosis-Spectrum Symptoms in 22q11.2 Deletion Syndrome

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Abstract

Olfactory functioning is a promising biomarker for psychosis in 22q11.2 deletion syndrome (22q11DS) but has not been well studied to date. This is a pilot effort to evaluate the potential for tests of olfactory functioning to contribute to risk and resilience prediction in 22q11DS, and is the first study to evaluate relationships among olfactory deficits, cognition and psychosis-spectrum symptoms in this disorder. Odor identification and discrimination were evaluated in 32 individuals with 22q11DS and 110 healthy comparison subjects (HC). Individuals with 22q11DS also had cognition assessed with the Penn Computerized Neurocognitive Battery, which evaluates executive functioning, episodic memory, complex cognition, and social cognition. Positive, negative, disorganized and general psychosis-spectrum symptoms were rated according to the Scale of Prodromal Symptoms. Age-normalized scores were calculated for odor identification and discrimination based on normative data. Both odor identification ($p < 0.001$, Cohen's $d = -2.15$, 95% CI $[-2.62, -1.68]$) and discrimination ($p < 0.001$, Cohen's $d = -1.81$, 95% CI $[-2.26, -1.35]$) were significantly impaired in 22q11DS relative to HC. There were no sex differences in either group. Neither odor identification nor discrimination was significantly correlated with overall cognition or any specific cognitive domain in 22q11DS. Impairment in odor discrimination was correlated with higher negative and overall psychosis-spectrum symptoms. There was no significant effect of catechol-O-methyltransferase Val(158)Met genotype or presence of velopharyngeal insufficiency on olfactory functioning. Olfactory deficits, particularly olfactory discrimination, are robust in 22q11DS and appear to be independent of cognitive deficits. They are also clinically relevant and related to psychosis-spectrum symptoms. Olfactory functioning appears to be a promising biomarker for psychosis in 22q11DS.

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** None of the above authors have any biomedical financial interests or potential conflicts of interest. **

Keywords

22q11.2 Deletion Syndrome; Psychosis; Schizophrenia; Olfaction

1. Introduction

Chromosome 22q11.2 deletion syndrome (22q11DS) is an important neurogenetic model for the study of psychosis-spectrum disorders (Gur et al., 2017). The deletion confers an approximately 25% risk for schizophrenia-spectrum disorders and affects multiple neurodevelopmentally relevant pathways, including development of midline features, neurotransmission, myelination, and dendritic spine morphology (Guna et al., 2015; McDonald-McGinn et al., 2014; Schreiner et al., 2013). Clinical characteristics and known predictors of psychosis-related outcomes are similar between 22q11DS and idiopathic psychotic disorders (i.e. those without known neurogenetic association) (Tang et al., 2017a; Tang et al., 2017b). Efforts are underway to understand the mediators of risk and resilience in 22q11DS, with the hypothesis that these may illuminate the pathways underlying schizophrenia risk at large (Gur et al., 2017).

Olfaction is a promising biomarker for psychosis in 22q11DS, but has not been extensively characterized in this population, to date. Deficits in both odor identification and discrimination are robust in idiopathic schizophrenia with large effect sizes; individuals at clinical risk for psychosis also appear to have significant deficits in both odor identification and discrimination, while non-ill first-degree family members of individuals with schizophrenia are primarily impaired in olfactory identification (Kamath et al., 2014; Moberg et al., 2014). Impairments are consistently present among patient populations regardless of illness phase, medication treatment, age, ethnicity, socioeconomic status, or cigarette smoking (Corcoran et al., 2005; Moberg et al., 2014). In addition, olfactory deficits appear to be clinically relevant – deficits in odor identification are correlated with severity of negative symptoms associated with psychosis (Corcoran et al., 2005; Kästner et al., 2013). - Odor interpretation was correlated with positive symptoms (Kästner et al., 2013). Furthermore, two studies reported that in individuals at clinical risk for psychosis, odor identification deficits were predictive of later transition to a psychotic disorder (Brewer et al., 2003; Woodberry et al., 2010), while they were predictive of functional outcome (but not conversion) in another study (Lin et al., 2015). In first-episode psychosis, odor identification deficits predicted [non-remission] of symptoms after one year (Good et al., 2006). Notably, there are putative mechanistic links between olfaction and psychosis risk that may also be relevant in 22q11DS. Olfactory deficits are associated with midline structural deficits, such as shallow olfactory sulcus (Takahashi et al., 2014; Turetsky et al., 2009), and smaller nasal volumes (Moberg et al., 2004). Odor-specific threshold deficits implicate abnormal cyclic adenosine 3', 5'-monophosphate (cAMP) signaling in idiopathic schizophrenia and clinical risk (Kamath et al., 2012a; Turetsky, & Moberg, 2009). The Val(158)Met catechol-O-methyltransferase (*COMT*) polymorphism has also been shown to affect olfactory processing (Kamath et al., 2012b).

Olfactory functioning has been evaluated in a limited number of patients with 22q11DS. The majority examine only odor identification: with the exception of one small study (Butcher et al., 2017), odor identification has been consistently impaired in 22q11DS relative to healthy comparison subjects (Buckley et al., 2017; Romanos et al., 2011) as well as unaffected siblings (Sobin et al., 2006). Individuals with the lower activity *COMT*Met allele were found to have poorer functioning than those with the Val allele (Bassett et al., 2007). One study also demonstrated deficits in odor discrimination and sensitivity (Romanos et al., 2011). Olfactory deficits appear to be significant even after accounting for otorhinolaryngologic problems, velopharyngeal insufficiency (VPI), psychiatric comorbidity, and methylphenidate medication (Romanos et al., 2011). Individuals with 22q11DS and VPI did not differ from those without VPI in mean odor identification scores, but decreased variance may suggest greater impairment (Sobin et al., 2006). Overall psychopathology, as reflected by total score on the Child Behavior Checklist, was found to be associated with odor sensitivity (Romanos et al., 2011). However, no existing study has explored relationships between olfactory functioning and psychosis-spectrum symptoms or cognitive deficits in 22q11DS.

The present study is a pilot effort to explore olfactory deficits in 22q11DS as potential biomarkers for psychosis risk. Specifically, we aim to describe both odor identification and discrimination function in 22q11DS relative to healthy comparison subjects. We also explore relationships among olfactory functioning and cognition, psychosis-spectrum symptoms, Val(158)Met *COMT* genotype, and presence of midline craniofacial defects (VPI).

2. Methods

2.1 Sample

Participants with 22q11DS were drawn from a larger ongoing study of brain and behavior in 22q11DS. Participants were primarily recruited from the “22q and You Center” at the Children’s Hospital of Philadelphia. The sample and assessment methods detailed below have also been described elsewhere (Tang et al., 2013; Tang et al., 2014). Olfactory functioning was assessed in 32 individuals aged 8 – 29 years with a laboratory confirmed 22q11.2 deletion using fluorescence *in situ* hybridization, array comparative genomic hybridization, multiplex ligation probe amplification, or SNP microarray. All individuals with 22q11DS undergoing neuropsychiatric evaluations while this pilot study was underway were asked for their consent for additional psychophysical olfactory testing. All participants who agreed to olfactory testing are included here. Healthy comparison subjects (HC) were drawn from multiple existing studies on neurodevelopment and olfaction conducted at the Brain and Behavior Laboratory at the University of Pennsylvania. Included in this study are 110 HC participants aged 14 – 28 years who underwent the same olfactory testing as participants with 22q11DS. HC participants did not have 22q11DS, DSM-IV Axis I psychopathology, Axis II cluster A personality disorder (schizotypal, schizoid, paranoid), or first degree relatives with psychotic disorder. All procedures were approved by relevant Institutional Review Boards. Informed consent/assent was obtained from each participant and accompanying parent/guardian.

Table 1 describes sample characteristics, with individual details listed in Supplemental Table 1. One participant had a history of threshold psychosis (major depressive disorder with psychotic features), ten individuals had clinically significant but subthreshold levels of psychosis symptoms, while the remainder had low or absent psychosis symptoms. Of note, participants with 22q11DS were significantly younger than HC, and included a higher proportion of Caucasians. Because this was a pilot effort to explore olfactory deficits as a potential biomarker for psychosis in 22q11DS, the HC sample had not been specifically recruited to match those with 22q11DS. Race did not affect within-group olfactory ability in either 22q11DS or HC, and has not been shown to be a significant moderator of olfactory functioning in the literature (Moberg et al., 2014); therefore, it was not considered as a factor in the analyses. However, increased age was significantly related to improved performance in both odor identification and discrimination. To account for the mismatch in age between 22q11DS and HC samples, olfactory performance scores were age-normalized using published normative data, as described below.

2.2 Measures

Odor identification and discrimination were evaluated with “Sniffin’ Sticks” using the same protocol in 22q11DS and HC (Hummel et al., 1997; Hummel et al., 2007). For identification, participants were presented birhinally with 16 odorants and asked to identify each odorant from a set of four choices per trial. For discrimination, participants were presented with three odorants and asked to discriminate which odor was different from the other two for 16 trials.

Participants with 22q11DS (n=28) underwent cognitive testing with the Penn Computerized Neurocognitive Battery, which includes 12 tasks assessing executive function, episodic memory, complex cognition, and social cognition (Gur et al., 2010). Standardized mean accuracy scores were calculated for each domain, and a standardized composite score was calculated from the sum.

Psychosis-spectrum symptoms were assessed in participants with 22q11DS (n=26) using the Structured Interview for Prodromal Syndromes, which assessed for positive, negative, disorganized and general symptoms related to psychosis (Miller et al., 2002; Miller et al., 2003). Symptoms were rated according to the Scale of Prodromal Symptoms (SOPS) with standardized anchors corresponding to a 7-point scale: 0=absent, 1=questionably present, 2=mild, 3=moderate, 4=moderately severe, 5=severe (but not psychotic), 6=severe and psychotic/extreme. Comorbid anxiety, mood, substance use, and attention-deficit hyperactivity disorders were assessed with relevant sections from the Kiddie-Schedule for Affective Disorders and Schizophrenia (Kaufman et al., 1997). Narrative case summaries were presented at consensus case conferences where SOPS scores and diagnoses were finalized by consensus by two or more doctoral level clinicians. Lifetime comorbid psychiatric diagnoses include anxiety disorders (n=19), ADHD (n=14), mood disorders (n=8), and alcohol use disorder (n=1, in full remission).

The *COMT* Val(158)Met polymorphism (rs4680) was genotyped from blood and saliva samples using both Applied Biosystems 7900H HT and 7500 Real-time PCR systems on a Taqman platform. Because the *COMT* gene is located within the 22q11.2 deletion region,

individuals with 22q11DS are hemizygous for this gene. Results were available from 23 individuals; 12 had the Val allele, 11 had the Met allele.

Medical history of midline craniofacial defects (including velopharyngeal insufficiency/submucosal cleft palate/bifid uvula, overt cleft palate, cleft lip/palate) was obtained for individuals with 22q11DS through patient and collateral interview, as well as review of medical records. Information was available for 22 individuals, including 17 with velopharyngeal insufficiency or submucosal cleft palate, 5 without. No individuals had a history of overtly cleft lip or palate.

2.3 Statistical Analyses

Age-normalized scores for odor identification and discrimination were calculated using summary statistics for age, binned by 5-year age groups (e.g. 10–15 years, 15–20 years, etc.) from normative data published on a large sample (Hummel et al., 2007; supplemental information was solicited from the first author). Continuous measures (e.g. olfaction scores, age) were compared using 2-sided t-tests, categorical variables (e.g. sex, race, smoking status) were compared using Fisher's exact tests, and effect sizes were calculated using the standard formula for Cohen's d. Variance was compared between male and female sex using the F test. Associations between olfactory measures and cognition/SOPS scores in 22q11DS were evaluated with linear regressions. Influential observations were evaluated by calculating hat diagonal regression diagnostics and Cook's distances. One observation with very high SOPS score was determined to be influential and was omitted from those models (Supplemental Table 1, Subject #25). P-values for the four separate cognitive domains were corrected for multiple comparisons using the Holm method (Holm 1979). All analyses were performed using R (R Core Team 2017). Significance threshold (α) was set at 0.05.

3. Results

3.1 Odor Identification and Discrimination are Impaired in 22q11DS

Both odor identification and discrimination are significantly impaired in patients with 22q11DS relative to HC, with large effect sizes evident (Table 1, Figure 1). Sex did not have a significant effect in either group for identification (22q11DS $p=0.13$, Cohen's $d=-0.55$, 95% CI $[-1.28, 0.19]$; HC $p=0.73$, Cohen's $d=-0.07$, 95% CI $[-0.44, 0.31]$) or discrimination (22q11DS $p=0.88$, Cohen's $d=-0.06$, 95% CI $[-0.79, 0.68]$; HC $p=0.47$, Cohen's $d=0.14$, 95% CI $[-0.24, 0.52]$). There were also no significant differences in variance between males and females for either group.

3.2 Olfactory Performance is Independent of Other Cognitive Domains in 22q11DS

Neither odor identification nor discrimination was significantly correlated with overall cognition among individuals with 22q11DS, though there was a positive trend between odor identification and overall cognition (Figure 2). There were no significant correlations between olfactory functioning (identification and discrimination) and any of the specific cognitive domains: executive functioning, episodic memory, complex cognition, and social cognition. Addition of sex as a covariate did not alter the findings.

3.3 Olfactory Functioning is Correlated with Psychosis Symptoms and Mood Disorders in 22q11DS

Odor discrimination was negatively correlated with negative symptoms, such that those with greater symptoms performed worse in odor discrimination. This was true for total SOPS score as well, but the relationship with positive symptoms did not reach significance. Odor identification was not significantly correlated with total SOPS score, positive, , or negative psychosis spectrum symptoms. Figure 3 shows relationships between olfaction performance and psychosis-spectrum symptoms. Addition of sex as a covariate did not alter the findings.

Lifetime history of mood disorder was significantly associated with decreased odor discrimination scores ($p=0.001$, $\beta = -1.67$, 95% CI $[-2.62, -0.71]$). Mood disorders were not correlated with odor identification scores. Lifetime histories of anxiety and ADHD disorders were not correlated with odor identification or discrimination. Addition of sex and total SOPS score as covariates did not alter the findings.

3.4 Olfaction Performance is Not Related to COMT Genotype or Velopharyngeal Insufficiency

COMT Val(158)Met genotype had no effect on odor identification or discrimination (Figure 4A). There was also no significant difference in odor identification or discrimination between individuals with and without velopharyngeal insufficiency (Figure 4B). Individuals with 22q11DS performed worse on both tasks regardless of *COMT* genotype and presence of VPI

4. Discussion

Olfactory functioning is a promising biomarker for psychosis in 22q11DS but has not been extensively evaluated in this population, to date. We report a pilot effort to characterize olfactory deficits in 22q11DS with respect to its potential role as a biomarker for psychosis. We show that odor identification and discrimination are significantly impaired in 22q11DS relative to HC. There is no significant relationship between performance on psychophysical olfactory measures and sex, cognition, *COMT* genotype, or presence of midline craniofacial defects. However, odor discrimination is significantly correlated with negative and overall psychosis-spectrum symptoms in 22q11DS. To our knowledge, this is the first report that investigates the relationship between olfactory deficits in 22q11DS, cognition and psychosis-spectrum symptoms.

The olfactory deficits in 22q11DS appear similar to, if not greater in magnitude than, those found in schizophrenia and clinical risk groups (Kamath et al., 2014; Moberg et al., 2014). Like individuals with schizophrenia and those at clinical risk, individuals with 22q11DS also appear to have deficits in both odor identification and discrimination; this is in contrast to first-degree family members of individuals with schizophrenia, who appear to have deficits only in odor identification (Kamath et al., 2014). The presence of olfactory deficits in 22q11DS is a robust and replicable finding (Buckley et al., 2017; Romanos et al., 2011; Sobin et al., 2006). It has been suggested that women with schizophrenia may perform slightly better than men in olfactory identification (Kästner et al., 2013), but this difference

is not present in other samples (Kamath et al., 2014). Sex differences in olfactory performance in 22q11DS have not been previously reported, and our results suggest no large sex difference in 22q11DS for odor identification or discrimination performance, though our study was underpowered to detect smaller effects.

Individuals with 22q11DS are significantly impaired in multiple cognitive domains compared to typically developing participants (Gur et al., 2014). However, we found no significant correlation between olfactory functioning and overall cognition, executive functioning, episodic memory, complex cognition or social cognition in 22q11DS. It is possible that a larger sample of individuals with 22q11DS would have revealed subtle relationships between cognition and olfaction, particularly odor identification where we found a trend toward positive correlation. In light of the results from this study, however, it is unlikely that cognitive deficits are the sole drivers of observed olfactory deficits. In schizophrenia, odor identification in particular (but not odor interpretation or sensitivity) has been related to memory and verbal IQ (Corcoran et al., 2005; Kästner et al., 2013; Moberg et al., 2006). However, this relationship may be mediated by increased negative symptoms in patients with greater impairment (Corcoran et al., 2005), and there is no relationship between odor identification and executive functioning or premorbid IQ (Kästner et al., 2013; Seidman et al., 1991). Therefore, it is likely that olfactory deficits – and particularly olfactory domains that do not require identification – represent an area of deficit in both 22q11DS and idiopathic schizophrenia that is independent of global cognitive impairment.

Importantly, odor discrimination appears to reflect negative psychosis-spectrum symptoms in 22q11DS. It is unclear why odor discrimination should be correlated with clinical symptoms while odor identification is not. This disparity highlights the importance of studying multiple olfactory domains, which has only been done in one other study of 22q11DS (Romanos et al., 2011). The lack of correlation between odor identification and psychosis symptoms departs from existing literature in idiopathic psychosis (Corcoran et al., 2005; Kästner et al., 2013). However, this may be explained by our young sample age, low representation of individuals with severe symptoms, and developmental delays that are present regardless of psychosis status. It is possible, for example, that olfactory functioning may be impaired in individuals prior to the development of psychosis. Odor discrimination may be less dependent on other cognitive functions than identification.

On the other hand, the finding that odor discrimination was related to negative but not positive symptoms is consistent with the existing literature in individuals with idiopathic schizophrenia (Corcoran et al., 2005; Kästner et al., 2013). A possible explanation is that negative symptoms are more stable across the course of illness, and therefore may be more reflective of underlying deficits that predispose individuals toward schizophrenia rather than downstream effects of the psychosis state – as appears to be the case with olfactory functioning deficits. It also remains to be seen whether task-specific findings for odor discrimination may be due to heterogeneity in circuits recruited for different olfactory tasks – e.g. identification potentially more related to other cognitive domains, while discrimination may be a “purer” olfactory task. Together with evidence for the prognostic utility of olfactory functioning in idiopathic clinical risk and early psychosis (Brewer et al., 2003;

Good et al., 2006; Lin et al., 2015; Woodberry et al., 2010), olfactory functioning is promising in its clinical relevance to psychosis in 22q11DS.

Our finding that there is no relationship between *COMT* Val(158)Met genotype and olfactory functioning contrasts with the finding of an earlier 22q11DS study of 18 participants where the Met allele was associated with greater impairment in odor identification (Bassett et al., 2007). Small sample sizes in both studies may play a role in this discrepancy. The Val(158)Met polymorphism was also shown to affect odor identification in idiopathic schizophrenia (Kamath et al., 2012b). Likely, genetic influences on olfactory functioning are complex, and unknown variables both within and outside the 22q11.2 deletion region may interact with *COMT* to influence olfaction. We also found that presence of midline craniofacial defects in the form of VPI has no significant effect on odor identification or discrimination. This is consistent with previous studies in 22q11DS (Romanos et al., 2011, Sobin et al., 2006). Therefore, the mechanisms underlying olfactory deficits in 22q11DS likely extend beyond peripheral anatomical abnormalities and implies central involvement.

There are several limitations to the current study. As this was a pilot effort, healthy comparison subjects were not specifically recruited to match those with 22q11DS. Consequently, there was a disparity in age and racial composition between the two groups. However, we accounted for the age difference by calculating and comparing age-normalized scores based on a large published normative sample. Furthermore, there was no evidence that race affects olfaction performance in this or other studies (Corcoran et al., 2005; Moberg et al., 2014). The limited sample size reported here is comparable to those of other studies in olfaction in 22q11DS, but may obscure smaller effects such as potential subtle relationships between olfaction and cognition. Effects of medical comorbidities on olfactory functioning were also not assessed for this reason. *COMT* genotype was not obtained in HC, and could not be assessed. Although we present evidence that olfactory functioning is clinically relevant with regard to psychosis-spectrum symptoms, longitudinal follow-up would be necessary to fully characterize and determine the value of olfactory function as a biomarker for psychosis risk in 22q11DS. Furthermore, the current study cannot differentiate between multiple possible mechanisms that may underlie olfactory dysfunction in 22q11DS, and is unable to determine whether the same pathways also lead to neuropsychiatric outcomes or if the deficits result from separate mechanistic disturbances. Potential mechanisms include abnormalities in prefrontal cortical development, midline craniofacial development, secondary messenger signaling, and dopaminergic pathways.

Altogether, we provide novel evidence suggesting that olfaction warrants further exploration as a biomarker for psychosis in 22q11DS. Deficits in odor identification and discrimination are robust. Critically, olfactory deficits do not appear to be explained by global cognitive impairment found in 22q11DS. Odor discrimination is also associated with global, positive, and negative psychosis-spectrum symptoms, and is therefore clinically relevant.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations:

22q11DS	22q11.2 Deletion Syndrome
HC	healthy comparison subjects
cAMP	cyclic adenosine 3', 5'-monophosphate
COMT	catechol-O-methyltransferase
VPI	velopharyngeal insufficiency
SOPS	Scale of Prodromal Symptoms

References

- Bassett AS, Caluseriu O, Weksberg R, Young DA, Chow EW, 2007 Catechol-O-methyl transferase and expression of schizophrenia in 73 adults with 22q11 deletion syndrome. *Biol Psychiatry* 61, 1135–1140. [PubMed: 17217925]
- Brewer WJ, Wood SJ, McGorry PD, Francey SM, Phillips LJ, Yung AR, Anderson V, Copolov DL, Singh B, Velakoulis D, Pantelis C, 2003 Impairment of olfactory identification ability in individuals at ultra-high risk for psychosis who later develop schizophrenia. *Am J Psychiatry* 160, 1790–1794. [PubMed: 14514492]
- Buckley E, Siddique A, McNeill A, 2017 Hyposmia, symptoms of rapid eye movement sleep behavior disorder, and parkinsonian motor signs suggest prodromal neurodegeneration in 22q11 deletion syndrome. *Neuroreport* 28, 677–681. [PubMed: 28574926]
- Butcher NJ, Marras C, Pondal M, Rusjan P, Boot E, Christopher L, Repetto GM, Fritsch R, Chow EWC, Masellis M, Strafella AP, Lang AE, Bassett AS, 2017 Neuroimaging and clinical features in adults with a 22q11.2 deletion at risk of Parkinson's disease. *Brain*
- Corcoran C, Whitaker A, Coleman E, Fried J, Feldman J, Goudsmit N, Malaspina D, 2005 Olfactory deficits, cognition and negative symptoms in early onset psychosis. *Schizophr Res* 80, 283–293. [PubMed: 16125904]
- Good KP, Whitehorn D, Rui Q, Milliken H, Kopala LC, 2006 Olfactory identification deficits in first-episode psychosis may predict patients at risk for persistent negative and disorganized or cognitive symptoms. *American Journal of Psychiatry* 163, 932–933. [PubMed: 16648339]
- Guna A, Butcher NJ, Bassett AS, 2015 Comparative mapping of the 22q11.2 deletion region and the potential of simple model organisms. *J Neurodev Disord* 7, p. 18. [PubMed: 26137170]
- Gur RE, Bassett AS, McDonald-McGinn DM, Bearden CE, Chow E, Emanuel BS, Owen M, Swillen A, Van den Bree M, Vermeesch J, Vorstman JAS, Warren S, Lehner T, Morrow B, 2017 A neurogenetic model for the study of schizophrenia spectrum disorders: the International 22q11.2 Deletion Syndrome Brain Behavior Consortium. *Mol Psychiatry*, doi: 10.1038/mp.2017.161.
- Gur RC, Richard J, Hughett P, Calkins ME, Macy L, Bilker WB, Brensinger C, Gur RE, 2010 A cognitive neuroscience-based computerized battery for efficient measurement of individual differences: standardization and initial construct validation. *J Neurosci Methods* 187, 254–262. [PubMed: 19945485]
- Gur RE, Yi JJ, McDonald-McGinn DM, Tang SX, Calkins ME, Whinna D, Souders MC, Savitt A, Zackai EH, Moberg PJ, Emanuel BS, Gur RC, 2014 Neurocognitive development in 22q11.2 deletion syndrome: comparison with youth having developmental delay and medical comorbidities. *Mol Psychiatry* 19, 1205–1211. [PubMed: 24445907]
- Holm S, 1979 A simple sequentially rejective multiple test procedure. *Scandinavian Journal of Statistics* 6, 65–70.
- Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G, 1997 'Sniffin' sticks': olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. *Chem Senses* 22, 39–52. [PubMed: 9056084]

- Hummel T, Kobal G, Gudziol H, Mackay-Sim A, 2007 Normative data for the “Sniffin’ Sticks” including tests of odor identification, odor discrimination, and olfactory thresholds: an upgrade based on a group of more than 3,000 subjects. *Eur Arch Otorhinolaryngol* 264:237–243. [PubMed: 17021776]
- Kamath V, Moberg PJ, Calkins ME, Borgmann-Winter K, Conroy CG, Gur RE, Kohler CG, Turetsky BI, 2012a An odor-specific threshold deficit implicates abnormal cAMP signaling in youths at clinical risk for psychosis. *Schizophr Res* 138, 280–284. [PubMed: 22537567]
- Kamath V, Moberg PJ, Gur RE, Doty RL, Turetsky BI, 2012b Effects of the val(158)met catechol-O-methyltransferase gene polymorphism on olfactory processing in schizophrenia. *Behav Neurosci* 126, 209–215. [PubMed: 22148860]
- Kamath V, Turetsky BI, Calkins ME, Kohler CG, Conroy CG, Borgmann-Winter K, Gatto DE, Gur RE, Moberg PJ, 2014 Olfactory processing in schizophrenia, non-ill first-degree family members, and young people at-risk for psychosis. *The World Journal of Biological Psychiatry* 15, 209–218. [PubMed: 22070564]
- Kästner A, Malzahn D, Begemann M, Hilmes C, Bickeböller H, Ehrenreich H, 2013 Odor naming and interpretation performance in 881 schizophrenia subjects: association with clinical parameters. *BMC Psychiatry* 13, 218. [PubMed: 24229413]
- Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D & Ryan N, 1997 Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *Journal of the American Academy of Child and Adolescent Psychiatry* 36, 980–8. [PubMed: 9204677]
- Lane DM 2013 Influential Statistics, in: Introduction to Statistics: An Interactive e-Book <http://onlinestatbook.com/2/regression/influential.html>.
- Lin A, Brewer WJ, Yung AR, Nelson B, Pantelis C, Wood SJ, 2015 Olfactory identification deficits at identification as ultra-high risk for psychosis are associated with poor functional outcome. *Schizophr Res* 161, 156–162. [PubMed: 25476117]
- McDonald-McGinn DM, Sullivan KE, Marino B, Philip N, Swillen A, Vorstman JA, Zackai EH, Emanuel BS, Vermeesch JR, Morrow BE, 2014 22q11.2 deletion syndrome. *Nat Rev Dis Primers* 1, 15071–15071.
- Miller TJ, McGlashan TH, Rosen JL, Cadenhead K, Cannon T, Ventura J, McFarlane W, Perkins DO, Pearlson GD, Woods SW, 2003 Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. *Schizophr Bull* 29, 703–715. [PubMed: 14989408]
- Miller TJ, McGlashan TH, Rosen JL, Somjee L, Markovich PJ, Stein K, Woods SW, 2002 Prospective diagnosis of the initial prodrome for schizophrenia based on the Structured Interview for Prodromal Syndromes: preliminary evidence of interrater reliability and predictive validity. *Am J Psychiatry* 159, 863–865. [PubMed: 11986145]
- Moberg PJ, Arnold SE, Doty RL, Gur RE, Balderston CC, Roalf DR, Gur RC, Kohler CG, Kanes SJ, Siegel SJ, Turetsky BI, 2006 Olfactory functioning in schizophrenia: relationship to clinical, neuropsychological, and volumetric MRI measures. *J Clin Exp Neuropsychol* 28, 1444–1461. [PubMed: 17050269]
- Moberg PJ, Kamath V, Marchetto DM, Calkins ME, Doty RL, Hahn C-G, Borgmann-Winter KE, Kohler CG, Gur RE, Turetsky BI, 2014 Meta-analysis of olfactory function in schizophrenia, first-degree family members, and youths at-risk for psychosis. *Schizophr Bull* 40, 50–59. [PubMed: 23641047]
- Moberg PJ, Roalf DR, Gur RE, Turetsky BI, 2004 Smaller nasal volumes as stigmata of aberrant neurodevelopment in schizophrenia. *American Journal of Psychiatry* 161, 2314–2316. [PubMed: 15569907]
- R Core Team, 2017 R: A language and environment for statistical computing R Foundation for Statistical Computing, Vienna, Austria <https://www.R-project.org>.
- Romanos M, Schecklmann M, Kraus K, Fallgatter AJ, Warnke A, Lesch K-P, Gerlach M, 2011 Olfactory deficits in deletion syndrome 22q11.2. *Schizophr Res* 129, 220–221. [PubMed: 21282042]

- Schreiner MJ, Lazaro MT, Jalbrzikowski M, Bearden CE, 2013 Converging levels of analysis on a genomic hotspot for psychosis: insights from 22q11.2 deletion syndrome. *Neuropharmacology* 68, 157–173. [PubMed: 23098994]
- Seidman LJ, Talbot NL, Kalinowski AG, McCarley RW, Faraone SV, Kremen WS, Pepple JR, Tsuang MT, 1991 Neuropsychological probes of fronto-limbic system dysfunction in schizophrenia. Olfactory identification and Wisconsin Card Sorting performance. *Schizophr Res* 6, 55–65. [PubMed: 1786234]
- Sobin C, Kiley-Brabeck K, Dale K, Monk SH, Khuri J, Karayiorgou M, 2006 Olfactory disorder in children with 22q11 deletion syndrome. *Pediatrics* 118, e697–e703. [PubMed: 16908619]
- Takahashi T, Wood SJ, Yung AR, Nelson B, Lin A, Yücel M, Phillips LJ, Nakamura Y, Suzuki M, Brewer WJ, Proffitt TM, McGorry PD, Velakoulis D, Pantelis C, 2014 Altered depth of the olfactory sulcus in ultra high-risk individuals and patients with psychotic disorders. *Schizophr Res* 153, 18–24. [PubMed: 24530137]
- Tang SX, Moore TM, Calkins ME, Yi JJ, McDonald-McGinn DM, Zackai EH, Emanuel BS, Gur RC, Gur RE, 2017a Emergent, remitted and persistent psychosis-spectrum symptoms in 22q11.2 deletion syndrome. *Transl Psychiatry* 7, p. e1180. [PubMed: 28742080]
- Tang SX, Moore TM, Calkins ME, Yi JJ, Savitt A, Kohler CG, Souders MC, Zackai EH, McDonald-McGinn DM, Emanuel BS, Gur RC, Gur RE, 2017b The Psychosis Spectrum in 22q11.2 Deletion Syndrome Is Comparable to That of Nondeleted Youths. *Biol Psychiatry* 82, 17–25. [PubMed: 27832840]
- Tang SX, Yi JJ, Calkins ME, Whinna DA, Kohler CG, Souders MC, McDonald-McGinn DM, Zackai EH, Emanuel BS, Gur RC, Gur RE, 2013 Psychiatric disorders in 22q11.2 deletion syndrome are prevalent but undertreated. *Psychol Med* 44, 1267–1277. [PubMed: 24016317]
- Tang SX, Yi JJ, Moore TM, Calkins ME, Kohler CG, Whinna DA, Souders MC, Zackai EH, McDonald-McGinn DM, Emanuel BS, Bilker WB, Gur RC, Gur RE, 2014 Subthreshold psychotic symptoms in 22q11.2 deletion syndrome. *J Am Acad Child Adolesc Psychiatry* 53, 991–1000.e2. [PubMed: 25151422]
- Turetsky BI, Crutchley P, Walker J, Gur RE, Moberg PJ, 2009 Depth of the olfactory sulcus: a marker of early embryonic disruption in schizophrenia? *Schizophr Res* 115, 8–11. [PubMed: 19767178]
- Turetsky BI, Moberg PJ, 2009 An odor-specific threshold deficit implicates abnormal intracellular cyclic AMP signaling in schizophrenia. *Am J Psychiatry* 166, 226–233. [PubMed: 19074977]
- Woodberry KA, Seidman LJ, Giuliano AJ, Verdi MB, Cook WL, McFarlane WR, 2010 Neuropsychological profiles in individuals at clinical high risk for psychosis: relationship to psychosis and intelligence. *Schizophr Res* 123, 188–198. [PubMed: 20692125]

Figure 1. Odor Identification and Discrimination in 22q11.2 Deletion Syndrome Compared to Healthy Controls –

Females are represented in red and males are represented in teal for this dotplot comparing olfactory measures between 22q11DS and HC. Both identification ($p < 0.001$, Cohen's $d = -2.15$, 95% CI $[-2.62, -1.68]$) and discrimination ($p < 0.001$, Cohen's $d = -1.81$, 95% CI $[-2.26, -1.35]$) were significantly impaired in 22q11DS. Means and variances did not differ between males and females for either olfactory domain. *22q11DS* = 22q11.2 deletion syndrome; *HC* = healthy comparison subjects.

Figure 2. Olfaction and Cognition in 22q11.2 Deletion Syndrome –

Relationships are illustrated between performance in odor identification (yellow) and discrimination (blue) and overall cognition. Linear regression lines are shown with shading representing 95% confidence intervals. Overall cognition was not significantly correlated with olfactory identification ($p=0.18$, Standardized β Coefficient = 0.50, 95% CI [-0.24, 1.23]) or discrimination ($p=0.98$, Standardized β Coefficient = 0.01, 95% CI [-0.75, 0.77]).

Figure 3. Olfaction and Psychosis-Spectrum Symptoms in 22q11.2 Deletion Syndrome – Overall psychosis-spectrum symptoms as represented by total SOPS score (blue), positive symptoms (yellow), and negative symptoms subscales (green) are shown in relation to (A) olfactory identification and (B) discrimination. Linear regressions are also shown with shaded 95% confidence intervals. There was no relationship between odor identification and total ($p=0.72$, $\beta = 0.001$, 95% CI $[-0.05, 0.07]$), positive ($p=0.16$, $\beta = 0.14$, 95% CI $[-0.06, 0.33]$), and negative psychosis-spectrum symptoms ($p=0.76$, $\beta = 0.03$, 95% CI $[-0.20, 0.14]$). Odor discrimination was more impaired with higher levels of total ($p<0.001$, $\beta = -0.07$, 95% CI $[-0.12, -0.04]$) and negative psychosis-spectrum symptoms ($p=0.004$, $\beta = -0.19$, 95% CI $[-0.32, -0.07]$), but was not significantly correlated with positive symptoms ($p=0.17$, $\beta = -0.11$, 95% CI $[-0.28, 0.05]$). One outlier with high SOPS scores was removed from the analyses.

Figure 4. Olfaction, COMT Genotype, and Midline Craniofacial Defects (VPI) in 22q11.2 Deletion Syndrome –

Odor identification and discrimination scores were compared among individuals with 22q11DS based on (A) *COMT* Val(158)Met genotype and (B) Presence of midline craniofacial defects. Means with 95% confidence intervals are represented. (A) There was no significant difference in odor identification ($p=0.71$, Cohen's $d=-0.16$, 95% CI [-1.03, 0.71]) or discrimination ($p=0.58$, Cohen's $d=-0.24$, 95% CI [-1.13, 0.65]) between individuals with Met (light gray) or Val (dark purple) genotypes. (B) There was no significant difference in odor identification ($p=0.11$, Cohen's $d=-0.87$, 95% CI [-1.98, 0.21]) or discrimination ($p=0.48$, Cohen's $d=0.38$, 95% CI [-0.70, 1.46]) between those with midline craniofacial defects (VPI, dark green) and those without (light green). *COMT*= catechol-O-methyltransferase; *VPI*= velopharyngeal insufficiency.

Table 1.

Sample Characteristics

DEMOGRAPHIC	22q11DS	Healthy Controls	p value	Cohen's d (95% CI)
n	32	110	-	-
Age (mean $\pm$ SD, yrs)	14.1 $\pm$ 5.3	21.9 $\pm$ 3.9	<0.005	-1.83 (-2.28, -1.38)
Sex (n, %Female)	16 (50%)	56 (51%)	1.00	-
Race (n, %Caucasian)	25 (78%)	60 (55%)	0.03	-
Smoking (n, %Never Smoked)	30 (94%)	92 (84%)	0.60	-
CLINICAL				
Total SOPS Score (mean $\pm$ SD)	13.1 $\pm$ 12.7	-	-	-
Positive Symptoms Subscale (mean $\pm$ SD)	2.5 $\pm$ 4.2	-	-	-
Negative Symptoms Subscale (mean $\pm$ SD)	4.9 $\pm$ 4.1	-	-	-
OLFACTION				
Identification (mean $\pm$ SD, z-score)	-2.78 $\pm$ 1.39	-0.37 $\pm$ 1.04	<0.005	-2.14 (-2.62, -1.68)
Discrimination (mean $\pm$ SD, z-score)	-2.91 $\pm$ 1.32	-0.82 $\pm$ 1.11	<0.005	-1.81 (-2.26, -1.35)

22q11DS = 22q11.2 deletion syndrome; CI = Confidence Interval; SD = standard deviation; yrs = years; “-” = Not Applicable