Published in final edited form as:

World J Biol Psychiatry. 2014 April ; 15(3): 209–218. doi:10.3109/15622975.2011.615862.

Olfactory processing in schizophrenia, non-ill first-degree family members, and young people at-risk for psychosis

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Abstract

Objectives—While deficits in odor identification and discrimination have been reported in schizophrenia, few studies have examined the relative specificity of these deficits in patients and at-risk youth.

Method—Sniffin' Sticks odor identification and discrimination were assessed in schizophrenia outpatients and non-ill first-degree relatives (Study One), as well as youth at clinical (CR) or genetic (GR) risk for schizophrenia (Study Two). Scores were z-transformed, using the performance of a demographically-matched adult or adolescent comparison group.

Results—Patients and relatives were impaired on odor identification, but odor discrimination impairment was limited to the patient group. A similar pattern of impairment emerged in at-risk youth. GR youth were impaired on odor identification but not discrimination, while CR youth were impaired on both tasks. In patients, olfactory impairment was correlated with negative symptomatology.

Conclusions—To our knowledge, this is the first study to show that CR youth are impaired on both olfactory tasks, as observed in adult schizophrenia patients. GR youth were impaired only on odor identification like their adult counterparts. These data suggest that odor identification impairment, in isolation, may represent a genetic marker of vulnerability for schizophrenia, while odor discrimination deficits may be a biomarker associated with the development of psychosis.

Keywords

olfaction; smell; prodrome; negative symptoms; psychosis prone

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Conflicts of Interest

VK, MEC, CGK, PJM, KBM, DEG, and CGC report no competing interests.

1. Introduction

Olfaction has emerged as an informative tool to study schizophrenia, owing to the neuroanatomical proximity of olfactory structures to frontotemporal brain regions implicated in the pathophysiology of the illness. The olfactory network is highly genetically predetermined (Jefferis, et al. 2001), and exhibits continuous neurogenesis in the olfactory epithelium (Hahn, et al. 2005). These unique aspects of this sensory system have furthered its relevance to schizophrenia, a complex genetic neurodevelopmental disorder. Structural and functional abnormalities of the olfactory system have been well-documented in schizophrenia and encompass all levels of olfactory sensory processing, including both macrostructural and intracellular impairments (for a review, see: Turetsky et al. (2009)). Indeed, aspects of olfactory disturbance are thought to be genetically-mediated, as nonpsychotic first-degree relatives of schizophrenia patients show similar, though in some cases attenuated, impairment on olfactory indices (Kopala, et al. 2001, Kopala, et al. 1998, Schneider, et al. 2007, Turetsky and Moberg 2009, Turetsky, et al. 2003, Ugur, et al. 2005).

In schizophrenia, impairment has been observed across a wide variety of olfactory measures, including odor identification, odor discrimination, odor memory, and odor detection threshold (for a review, see: Moberg, et al. 1999). Among olfactory measures, odor identification tasks have received the most attention, with robust odor identification deficits reliably observed across schizophrenia samples. Notably, these deficits appear to predict transition to schizophrenia (Brewer, et al. 2003) and are independent of task complexity (Kopala, et al. 1995), neuroleptic use (Kopala, et al. 1993, Moberg, et al. 1999), sex differences (Good, et al. 2007, Moberg, et al. 1999), and smoking history (Moberg, et al. 1999). Birhinal and unirhinal odor identification deficits have also been observed in first- and second-degree family members of schizophrenia patients (Kopala, et al. 2001, Kopala, et al. 1998, Roalf, et al. 2006, though see: Compton and Chen, 2008), as well as individuals with schizotypy and schizophrenia-spectrum disorders (Good, et al. 2007, Park and Schoppe 1997). These findings of poor odor identification in schizophrenia patients, their non-ill family members and other genetically related populations have raised the possibility that odor identification impairment may be a marker of genetic vulnerability to the illness.

Odor discrimination, the ability to distinguish whether repeated odor presentations are the same or different from each other, is another aspect of olfactory processing that has been relatively understudied in schizophrenia. Two prior reports by Rupp et al. (2005a, 2005b) found that male schizophrenia patients were impaired in their ability to both identify and discriminate odors relative to healthy controls. In the only study of healthy individuals genetically related to schizophrenia patients, Ugur et al. (2005) observed odor discrimination impairment in ten patients diagnosed with schizophrenia or schizoaffective psychosis, but not in their monozygotic twins. While these limited findings suggest that odor discrimination may be related to the development of overt illness, further investigation of odor discrimination in schizophrenia, first-degree relatives, and at-risk samples is warranted.

The overall objective of the current study was to examine odor identification and discrimination ability in schizophrenia probands and a sample of healthy first-degree relatives. In addition, we present preliminary olfactory data from a cohort of at-risk youth who comprised clinical and genetic risk subgroups. For both studies, participants were administered measures of odor discrimination and odor identification. We further assessed the relationship between olfactory performance indices and clinical characteristics in the schizophrenia and at-risk samples.

2. Method

2.1 Recruitment and Participants

Study One—Adult schizophrenia patients ($n = 65$), non-ill adult first-degree relatives of schizophrenia patients ($n = 24$), and neurologically and psychiatrically healthy adults ($n = 66$), ages 18 to 65, were recruited by the Schizophrenia Research Center at the University of Pennsylvania Medical Center. Consensus best-estimate DSM-IV-TR (American Psychiatric Association 2000) diagnoses for all subjects were established using data gathered during administration of either the Diagnostic Interview for Genetic Studies (DIGS; Nurnberger, et al. 1994) or the Structured Clinical Interview for DSM-IV (SCID; First, et al. 1996), the Family Interview for Genetic Studies (FIGS; NIMH Genetics Initiative 1992), and any available information from medical record review, family and care providers. The Brief Psychiatric Rating Scale (BPRS; Rhoades and Overall 1988) and the Scales for the Assessment of Negative Symptoms (SANS; Andreasen 1984a) and Positive Symptoms (SAPS; Andreasen 1984b) were administered to characterize the clinical status of each schizophrenia proband. Of the patients with schizophrenia, 5 were unmedicated, 40 were taking second generation antipsychotic medication, 9 were taking first generation antipsychotic medication (of which 1 individual was also on an anti-depressant), 2 were taking a combination of both first and second generation antipsychotic medications and 9 were not on an antipsychotic medication but were taking another psychotropic medication (e.g., antidepressant or anti-anxiolytic agents) at the time of testing. Antipsychotic medication dosages were converted to chlorpromazine equivalents using published reference tables (Kroken, et al. 2009). The family member cohort was comprised of healthy first-degree relatives (father, mother, offspring, or full sibling) of an individual affected with the sole diagnosis of schizophrenia. Individuals in the non-ill first-degree relative group represented 5 parents, 15 siblings, and 4 offspring from 20 families. Individuals were excluded from the study based on the following: a lack of English proficiency, any history of neurological disorder, head trauma with loss of consciousness, lifetime history of substance dependence, substance abuse within the preceding six months, or any medical condition that might affect cerebral or olfactory functioning (e.g., nasal fracture, cold, allergy, etc.). Control participants with a history of Axis I, Axis II cluster A personality disorder, or family history of Axis I psychotic disorder in a first-degree relative were excluded. Furthermore, family members were excluded for any Axis I psychotic disorder or prodromal psychotic symptoms but not for a history of nonpsychotic axis I disorder if resolved for a year or more.

Groups did not differ with respect to age ($F_{2,152} = 1.38, p = .25$) or sex composition ($\chi^2 = 3.61, df = 2, p = .16$). Groups differed with regard to race ($\chi^2 = 15.44, df = 6, p = .02$), as the schizophrenia group was comprised of significantly fewer Caucasian subjects (29.2%) compared to the cohort of controls (59.1%) and family members (50.0%). Additionally, groups differed with regard to education ($F_{2,152} = 11.71, p < .001$). Controls had a significantly higher level of educational attainment compared to patients ($F_{1,152} = 22.81, p < .001$) and family members ($F_{1,152} = 6.08, p = .01$). Family members and patients did not differ with regard to educational attainment ($F_{1,152} = 1.07, p = .30$). The three groups did not differ, however, with regard to paternal education ($F_{2,129} = 0.58, p = 0.56$), a more accurate estimate of ability that minimizes the confounds of the illness process (Resnick 1992). Overall group differences in smoking, as quantified by pack-days, were statistically significant ($F_{2,137} = 3.11, p = .05$). Not surprisingly, patients reported a higher smoking burden relative to controls ($F_{1,137} = 5.98, p = .02$). Family members did not differ significantly from patients ($F_{1,137} = 1.67, p = .20$) or controls ($F_{1,137} = 0.16, p = .69$). Clinical and demographic variables for Study One are presented in Table 1.

Study Two—Adolescents and young adult participants were recruited through the Neurodevelopment in Adolescence and Young Adulthood (NAYA) longitudinal research program of young persons at risk for psychosis and multicenter genetics studies at the Schizophrenia Research Center of the University of Pennsylvania. Participants in the NAYA program were recruited into categorical risk groups as follows: 1) clinical risk participants (CR; $n = 10$) who had prodromal symptoms (operationally defined below) but no family history of schizophrenia, 2) genetic risk participants (GR; $n = 14$) who had a first-degree relative with schizophrenia, and 3) low risk participants (LR; $n = 17$) who had no prodromal symptoms, no family history of schizophrenia, and no DSM-IV Axis I psychotic disorder or Axis II Cluster A (schizotypal, schizoid, paranoid) diagnosis. NAYA inclusion was limited to subjects between the ages of 10 and 25 years of age.

In addition to the aforementioned assessments administered to individuals in Study One (DIGS or SCID), all NAYA participants were administered the SCID Module E (Anxiety Disorders), and the Structured Interview for Prodromal Syndromes (SIPS; McGlashan, et al. 2003) that includes the Scale of Prodromal Symptoms (SOPS; McGlashan, et al. 2001, McGlashan, et al. 2003, Miller, et al. 1999). For participants under the age of 18, collateral information was also obtained from an interview with a parent or caregiver. Classification of a subject as CR required: 1) the presence of at least one positive symptom (rated 3–5 in severity), or at least two negative and/or disorganized symptoms (rated 3–6 in severity) on the SOPS, and 2) presence of symptoms during the 6 months prior to testing. In the CR group, most participants showed a mixture of positive, negative and disorganized symptoms ($n = 8$), one exhibited solely positive symptoms, and one solely disorganized symptoms. Individuals in the GR cohort were 7 siblings and 7 offspring from 13 families. Five individuals in the genetic risk group also met criteria for prodromal symptoms, with 3 showing a mixture of positive, negative and disorganized symptoms, and 2 exhibiting only positive symptoms. All participants were assessed for current or past DSM-IV Axis I or Axis II Cluster A disorders (First, et al. 1995). An integrated history of developmental, medical, psychiatric and social history was compiled for each participant, and consensus lifetime best estimate diagnoses were achieved by case review of at least two doctoral level clinicians.

Overall exclusion criteria for NAYA subjects included: 1) presence or history of pervasive developmental disorder (e.g., autism) or mental retardation endorsed by informant, 2) presence or history of medical or neurological disorder that may affect brain function (e.g., hypertension, cardiac disease, endocrine disorders, renal disease, pulmonary disease, history of seizures, head trauma or CNS tumors), 3) lack of English proficiency, 4) a history of a bleeding disorder, and 5) a standard score of 70 or greater on the Reading Subtest of the Wide Range Achievement Test – 3rd edition (WRAT-3R; Wilkinson 1993), a standardized estimate of verbal intelligence.

NAYA participants did not differ with respect to age ($F_{2,38} = 1.15, p = .33$), race ($\chi^2 = 11.84, df = 8, p = .16$), education ($F_{2,38} = 2.06, p = .14$), paternal education ($F_{2,31} = 0.45, p = 0.64$), or pack-days ($F_{2,37} = 0.86, p = .43$). Groups differed with respect to sex composition ($\chi^2 = 6.21, df = 2, p = .04$) as the clinical risk group had a larger percentage of males compared to the low risk and genetic risk cohorts. Clinical and demographic variables for Study Two are presented in Table 2.

2.2 Materials and Study Procedures

Following a full explanation of study procedures, written informed consent (for participants 18 years and older) or parental consent and assent (for participants younger than 18 years) 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). Participants across both studies were administered the Sniffin' Sticks Odor Identification and Discrimination test (Hummel, et al. 1997, Kobal, et al. 1996). During the odor identification task, subjects were presented with 16 odor-impregnated markers which they smelled and identified in a four-alternative multiple choice format. This commercially-available test has been used extensively in Europe for the assessment of chemosensory function. The task and psychometric properties are described in detail elsewhere (Hummel, et al. 1997). The task was administered birhinally by a trained technician, who placed the pen under the participant's nares, and recorded the answer following the subject's response. During the 16-trial odor discrimination test, the subject was presented with three odors using pen-like odor dispensers. The subject smelled each of the triplets and stated which one odor differed from the other two. The number of odors correctly identified and discriminated was tallied separately for each task.

2.3 Statistical Analyses

To ensure comparability across psychophysical tests, the raw scores for odor identification and odor discrimination for all participants were rescaled to standard equivalents (Z transformation) using the means and standard deviations of the healthy control group (Study One) or low risk group (Study Two). For Study One, group differences were examined using the Generalized Linear Latent and Mixed Models (GLLAMM) algorithm implemented in Stata 9.0 (StataCorp, College Station, Texas). In order to account for shared variance for participants in the same family, subject and family were included as hierarchically nested random-effects factors, and group (patient/relative/control), olfactory task type and sex were included as fixed-effects predictors of response. Race and smoking burden (pack-days) were also included as covariates in the analysis. Significance levels were assessed using the Wald test statistic with χ^2 distribution. Statistically significant group differences were parsed by post hoc computation of appropriate linear combinations of model coefficients, along with associated z -statistics. An ANCOVA was conducted to examine olfactory differences between patients taking antipsychotic medications and patients not taking antipsychotic medications, with pack-days as a covariate in the analysis. Within the patient group, relationships between olfactory performance and clinical assessments (negative symptoms, positive symptoms, general psychiatric symptoms), medication dosage, and illness characteristics (duration of illness, age of onset) were measured by Pearson correlations (r).

For Study Two, the GLLAMM algorithm was conducted with subject and family as random-effects factors, and group (CR/GR/LR), olfactory task type and sex as fixed-effects predictors. The relationship between olfactory performance and prodromal symptoms was examined using Pearson correlations. Effect sizes (Cohen's d) were calculated using criteria set forth by Cohen (1988; 1992).

3. Results

3.1 Study One: Schizophrenia and Non-ill First-Degree Family Members

Odor Identification and Odor Discrimination—Results of the GLLAMM analysis revealed a statistically significant main effect of group ($\chi^2 = 45.94$, $df = 2$, $p < 0.0001$; see Figure 1 and Table 2). In paired contrasts, both patients ($\chi^2 = 45.70$, $df = 1$, $p < 0.0001$) and family members ($\chi^2 = 4.18$, $df = 1$, $p < 0.05$) differed from controls. Examining each task separately, there were statistically significant main effects of group for both odor identification ($\chi^2 = 239.50$, $df = 2$, $p < 0.0001$) and odor discrimination ($\chi^2 = 30.69$, $df = 2$, $p < 0.0001$). However, in paired contrasts, patients were impaired on both odor identification ($\chi^2 = 140.85$, $df = 1$, $p < 0.0001$, $d = .77$) and discrimination ($\chi^2 = 28.20$, $df = 1$, $p < 0.0001$, $d = 1.02$), while family members were impaired on identification ($\chi^2 = 185.74$, $df = 1$, $p <$

0.0001, $d = .55$) but not discrimination ($\chi^2 = 0.75$, $df = 1$, $p = 0.39$, $d = .04$). The main effect of sex ($\chi^2 = 2.75$, $df = 1$, $p = 0.10$) and diagnosis x sex interaction ($\chi^2 = 4.32$, $df = 2$, $p = 0.11$) were not significant. Group differences between patients taking antipsychotic medication and those not on antipsychotic medication were not statistically significant ($F_{1,57} = 0.79$, $p = .38$).

Relationship of Olfactory Performance to Illness Characteristics—In

schizophrenia patients, increased negative symptomatology was associated with reduced odor discrimination performance ($r = -.37$, $p < .01$) and reduced odor identification ability ($r = -.39$, $p = .001$). Overall positive symptomatology was not significantly related to odor discrimination ($r = -.07$, $p = .59$) or odor identification ($r = -.04$, $p = .74$) performance. Chlorpromazine equivalents (all p 's $> .46$) and overall severity of psychiatric symptoms, as indicated by BPRS total score, were not significantly related to odor identification or discrimination scores (all p 's $> .11$). Similarly, odor identification and discrimination accuracy were not associated with illness duration (all p 's $> .24$) or age of onset (all p 's $> .15$). Odor discrimination and identification were significantly associated in the patients ($r = .40$, $p = .001$), but not in non-ill first-degree family members or adult controls (p 's $> .09$).

3.2 Study Two: At-risk Youth

Odor Identification and Odor Discrimination—Results mirrored those observed in Study One. There was a statistically significant main effect of group across the two tasks ($\chi^2 = 16.40$, $df = 2$, $p < 0.001$; see Figure 2 and Table 2), and separately for odor identification ($\chi^2 = 14.49$, $df = 2$, $p < 0.001$) and discrimination ($\chi^2 = 6.30$, $df = 2$, $p < 0.05$). In paired contrasts, individuals in the CR group were significantly impaired at both identifying ($\chi^2 = 11.42$, $df = 1$, $p < 0.001$, $d = 1.23$) and discriminating odors ($\chi^2 = 5.68$, $df = 1$, $p < 0.05$, $d = .88$) relative to the LR group. In contrast, GR participants were impaired, relative to LR subjects on the odor identification task ($\chi^2 = 7.70$, $df = 1$, $p < 0.01$, $d = 1.07$), but were intact at discriminating odors ($\chi^2 < 0.1$, $df = 1$, $p = 0.96$, $d < 0.01$). There was no statistically significant main effect of sex ($\chi^2 < 0.1$, $df = 1$, $p = 0.82$) or diagnosis x sex interaction ($\chi^2 = 0.18$, $df = 2$, $p = 0.92$). Exclusion of GR youth with prodromal symptoms ($n = 5$) did not alter the significant effects observed (odor identification: $\chi^2 = 5.94$, $df = 1$, $p = 0.01$; odor discrimination: $\chi^2 < 0.1$, $df = 1$, $p = 0.85$).

Relationship of Olfactory Performance to Prodromal Symptoms—In NAYA

participants who met criteria for clinical risk, prodromal symptom severity (SOPS total score) was not associated with odor identification or discrimination ability (all p 's $> .26$). Odor discrimination and odor identification were not significantly associated in the clinical risk, genetic risk, or low risk subgroups (p 's $> .34$).

4. Discussion

The findings from the current investigation provide evidence for distinct profiles of olfactory disturbance in individuals with schizophrenia and youth at-risk for psychosis. Notably, we found that adult schizophrenia patients and non-ill family members were impaired on the odor identification task relative to demographically-matched control participants, while odor discrimination impairment was limited only to the patient group (Study One). These findings replicate the observation of odor identification impairments in prior family studies, including twin pairs discordant for schizophrenia (Kopala, et al. 1998) and nonpsychotic first- and second-degree relatives of psychotic subjects (Kopala, et al. 2001, Roalf, et al. 2006). Previous twin studies in healthy people have suggested that odor identification tasks, compared to odor pleasantness perception and odor detection tests, show significant heritability (Finkel, et al. 2001). This genetic loading was thought to reflect, in

part, the semantic load of odor identification tasks. In contrast, one prior study observed intact odor identification performance in relatives compared to clinic controls (Compton and Chien 2008). As noted by the authors, however, their control group performed approximately six to eight points lower on the University of Pennsylvania Smell Identification Test (UPSIT) compared to prior control samples and normative data. Thus, microsmic range scores in the controls could have prevented the observation of significant group differences between the relative and control groups. Nevertheless, our findings, taken together with the extant literature, provide additional support for the genetic mediation of odor identification abnormalities in schizophrenia.

Odor discrimination impairment was limited to the patient sample in the current investigation. Our findings replicate and extend the prior observation of discrimination deficits in male probands compared to healthy male controls (Rupp, et al. 2005a, Rupp, et al. 2005b), as we found that male and female patients were similarly impaired at discriminating odors. Importantly, first-degree relatives were intact at discriminating odors, similar to the non-ill monozygotic twins of schizophrenia/schizoaffective psychosis patients from the Ugur et al. (2005) study. Despite this prior finding of intact odor discrimination in relatives, the fact that family members in the current study performed comparable to controls on the task was surprising. Similar to odor identification tasks, the ability to discriminate odors relies on intact odor perception and executive functioning abilities (Hedner, et al. 2010). This is due to the fact that accurate delineation of the difference between a target odor and distracters relies on forming a representation of an odor and holding it in working memory stores. As unaffected family members have well-documented difficulties with working memory (Snitz, et al. 2006), as well as structural and functional impairments in olfactory processing, we expected odor discrimination ability to be impaired in this group. Our data do not support this hypothesis and suggest instead that odor discrimination impairments may be a manifestation of the disease process.

Preliminary data on olfactory performance in adolescent and young adult participants at risk for psychosis were included in the current investigation (Study Two). Notably, at-risk participants showed a similar pattern of olfactory impairment as the Study One cohort. Clinical risk youth were impaired at identifying and discriminating odors relative to the low risk group, while impairment in the young genetic risk cohort was limited to odor identification. Prior studies in at-risk youth have similarly observed robust deficits in odor identification (Brewer, et al. 2003, Woodberry, et al. 2010) with large effect sizes reported (Cohen's $d = -0.84$ to -2.14). In one highly relevant study, Brewer et al. (2003) prospectively reviewed a large cohort of ultra-high risk youth and found that those adolescents who went on to develop schizophrenia made significantly more odor identification errors compared to individuals who remained well or developed a different psychotic disorder. These results are particularly striking when considering the specificity to the development of schizophrenia over other psychotic disorders. While odor identification impairment has been similarly observed in young first-degree relatives, the effect size was attenuated (Cohen's $d = -0.50$; medium) compared to those found in the early onset psychosis samples (Corcoran, et al. 2005) and the aforementioned clinical risk samples.

No previous published study has examined odor discrimination performance in at-risk youth. Findings from the current investigation suggest that young clinical risk subjects show impairments similar to those observed in adult schizophrenia patients. In contrast, GR youth show impairments similar to unaffected adult relatives. It is notable that GR youth with prodromal symptoms ($n = 5$) resembled other GR youth, rather than CR subjects who also had prodromal symptoms but did not share a family history of schizophrenia - i.e., they were impaired in odor identification but not odor discrimination. Though the small number of subjects limits the conclusions that can be drawn, our preliminary results suggest that the

symptoms cross-sectionally judged to be prodromal in GR youth may reflect more trait-like schizotypal personality features, which are known to be elevated in schizophrenia family members, rather than the initial warning signs of a developing psychotic illness. We would hypothesize that the absence of discrimination deficits in GR youth, either with or without prodromal symptoms, would be predictive of those who do not progress to schizophrenia. A larger longitudinal sample is required to test this hypothesis.

In patients, greater olfactory impairment was associated with increased negative symptom severity. Conversely, correlations between olfactory performance and positive symptomatology, general psychiatric symptoms, and antipsychotic medication dosage did not approach statistical significance. The association between negative symptoms and olfactory disturbance has been observed across a wide variety of schizophrenia samples (Brewer, et al. 2001, Corcoran, et al. 2005, Good, et al. 2006, Goudsmit, et al. 2003, Malaspina and Coleman 2003, Malaspina, et al. 2002, Moberg, et al. 2006, Seckinger, et al. 2004) and further suggests that abnormalities in common neural pathways in the orbitofrontal-limbic neurocircuitry may underlie both olfactory processing and negative symptoms in schizophrenia.

The differential sensitivity of the odor discrimination test, relative to odor identification, could arise in two different ways. Odor discrimination may simply be an easier task than odor identification, since it does not require engagement of the semantic memory system in order to associate an odor with a verbal label. It may be, therefore, that the two tasks are differentially sensitive to milder vs. more severe levels of olfactory impairment, with impairment on both tasks (as observed in the patient and CR samples) reflecting greater dysfunction of a shared neural substrate. Alternatively, the two tasks could be probing two different neural substrates, both of which are dysfunctional in patients but only one of which is disrupted in first-degree relatives. While the neuroanatomy of the olfactory system has been clearly delineated, an understanding of the subregions associated with specific olfactory behavioral tasks is still in its infancy. However, recent evidence suggests that there may, in fact, be separable neural substrates for odor identification and discrimination. In particular, Frasnelli et al. (2010) found that odor identification performance was significantly associated with parietooccipital sulcus, entorhinal and piriform cortex volume, whereas odor discrimination performance was significantly correlated with insula and precentral gyrus volume. Thus, it is possible that the prodromal state and overt psychosis, as opposed to genetic risk, are associated with compromise of these discrete brain regions. These findings highlight the potential utility of studying odor discrimination ability as a biomarker of vulnerability for psychosis in future investigations.

One important question, though, is whether these olfactory deficits are merely nonspecific markers of more global cognitive dysfunction, or whether they are unique probes of select neural substrates. Although olfactory performance has been associated with broader measures of verbal and executive dysfunction in some studies (Compton, et al. 2006, Purdon 1998, Seckinger, et al. 2004), others have clearly demonstrated the absence of any association between olfactory deficits and other cognitive deficits including memory, concept formation, and sustained attention (Seidman, et al. 1997, Seidman, et al. 1991, Stedman and Clair 1998). Similarly, olfactory impairment has been observed despite intact performance on other non-olfactory tests of identical format and complexity (e.g., picture identification and color naming tasks; Houlihan, et al. 1994, Kopala, et al. 1995). These findings suggest that olfactory deficits, in schizophrenia, cannot be solely attributed to nonspecific factors such as patient motivation, global cognitive impairment, or fluctuations in attention. Since olfactory deficits have also been shown to be a specific predictor of conversion to psychosis in ultra-high risk youths (Brewer et al. 2003), we anticipate that this will also be true for this younger cohort. However, further work is needed to determine the

extent to which dynamic prefrontal changes and variability in cognitive functioning observed in at-risk youth contribute to the olfactory deficits observed in this younger cohort. Also, in the current study, there were significantly more males in the CR group than the GR and low-risk groups. While sex effects for odor identification have been observed in healthy individuals, no overall sex differences or group-by sex interaction were observed in either sample. Furthermore, results of a comprehensive meta-analysis by Moberg et al. (1999) found that sex was not a significant moderator of study effect size in studies on olfactory performance between schizophrenia patients and controls.

Collectively, the results of the current study reaffirm the presence of odor identification deficits in family members of schizophrenia probands. Our findings further suggest that olfactory processing abnormalities dissociate in schizophrenia, with certain aspects reflecting heritable vulnerability deficits and others representing overt manifestations of the disease. While the at-risk data in the current investigation was limited by the small sample size, our preliminary findings indicate that clinical and genetic risk youth show a dissociation of olfactory task performance similar to that observed in the adult sample. Future studies examining larger at-risk samples across olfactory probes are warranted, to determine whether odor discrimination deficits prior to the onset of illness can identify those individuals who are most likely to develop overt psychosis in the future.

Acknowledgments

We wish to thank Dana Marchetto, B.A., and Jared Hammond, B.A., for assistance with subject recruitment, task administration and data entry, Larry Macy, Ph.D., and Lan Gao, M.S., for assistance with data management, as well as the Hofmann Trust for their support of this research through the Brain and Behavior Research Foundation (formerly NARSAD, the National Alliance for Research on Schizophrenia and Depression).

BIT and REG report investigator-initiated research support from AstraZeneca Pharmaceuticals and Pfizer Inc. This study was funded by National Institutes of Health Grants MH63381 to Dr. Moberg, MH59852 to Dr. Turetsky, K08MH79364 to Dr. Calkins, K23MH079498 to Dr. Borgmann-Winter, MH66121 to Dr. Gur, Independent Investigator Awards from NARSAD to Dr. Moberg and Dr. Borgmann-Winter, and unrestricted funds from the Children's Hospital of Philadelphia to Dr. Borgmann-Winter.

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Figure 1. Olfactory task performance ($\pm$ SE) in schizophrenia patients (SZ) and first-degree family members (FDFM), with the performance of healthy comparison subjects (HC) set to zero.

Figure 2. Olfactory task performance ($\pm$ SE) in young people at clinical risk (CR) and genetic risk (GR) for psychosis, with the performance of low risk (LR) subjects set to zero.

Table 1

Demographic Factors, Clinical Characteristics and Raw Olfactory Performance Scores for Study One

<i>Characteristic</i>	STUDY ONE		
	Schizophrenia (<i>n</i> = 65)	Relatives (<i>n</i> = 24)	Controls (<i>n</i> = 66)
	Mean ± SD (Range)	Mean ± SD (Range)	Mean ± SD (Range)
Age (years)	37.3 ± 10.4 (19 – 58)	36.7 ± 16.9 (18 – 63)	33.9 ± 11.4 (19–59)
Sex (Male:Female)	36:29	8:16	34:32
Education level (years)*	12.6 ± 2.4	13.2 ± 2.0	14.8 ± 3.7
Mother Education (years)	13.1 ± 2.9	12.0 ± 2.6	14.2 ± 2.4
Father Education (years)	13.2 ± 3.8	13.1 ± 3.8	13.9 ± 3.1
Pack-days*	0.6 ± 1.6	0.2 ± 0.4	0.1 ± 0.3
Chlorpromazine Equiv (mg/day)	319.5 ± 357.6 (0 – 1822)	-	-
Illness Duration (years)	15.9 ± 10.0	-	-
Age of Onset (years)	21.7 ± 7.1	-	-
BPRS ¹ Total Score	32.1 ± 8.8	-	-
SANS ² Total Score	25.9 ± 16.9	-	-
SAPS ³ Total Score	14.5 ± 14.3	-	-
Olfactory Performance			
Odor Identification (16 items)	11.35 ± 2.49	12.46 ± 1.79	13.30 ± 1.65
Odor Discrimination (16 items)	9.63 ± 2.37	11.92 ± 1.77	12.00 ± 1.91

* Significant group difference ($p < 0.05$)¹ BPRS = Brief Psychiatric Rating Scale (Rhoades and Overall 1988)² SANS = Scale for the Assessment of Negative Symptoms (Andreasen 1984a)³ SAPS = Scale for the Assessment of Positive Symptoms (Andreasen 1984b)

Table 2

Demographic Factors, Clinical Characteristics and Raw Olfactory Performance Scores for Study Two

	STUDY TWO		
	Clinical Risk (<i>n</i> = 10)	Genetic Risk (<i>n</i> = 14)	Low Risk (<i>n</i> = 17)
	Mean ± SD (Range)	Mean ± SD (Range)	Mean ± SD (Range)
Age (years)	19.9 ± 2.64 (16 – 24)	19.3 ± 4.12 (10 – 25)	21.0 ± 2.5 (15 – 25)
Sex (Male:Female) *	8:2	4:10	6:10
Education level (years)	12.5 ± 2.2	12.0 ± 3.2	14.0 ± 2.9
Mother Education (years)	15.1 ± 2.6	13.6 ± 2.2	15.2 ± 2.4
Father Education (years)	14.8 ± 3.5	14.0 ± 5.2	15.5 ± 3.1
Pack-days	0.1 ± 0.1	0.04 ± 0.1	0.1 ± 0.3
SOPS ^I Total Score	36.4 ± 18.5	14.6 ± 11.1	2.9 ± 3.7
Olfactory Performance			
Odor Identification (16 items)	11.40 ± 1.07	11.93 ± 1.49	13.12 ± 1.50
Odor Discrimination (16 items)	10.10 ± 2.02	11.85 ± 1.63	12.06 ± 1.60

* Significant group difference ($p < 0.05$)

^I SOPS = Scale of Prodromal Symptoms (McGlashan, et al. 2001, McGlashan, et al. 2003, Miller, et al. 1999)