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Structural anomalies of the peripheral olfactory system in psychosis high-risk subjects

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ABSTRACT

Background: Olfactory impairments are prominent in both schizophrenia and the preceding at-risk state. Their presence prior to illness predicts poor functional outcome. In schizophrenia, these impairments reflect peripheral olfactory structural abnormalities, which are hypothesized to arise during early embryonic development. If this is correct, then similar structural anomalies should be apparent among clinical high-risk subjects.
Methods: Thirty-nine clinical high-risk (CR) subjects (24 M/15F) were compared to 36 low-risk (LR) subjects (19 M/17F). Olfactory measures derived from 3 T MRI scans included olfactory bulb volume, primary olfactory cortical gray matter volume, and the depth of the olfactory sulcus overlying the bulb. Additionally, nasal cavity volumes were assessed with acoustic rhinometry.
Results: Male CR subjects exhibited bilateral reductions in olfactory bulb volume and abnormal asymmetries of the posterior nasal cavities and olfactory sulci (left reduced relative to right). Post-hoc contrasts also indicated reduced left, but not right, olfactory cortical gray matter volume. Female CRs had no significant abnormalities, although they exhibited similar trend effects. Left olfactory bulb volume correlated, across all CR subjects, with negative, but not positive, symptoms. In a classification analysis, with 80% target specificity, olfactory measurements distinguished male CR from male LR subjects with 93% sensitivity. Among females, the comparable sensitivity was 69%.
Conclusion: Psychosis-risk youths exhibit an array of sexually dimorphic and laterally asymmetric anomalies of the peripheral olfactory system. These are consistent with a developmental disruption primarily affecting male fetuses. These structural biomarkers may enhance the identification of at-risk subjects with poor prognosis, before their clinical trajectory is apparent.

1. Introduction

Olfactory deficits are a prominent feature of schizophrenia (Moberg et al., 1999). A growing body of evidence indicates that olfactory performance impairments precede the onset of overt psychosis (Kamath et al., 2012, 2014) and these may, among individuals who are at clinical high risk, be predictive of those who will develop frank psychosis (Brewer et al., 2003; Woodberry et al., 2010) or otherwise progress to a poor functional outcome (Lin et al., 2015). It is also clear that olfactory deficits are not merely specific exemplars of the relatively diffuse cognitive impairment that characterizes schizophrenia. Rather they are the consequence, at least in part, of structural and functional abnormalities of the peripheral olfactory system. These abnormalities include reduced nasal cavity volumes (Moberg et al., 2004; Turetsky et al., 2007), reduced olfactory bulb volumes (Nguyen et al., 2011; Turetsky et al., 2000), physiological and molecular anomalies of olfactory receptor neurons in the nose (Borgmann-Winter et al., 2016; Turetsky et al., 2009b), shallow olfactory sulci in the prefrontal cortex (Takahashi et al., 2013; Turetsky et al., 2009a), and reduced gray matter volumes in the primary olfactory cortex (Prasad et al., 2004; Sim et al., 2006; Turetsky et al., 2003). While olfactory deficits have been observed in both men and women, there is evidence to suggest that they may be more pronounced in males (Malaspina et al., 2012; Seidman et al., 1997; Turetsky et al., 2007).

We have hypothesized that these anomalies are markers of aberrant intrauterine neurodevelopmental processes occurring during the late first and early second trimesters of pregnancy (Turetsky et al., 2007, 2009a). This is when the neural architecture of olfactory system, the earliest and most primitive sensory network, is constructed (Farbman, 1994; Kostovic et al., 1993). This also coincides with a period of heightened fetal developmental risk for schizophrenia. Environmental

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stressors (e.g., maternal infection, famine) during this period increase the incidence of adult schizophrenia, presumably by altering brain development and increasing susceptibility to a subsequent "second hit" (Brown, 2006; van Os and Selten, 1998). The coincidental development of the olfactory system during this risk period makes it especially sensitive to these developmental perturbations. Olfactory anomalies may therefore serve as neural markers of an early fetal developmental disturbance. If this hypothesis is correct, it implies that structural anomalies of the olfactory system will be evident prior to the onset of clinically diagnosable signs and symptoms of schizophrenia.

There is now some evidence to support this assertion (Roalf et al., 2017; Takahashi et al., 2014). We recently examined the volumes of several temporal lobe regions in a large community-based cohort of youths who met screening criteria for psychosis spectrum features without overt psychosis (Roalf et al., 2017). The only region that differentiated this young at-risk cohort from both healthy adolescents and those with psychopathology outside the psychosis spectrum (e.g., anxiety, mood disorders) was the left entorhinal/perirhinal cortex, which is the target for primary afferent neurons from the olfactory bulb. Importantly, volume reductions in this region were associated with greater negative symptomatology and cognitive impairment, but not positive symptomatology, which is consistent with observations regarding olfactory deficits in schizophrenia.

This suggests, but does not actually establish, the existence of developmental anomalies in peripheral olfactory structures. A thorough investigation of the structural integrity of the peripheral olfactory system has never been conducted in clinical high-risk subjects, despite the evidence for olfactory behavioral impairments in this population. Here, we present a comprehensive examination of these peripheral structures in a new sample of high-risk subjects. Measures of interest include the volumes of the nasal cavities, the olfactory bulbs and the olfactory cortex, and the depths of the olfactory sulci – which develop in tandem with the underlying olfactory tracts. We consider the relationship of these structural measures to olfactory behavioral performance, and the real-world utility of these measures as biomarkers that can aid in identifying at-risk individuals. Since there is evidence supporting sexual disparities in both normal olfactory ability and schizophrenia olfactory impairments, as well as illness-related developmental anomalies in other brain regions, we focus especially on the presence or absence of anomalies compared to same-sex healthy comparison subjects. Our primary hypotheses are: 1) structural anomalies of the peripheral olfactory system will be evident in individuals at clinical high risk for psychosis, prior to the onset of an overt psychotic illness; 2) these abnormalities will be more prominent among male at-risk subjects, rather than females.

2. Methods and materials

2.1. Subjects

Young adults and adolescents were recruited into one of two groups: 1) Clinical Risk (CR) individuals who exhibited sub-psychotic symptoms ($n = 39$), but did not meet DSM-IV criteria for a psychotic disorder, and 2) Low Risk (LR) comparison subjects who were symptom free, without an Axis II Cluster A diagnosis or a family history of psychosis ($n = 36$). Subjects ranged in age from 15 to 28. Written informed consent was obtained from all participants over the age of 18. Parental consent and the subject's assent were obtained for those under 18.

Consensus diagnoses for all subjects were established using data gathered from either the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994) or the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) (Kaufman et al., 1997), the Family Interview for Genetic Studies (FIGS) (NIMH Genetics Initiative, 1992), and any available information from medical records, family, and care providers. Collateral information was obtained from a parent or caregiver for all participants under the age of 18. All participants were administered the Structured Interview for Prodromal Syndromes (SIPS), which included the Scale of Prodromal Symptoms (SOPS) (Miller et al., 2003).

Classification of a subject as CR required at least one positive symptom (rated 3–5 in severity) or two negative and/or disorganized symptoms (rated 3–6 in severity) on the SOPS in the six months prior to testing. Among CR subjects, 23 met inclusion criteria for both positive and negative/disorganized symptoms, 14 exhibited solely positive symptoms, while 2 exceeded threshold only for negative/disorganized symptoms.

Individuals were excluded for lack of English proficiency, any medical condition that could affect brain function, significant loss of consciousness or head trauma, current substance abuse, past substance dependence, positive urine drug screen, or any medical condition that could alter olfactory functioning (e.g., upper respiratory infection, allergies, obvious craniofacial abnormality). Individuals with an estimated IQ < 70 (WRAT-3R) (Wilkinson, 1993) were also excluded. No subjects had a history of past or current treatment with psychiatric medications.

Descriptive clinical and demographic measures are presented in Table 1. CR and LR groups did not differ in age [$t(73) = 1.67$, $p = 0.10$], sex [$\chi^2(1) = 0.59$, $p = 0.44$], racial composition [$\chi^2(2) = 3.73$, $p = 0.16$] or smoking status [$\chi^2(1) = 3.04$, $p = 0.08$]. When males and females were examined separately, however, there was a significant difference in smoking status for females [$\chi^2(1) = 3.94$, $p = 0.05$] but not males [$\chi^2(1) = 0.37$, $p = 0.54$]. CRs had lower levels of education [$t(72) = 3.50$, $p = 0.0008$] and parental education [mothers: $t(72) = 2.00$, $p = 0.049$; fathers: $t(67) = 2.94$, $p = 0.004$]. Not surprisingly, they also differed in levels of clinical symptomatology, as denoted by both SOPS and Global Assessment of Functioning (GAF) ratings. Within the CR group, there were no differences in clinical symptomatology between males and females.

2.2. Olfactory psychophysical assessments

2.2.1. Odor detection thresholds

Odor detection ability was assessed using two different odorants, lyral and citralva. Odors were presented birhinally in a single reversing staircase, forced-choice task format, with the order counterbalanced across subjects. Two vials, one containing mineral oil and the other containing odorant diluted in mineral oil, were presented sequentially to the subject's nares. The subject was asked to identify the vial that "smells stronger." Odor concentrations ranged from 10^{-1} M (strongest) to 10^{-9} M (weakest) in 0.5 log step dilution increments. The test began at the 10^{-5} M step, and odor concentration was increased in full-molar steps until correct detection occurred on five consecutive trials at a

Table 1
Demographic and clinical characteristics.

	Clinical risk ($n = 39$)	Low risk ($n = 36$)
	Mean ± SD (range)	Mean ± SD (range)
Age (years)	19.9 ± 2.64 (16–24)	21.0 ± 2.5 (15–25)
Sex (male: female)	24: 15	19: 17
Race (Cauc., Afr. Amer., other)	10: 21: 8	16: 12: 8
Education level (years)[a]	11.9 ± 2.0	13.8 ± 2.6
Mother education (years)[a]	14.2 ± 2.3	15.3 ± 2.4
Father education (years)[a]	13.7 ± 2.8	15.7 ± 2.7
Smoker: nonsmoker (#)	12 (7 M/5F): 27 (17 M/10F)	5 (4 M/1F): 31 (15 M/16F)
SOPS:[b] total score[a]	33.3 ± 15.5	3.2 ± 4.9
Positive subscale[a]	12.6 ± 5.4	1.0 ± 2.0
Neg./disorg. subscales[a]	15.0 ± 8.6	1.5 ± 2.0
GAF[c] score[a]	56.0 ± 11.2	85.5 ± 6.5

[a] Significant group difference ($p < 0.05$).
[b] SOPS = Scale of Prodromal Symptoms.
[c] GAF = Global Assessment of Functioning.

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