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Contributions of Olfactory and Neuropsychological Assessment to the Diagnosis of First-Episode Schizophrenia

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Abstract

Objective: First-episode schizophrenia and schizoaffective patients (SZ+) show olfactory impairments, but how these relate to cognitive dysfunction remains unclear. We examined the relationship between cognitive and olfactory dysfunction in SZ+ and the clinical utility of these measures in the assessment of SZ+ patients.

Method: First-episode SZ+ patients (n = 63) and controls (n = 63) were administered tests of odor identification and discrimination in addition to measures of manual dexterity, processing speed, attention and working memory, executive functioning, ideational fluency, and memory. We analyzed the relationships between olfactory and cognitive variables and conducted stepwise multiple regressions to identify which cognitive indices best predicted olfactory performance within the SZ+ group. Linear discriminant analysis (LDA) was used to identify which measures best distinguished cases from controls.

Results: Among patients, odor discrimination correlated with perseverative errors and odor identification correlated with bilateral manual dexterity. Odor discrimination performance was best predicted by perseverative errors and letter fluency, while odor identification ability was best predicted by manual dexterity. Stepwise LDA revealed that manual dexterity, letter-guided word fluency, and odor discrimination best distinguished SZ+ from healthy adults.

Conclusions: These findings indicate that manual dexterity, letter-guided word fluency, and odor discrimination may provide incremental information that strengthens a diagnosis of SZ+. Though odor discrimination tasks have received limited attention in schizophrenia studies, the extant data along with the present results indicate that odor discrimination tasks may have utility over odor identification measures as a neurodevelopmental risk marker. Additional studies examining odor discrimination as a predictor of SZ spectrum illness are warranted.

Keywords

smell; schizophrenia risk; early psychosis; cognition

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Persons with schizophrenia reliably demonstrate olfactory dysfunction in all phases of the illness (Moberg et al., 2014) with deficits manifesting in the prodromal period (Brewer et al., 2001; Brewer et al., 2003; Woodberry et al., 2010) and worsening over the disease course (Moberg et al., 1997). In the schizophrenia prodrome and early phases of the illness, patients show deficits across measures of odor identification (Brewer et al., 2001; Good, Whitehorn, Rui, Milliken, & Kopala, 2006), odor detection threshold (Kamath et al., 2012), odor hedonic processing (Kamath, Turetsky, Calkins, et al., 2013), and odor discrimination (Kamath et al., 2014), that are independent from antipsychotic medication use and smoking burden (Houlihan, Flaum, Arnold, Keshavan, & Alliger, 1994; Kopala, Clark, & Hurwitz, 1993). Behavioral olfactory deficits correspond with structural and functional abnormalities of the olfactory system thought to reflect neurodevelopmental disruptions tied to the early prenatal period of heightened schizophrenia risk (Takahashi et al., 2013; Turetsky et al., 2000). In investigations employing meta-analytic and longitudinal methods, olfactory tasks distinguish clinical high-risk individuals with subthreshold psychosis from persons less likely to develop schizophrenia, such as unaffected first-degree relatives and individuals with schizotypal personality disorder (Brewer et al., 2003; Moberg et al., 2014) and differentiate first-episode schizophrenia patients from individuals with affective psychosis (Kamath, Lasutschinkow, Ishizuka, & Sawa, 2017), though see Brewer et al. (2001). Olfactory dysfunction in schizophrenia is also strongly associated with persistent negative symptoms and poor functional outcome (Good et al., 2010). These findings highlight the potential utility of olfactory measures in the clinical assessment of schizophrenia, particularly for identifying patients at risk for unremitting negative symptoms.

Though studies of olfaction have gained increasing attention in the schizophrenia literature, comparably fewer studies have examined the neurocognitive correlates of olfactory dysfunction. As neuropsychological impairment is a core feature of schizophrenia (Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009; Szoke et al., 2008), an important question is how olfactory tasks contribute to the neuropsychological assessment of SZ+ patients and to what extent olfactory measures are associated with other cognitive abilities. To answer this question, Kopala et al. (1995) and Houlihan et al. (1994) administered measures of odor identification and additional color and picture identification tests of similar format and complexity to schizophrenia patients and controls. Despite performing poorly on the olfactory task, patients were indistinguishable from controls on the color and picture identification tests. As odor identification tasks typically require the examinee to select the verbal label that identifies the perceived odorant, prior work has also examined the influence of semantic processing deficits on poor odor identification performance. Two studies found that olfactory and semantic processing deficits in schizophrenia were uncorrelated (Good, Martzke, Milliken, Honer, & Kopala, 2002; Kamath, Turetsky, Seligman, et al., 2013). Finally, two reports by Seidman et al. (1997; 1991) found no relationship between inattention and odor identification in schizophrenia, suggesting that a core neurocognitive feature of the illness cannot completely explain the olfactory deficits observed.

Several studies have examined the degree to which executive dysfunction and memory deficits in schizophrenia contribute to poor odor identification performances. The primary olfactory regions are centrally located within the medial forebrain and show robust and

bidirectional connections with frontotemporal regions implicated in the pathophysiology of schizophrenia. Cognitive measures purported to probe functions of the frontotemporal lobes have shown conflicting relationships with olfactory performance in schizophrenia. Moberg et al. (2006) and Seidman et al. (1997; 1991) found no association between odor identification ability and performance on a card-sorting measure requiring cognitive flexibility, whereas others found that poor odor identification was correlated with poor set maintenance (Stedman & Clair, 1998) and fewer categories completed (Brewer, Edwards, Anderson, Robinson, & Pantelis, 1996) on different versions of the Wisconsin Card Sorting Test (Heaton, 1981; Nelson, 1976). Similarly, an association between odor identification and response inhibition was noted in one schizophrenia sample (Purdon, 1998) but was not replicated in a subsequent study (Moberg et al., 2006). Examinations of memory performance are more consistent with studies showing associations between odor identification and verbal and visual memory scores (Compton et al., 2006; Good et al., 2002; Moberg et al., 2006). Additional investigations found relationships between odor identification and intellectual indices of verbal reasoning (Seckinger et al., 2004; Seidman et al., 1997) and processing speed (Corcoran et al., 2005; Goudsmit et al., 2004; Seckinger et al., 2004). A study of neurocognition in a large psychosis cohort found that performance on an odor identification test was associated with measures of attention and working memory (Seidman et al., 2016).

To date, studies examining the cognitive correlates of olfactory measures in schizophrenia have been limited to measures of odor identification. Odor discrimination represents another higher order olfactory domain that may have utility in distinguishing schizophrenia patients from individuals less likely to develop overt illness. During an odor discrimination task, examinees are typically presented with three odorants in succession and are asked to determine which odor is different from two identical odorants. Early studies by Rupp et al. (2005a; 2005b) found that men with schizophrenia showed poor odor discrimination ability relative to controls. Ugur et al. (2005) similarly reported odor discrimination impairment in ten patients diagnosed with schizophrenia or schizoaffective psychosis, but not in their unaffected monozygotic twins. In a larger sample, odor discrimination impairment was present in schizophrenia patients and youths at clinical risk for psychosis but not in unaffected first-degree relatives (Kamath et al., 2014), first-episode patients with affective psychosis (Kamath et al., 2017), or outpatients with bipolar disorder, major depression, or anxiety (Kamath et al., 2018). In contrast, odor identification deficits have been reported in first-degree relatives of schizophrenia patients (Kamath et al., 2014) and in individuals with depression (Kamath et al., 2018). Taken together, these findings raise the possibility that odor discrimination tasks have greater specificity to schizophrenia than measures of odor identification.

Though studies have yet to assess the cognitive correlates of odor discrimination performance in schizophrenia, prior work in healthy individuals found relationships between odor discrimination and measures of letter fluency and working memory abilities (Hedner, Larsson, Arnold, Zucco, & Hummel, 2010). This latter association is not surprising as the task relies on holding information in working memory stores prior to selecting the target odor from distractor odorants. Given the well-documented executive deficits in schizophrenia and the focus on odor identification in prior studies, studies examining

the cognitive correlates of odor discrimination in schizophrenia appear warranted. In the current study, we assessed group differences in olfactory and cognitive abilities between first-episode psychosis patients with schizophrenia, schizoaffective disorder, or schizophreniform disorder (SZ+) and healthy controls, the relationship between olfactory and cognitive indices within each group, and cognitive predictors of odor identification and discrimination performance within the SZ+ group. We then used stepwise discriminant analysis to determine what combination of olfactory and cognitive tests contribute to the discrimination of SZ+ patients from controls. Based on prior work, we hypothesized that odor identification and discrimination measures would be associated with different cognitive domains. In particular, we hypothesized that measures of odor identification would be associated with verbally-mediated measures of fluency and verbal memory and that odor discrimination tasks would be associated with measures of working memory and executive functioning.

Method

Sample Demographics and Selection Criteria

The cohort used in the present study is part of an ongoing longitudinal assessment of first episode psychosis in the Johns Hopkins Schizophrenia Center. The study is approved by the Johns Hopkins School of Medicine Institutional Review Board and was conducted using guidelines established in accordance with The Code of Ethics of the World Medical Association (1964 Declaration of Helsinki). Following a detailed and careful screening and consent process, written informed consent was obtained for all participants 18 years and older. Parental consent and assent was obtained for all participants under age 18. Adults and adolescents with SZ+ (n = 63) and healthy adults and adolescents (n=63) without family history of psychosis were recruited. Patient diagnoses were established using the Structured Clinical Interview for DSM-IV-Patient Edition (SCID; First, Spitzer, Gibbon, & Williams, 1996) and information from the patient's caregiver and/or medical record. For the patient group, participation was limited to individuals between 13 and 35 years of age with the onset of psychosis within 24 months of study enrollment. Individuals were excluded based on history of head trauma, neurologic disorder, cancer, viral infection, nasal trauma/surgery, current pregnancy, and active substance abuse. Participants who produced a positive urine drug screen, except marijuana, were excluded from participation. Finally, individuals with a reported history of intellectual disability or an estimated premorbid intellect below 75 on the Hopkins Adult Reading Test (HART; Schretlen et al., 2009) were excluded.

The SZ+ group consisted of persons diagnosed with schizophrenia (n = 49), schizoaffective disorder (n = 12) or schizophreniform disorder (n = 2). Seven patients were unmedicated at the time of the study visit, of which 6 reported first or second generation antipsychotic medication use in the past. Two patients were taking a first-generation antipsychotic medication, 51 were taking second-generation antipsychotic medication, and three were taking a combination of both first- and second-generation antipsychotic medications. Antipsychotic medication dosages were converted to chlorpromazine equivalents using published reference tables (Woods, 2005). Medication dosage information was unavailable for three patients.

SZ+ patients were slightly younger, $t(124)=1.84$, $p=.07$, completed fewer years of schooling, $t(124)=3.93$, $p<.001$, and had higher smoking levels, $t(124)=-2.99$, $p=.003$, than controls. Patients and controls did not differ with respect to racial composition, $x^2=.40$, $df=3$, $p=.94$, or sex, $x^2=1.4$, $df=1$, $p=.24$. Means, standard deviations, and frequencies for clinical and demographic variables are presented in Table 1.

Olfactory Assessment

All participants were instructed not to wear fragrances, smoke, or consume anything two hours prior to olfactory testing. Individuals were rescheduled if they had serious allergies or a sinus cold on the day of testing. Odor identification and discrimination ability was measured using the Sniffin' Sticks Odor Identification and Discrimination Test (SS-OIT and SS-ODT; Hummel, Sekinger, Wolf, Pauli, & Kobal, 1997; Kobal et al., 1996). Tasks were administered birhinally by a trained technician in a ventilated room. During the 16-trial forced-choice odor identification test, odor-impregnated pens were presented to the participant's nares. Each participant was asked to identify the correct odor from a list of four descriptors. Subjects were permitted to smell the scented pen again if requested. During the 16-trial odor discrimination test, a triplet of scented pens were placed under the individual's nares in succession. Each triplet is comprised of two distracter pens with identical odorants and a third "target" pen which contains a different odorant. Subjects were asked to identify which pen contained the different odorant. During the task, subjects were allowed to smell each scented pen once. Accuracy scores were calculated by totaling the number of odors correctly identified and discriminated.

Neuropsychological Measures

Each participant was administered a comprehensive neuropsychological battery (Schretlen et al., 2007; Schretlen et al., 2013) of nine tests spanning six cognitive domains described previously by Heinrichs & Zakzanis (1998) and others (Seidman et al., 2002; Zubieta, Huguelet, O'Neil, & Giordani, 2001). Concept formation and perseverative responding were assessed with the Modified Wisconsin Card Sorting Task (MWCST; Nelson, 1976). Auditory-verbal and visuospatial learning and memory were measured with the Hopkins Verbal Learning Test (HVLT; Brandt, 2001) and the Brief Visuospatial Memory Test (BVMT; Benedict, 1997, respectively. Manual dexterity and speeded visuospatial discrimination were assessed using the Grooved Pegboard (GPB; Klove, 1963) and the Salthouse Perceptual Comparison Test (PCT; Salthouse, 1996). Ideational fluency was measured with the verbal (VF) and design fluency (DF) subtests of the Calibrated Ideational Fluency Assessment (CIFA; Schretlen & Vannorsdall, 2010). Simple attention, working memory, and divided auditory attention were measured using the Digit Span subtest of the Wechsler Adult Intelligence Scale (DS; Wechsler, 1956) and the Brief Test of Attention (BTA; Schretlen, 1989). Measures were administered and scored according to standard instructions by a trained research assistant.

Statistical Analysis

All analyses were conducted using SPSS, version 24. Group comparisons of cognitive measures were adjusted for age, sex, and education. Pack-days was additionally included as a covariate for analyses of olfactory measures. Medication dose was not associated

with primary outcome variables. Analysis of covariance was conducted to examine group differences in olfactory and cognitive measures between SZ+ patients and controls. Partial correlations were performed to assess associations between olfactory scores and cognitive test performances within each group. Using procedures detailed by Uitenbroek (1997), we maintained an experiment-wise significance level of $p<.05$ using a partial Bonferroni correction in which we accounted for the average correlation among cognitive variables. The average Pearson r among these variables was 0.28 for controls and 0.38 for SZ+ patients. The partial Bonferroni-corrected p value that defined significance was <0.0076 for controls and <0.0099 for SZ+ patients. Stepwise multiple regressions were employed to determine which cognitive variables best predicted performance on measures of odor identification and odor discrimination in the schizophrenia group. Finally, a stepwise linear discriminant analysis was performed to establish a parsimonious set of tests that would optimize discrimination of patients and controls.

Results

Group Differences in Olfaction and Cognition

Overall group differences were examined between SZ+ patients and controls. Controls showed better performance across all olfactory and cognitive measures administered. Controls were better at discriminating, $F(1,120)=6.63$, $p=.01$, and identifying odors, $F(1,120)=6.90$, $p=.01$. On measures of processing speed, controls showed faster completion times on the GPB, $F(1,121)=41.28$, $p<.001$, as well as faster visuospatial discrimination for PCT letters, $F(1,121)=9.54$, $p=.002$, and patterns, $F(1,121)=16.06$, $p < .001$. Compared to SZ+ patients, controls had longer auditory attention and working memory spans, $F(1,121)=9.67$, $p=.002$, and superior divided auditory attention, $F(1,121)=21.58$, $p<.001$. On measures of auditory-verbal and visuospatial learning, controls encoded more words, $F(1,121)=19.60$, $p<.001$, and more figures, $F(1,121)=16.46$, $p < .001$, with superior word recall, $F(1,121)=24.56$, $p<.001$, and figure recall, $F(1,121)=16.79$, $p<.001$. Controls generated more words on letter-guided, $F(1,121)=18.28$, $p<.001$, and category-guided, $F(1, 121)=17.88$, $p<.001$, verbal fluency indices, as well as more novel designs, $F(1,121)=20.39$, $p<.001$. On executive functioning tests of concept formation, controls completed more MWCST categories, $F(1,121)=10.73$, $p=.001$, and made fewer perseverative errors, $F(1,121)=8.86$, $p=.004$. Mean scores, standard deviations and effect sizes are presented in Table 2.

Relationships between Olfactory and Cognitive Measures

We examined the relationship between olfactory and cognitive measures. All partial correlations performed are shown on Table 3 and include age, sex, education, and cigarette packs per day. In controls, better odor identification was associated with faster manual dexterity on the GPB, $r(57)=-.34$, $p=.01$, and better odor discrimination was associated with PCT pattern completion speed, $r(57)=.27$, $p=.04$. These correlations were not robust to partial Bonferroni correction for multiple comparisons.

In SZ+ patients, odor identification was associated with HVLT learning, $r(57)=.29$, $p=.03$, HVLT delay, $r(57)=.29$, $p=.02$, Digit Span, $r(57)=.33$, $p=.011$, BTA, $r(57)=.30$, $p=.02$, and

GPB, $r(57)=-.36$, $p<.01$. This latter association between GPB and odor identification was the only correlation robust to correction for multiple comparisons. Odor discrimination performance was correlated with HVLT Delay, r(57) = .32, $p=.02$, WCST categories completed, $r(57)=.35$, $p<.01$, and WCST perseverations, $r(57)=-.46$, $p<.001$. The association between perseverative errors and odor discrimination was the only correlation robust to correction for multiple comparisons.

Cognitive Predictors of Olfactory Performance in SZ+ Patients

Within the schizophrenia group, two stepwise multiple linear regressions were conducted to predict odor identification and discrimination based on the 14 cognitive indices. Demographic and smoking variables were entered in block 1 and cognitive variables were entered stepwise in block 2. A statistically significant relationship was found for odor identification, $F(4,57)=2.59$, $p=.04$, with an R^2 of .19. All other cognitive variables were excluded by the stepwise selection, except for GPB, which was a significant predictor of odor identification ($\beta=-.36$, $p<.01$). The psychosis groups' odor identification score decreased by 0.04 points for every one second longer they took on GPB. Two significant regression models were produced for odor discrimination. The first model ($R^2=.29$, $F(4,57)=4.58$, $p=.001$) only contained WCST perseverative errors ($\beta=-.47$, $p<.001$). The second model ($R^2=.34$, $F(4,56)=4.9$, $p<.001$) included both WCST perseverative errors ($\beta=-.60$, $p<.001$) and letter fluency ($\beta=-.28$, $p=.03$). The final model found that each perseverative error was associated with a 0.26 point decrease in a patient's discrimination score and each additional word said on letter fluency was associated with a 0.07 decrease in the patient's discrimination score.

Linear Discriminant Function Analysis

We next examined what olfactory and neuropsychological test scores differentiated SZ+ patients from controls. The overall DFA was statistically significant (Wilks $\lambda=.614$, $\chi^2=59.849$, $df=3$, $p<.001$; canonical correlation coefficient = 0.62) and accounted for approximately 39% of the variance of our diagnosis grouping. The stepwise function first identified manual dexterity, Wilks $\lambda=.688$, $F(1,124)=56.273$, $p<.001$. Letter fluency was identified second, Wilks $\lambda=.634$, $F(1,123)=35.429$, $p<.001$, and odor discrimination was identified third, Wilks $\lambda=.614$, $F(1,122)=25.619$, $p<.001$. The reclassification of cases was successful with 78.6% of the cases correctly reclassified into their original categories (see Table 4). The psychosis patients were more often misclassified as healthy controls (25.4%), than healthy controls were misclassified as SZ+ patients (17.5%).

Discussion

The main findings of this study are that olfactory deficits are present in first-episode SZ+ patients, show unique relationships with specific neurocognitive tests, and contribute to the discrimination between healthy controls and first-episode SZ+ patients. Our finding that first-episode SZ+ patients show statistically significant deficits on measures of olfactory and neurocognitive domains is consistent with numerous prior reports and matches effect sizes documented in prior meta-analytic reviews. A meta-analysis of 2,204 first-episode patients with schizophrenia reported medium to large effect sizes for the cognitive indices

assessed in the current study (Mesholam-Gately et al., 2009). We similarly found medium effect sizes for MWCST categories completed and perseverative errors and large effect sizes for measures of manual dexterity, divided auditory attention, auditory-verbal learning and memory. Moberg et al.'s (2014) meta-analysis of olfactory functioning in 4,491 schizophrenia patients found medium to large effect sizes for odor discrimination and odor identification, respectively. Though the effect size we found for odor discrimination was comparable, the effect size we found for odor identification in our first-episode SZ+ sample was smaller than the large effect sizes observed in Moberg's meta-analysis of 72 studies ($d = -0.93$, 95% CI: $-1.06 < \delta < -0.79$). To date, most olfactory studies have examined chronic schizophrenia samples with a lengthier odor identification measure. Thus, effect sizes may be greater due to the different measures employed or to characteristics that can moderate olfactory performance, including illness duration (Moberg et al., 1997) and older age (Doty & Kamath, 2014).

An important question regarding the measurement of olfactory indices in schizophrenia is whether assessing both odor identification and discrimination captures new or redundant information about a patient's olfactory abilities. In healthy individuals, Hedner et al. (2010) found that similar cognitive factors contributed to odor discrimination and identification, suggesting these tasks recruit similar neuropsychological functions. In contrast, Lötsch et al. (2008) examined the utility of administering multiple olfactory measures in over 2,000 clinic patients and healthy adults. The authors found that assessing olfactory functioning in multiple ways aided in the clinical evaluation of smell loss, particularly at the earliest disease stages. Similar to prior investigations in schizophrenia cohorts, our findings suggest that different cognitive factors contribute to poor odor discrimination and identification performance in psychosis patients. We found that odor identification was uncorrelated with card-sorting ability (Moberg et al., 2006; Seidman et al., 1997; Seidman et al., 1991) and associated with auditory-verbal learning and memory (Compton et al., 2006; Good et al., 2002), attention, and speeded measures (Corcoran et al., 2005; Goudsmit et al., 2004; Seckinger et al., 2004). Though only the latter association survived correction for multiple comparisons, the associations we reported are consistent with prior work in schizophrenia. Among 14 cognitive measures, bilateral manual dexterity best predicted odor identification ability in regression analysis. Odor discrimination performance in the SZ+ group was positively correlated with WCST categories completed, HVLT delayed recall, and inversely associated with perseverative errors. Only the relationship between odor discrimination and perseverative errors survived correction for multiple comparisons. Regression analysis revealed that two models best predicted intact odor discrimination ability. Making fewer perseverative errors was associated with better odor discrimination ability. Additionally, fewer perseverative errors and reporting fewer words on letter fluency testing also predicted intact odor discrimination ability. One possible interpretation of this finding is that more rule-bound cognitive processing resulted in both fewer perseverative errors and fewer words produced, and that this also is associated with better odor discrimination. Alternatively, the counterintuitive letter fluency finding may be a spurious finding, as prior studies in healthy adults found a positive relationship between verbal fluency productivity and odor discrimination performance (Hedner et al., 2010).

Our findings support the contention that discriminating and identifying odors recruit different cognitive functions and raise the possibility that each task is sensitive to different neural substrates affected in schizophrenia. Findings in healthy individuals indicate that performance on these tasks show separable neuroanatomical substrates (Frasnelli et al., 2010), as odor identification accuracy is associated with increased volume of the parietooccipital sulcus and entorhinal and piriform cortices. In schizophrenia, poor odor identification performance is associated with temporal lobe, particularly entorhinal, abnormalities (Moberg et al., 2006; Turetsky, Moberg, Roalf, Arnold, & Gur, 2003). Though the neuroanatomical correlates of odor discrimination performance have not been examined in schizophrenia, work in healthy individuals indicates that odor discrimination performance is associated with insula, precentral gyrus, and right orbitofrontal cortex (OFC) volumes (Frasnelli et al., 2010; Zatorre & Jones-Gotman, 1991). Thus, use of both olfactory tasks may capture unique information regarding a patient's functioning, particularly in the prodromal and early stages of illness.

Perhaps the most novel finding of this study concerns the question of whether olfactory dysfunction in schizophrenia has clinical utility in the assessment of schizophrenia patients. The results of our stepwise discriminant analysis (DFA) between SZ+ patients and controls demonstrated statistically significant group separation with 78.6% correct initial subject classification. These findings show that first-episode SZ+ patients are distinguishable from controls using measures of speeded manual dexterity, letter-guided verbal fluency, and odor discrimination. Though measures of processing speed and letter fluency have been shown to elicit significant group differences in early psychosis (Mesholam-Gately et al., 2009), studies examining olfactory tasks in first-episode psychosis are limited to odor identification tasks. One of the earliest examinations found stability of poor odor identification difficulties in a neuroleptic-naïve first-episode cohort over a six-month interval (Brewer et al., 2001). Furthermore, olfactory dysfunction has been shown to be closely associated with negative symptoms in first-episode cohorts (Brewer et al., 2001; Kamath et al., 2017), with poor baseline odor identification scores predicting the presence of unremitting negative symptoms at one-year follow-up (Good et al., 2006) and poor outcome at four-year follow-up (Good et al., 2010). Among neuropsychiatric conditions, however, odor identification tasks have not reliably shown specificity to schizophrenia because odor identification difficulties have been reported in persons with PTSD (Dileo, Brewer, Hopwood, Anderson, & Creamer, 2008; Vasterling, Brailey, & Sutker, 2000), major depression (Kamath et al., 2018), and bipolar psychosis (Kamath et al., 2018). In contrast, odor discrimination tasks have been shown to distinguish youth at clinical risk for psychosis (CR) from young first-degree family members at genetic risk (GR) and low risk (LR) controls (Kamath, Turetsky, Calkins, et al., 2013; Kamath et al., 2014), and to distinguish adults with SZ from their unaffected first-degree family members (Kamath et al., 2014). Conversely, odor identification was impaired in *both* CR and GR cohorts, as well as adult schizophrenia patients and adult first-degree family members. Taken together, these data demonstrate that abnormal odor discrimination may serve as a neurodevelopmental marker of SZ+ risk, owing to their sensitivity to abnormalities in orbitofrontal-limbic circuitry and specificity to SZ+ cohorts. Odor identification impairment, in isolation, may represent a genetic vulnerability marker of psychosis that has less utility as a predictor of conversion. Further studies employing odor

discrimination measures in at-risk cohorts are needed to determine their utility in predicting conversion to schizophrenia.

An intriguing unexpected finding that emerged from this study concerns one participant who entered the study as a healthy control, developed first-episode psychosis and was diagnosed with schizophrenia the following year. The DFA "misclassified" this participant as having schizophrenia at baseline based on his poor olfactory and cognitive performance. In retrospect, it appears that the DFA classification anticipated his later development of schizophrenia. If one considers his DFA classification as correct, the correct classification rate marginally improves from 78.6% to 79.4%, as shown in Table 4.

Collectively, our results indicate that a relatively simple and inexpensive odor discrimination task could improve the clinical assessment of first-episode schizophrenia patients along with measures of speeded manual dexterity and letter-guided verbal fluency. Future studies examining the neuroanatomical correlates of odor identification and discrimination performance in psychosis patients would be useful in determining whether these findings reflect involvement of separable neuroanatomical substrates. Given that odor discrimination deficits are present in at-risk youth (Kamath et al., 2014) and twins discordant for schizophrenia (Ugur et al., 2005), and differentiate schizophrenia patients from individuals with affective psychosis (Kamath et al., 2017), further examination of odor discrimination in the schizophrenia prodrome appears warranted.

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Public Significance Statement

Our findings suggest that smell deficits are present in first-episode schizophrenia patients, show unique relationships with specific measures of cognitive ability, and may help discriminate first-episode schizophrenia patients from healthy controls. Additional studies on the use of odor discrimination as a biomarker in the early identification of schizophrenia patients are needed.

Table 1

Demographic and Clinical Characteristics

	Patients (*n* = 63)	**Controls (*n* = 63)**
	Mean (SD) / *n*	**Mean (SD) / *n***
Age (years)	22.44 (4.15)	23.75 (3.80)
Sex (Men: Women)	48:15	42:21
Race (AA: W: O)	33:25:5	33:25:5
Education level (years)*	12.98 (2.54)	14.63 (2.17)
Pack-days*	0.10 (0.22)	0.01 (0.07)
Illness Duration (months)	14.86 (11.55)	--
Age of Onset (years)	21.22 (4.28)	--
Chlorpromazine Equivalents (*n* = 60)	314.61 (292.96)	--
MMSE Total Score (*n* = 62)	27.40 (2.30)	--
SANS Total Score (*n* = 61)	33.25 (20.66)	--
SAPS Total Score (*n* = 61)	17.70 (16.99)	--

Note. AA = African-American, W = white, O = Biracial/Other; Mini Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975); Scale for the Assessment of Positive and Negative Symptoms (SAPS and SANS;Andreasen, 1984)

Table 2

Mean Raw Scores[†] (SD) and Effect Sizes of Olfactory and Neuropsychological Measures

Neuropsychological Domain	Test	Test Index Used	Psychosis (*n* = 63)	Controls (*n* = 63)	Effect Size[‡]
Olfactory Functioning	SS-ODT	Odor discrimination accuracy	9.69 (2.41)[b]	10.83 (2.41)[b]	−0.48
	SS-OIT	Odor identification accuracy	11.06 (2.23)[b]	12.15 (2.23)[b]	−0.49
Processing Speed	GPB	Mean completion time over two trials bilaterally	88.24 (16.65)[a]	68.59 (16.65)[a]	−1.18
	PCT	Sum of letter completions	28.89 (8.47)	33.70 (8.47)	−0.57
		Sum of pattern completions	38.48(8.47)	44.72 (8.47)	−0.74
Attention and Working Memory	DS	Sum of longest forward and backward span	10.46 (2.30)	11.78 (2.30)	−0.57
	BTA	Sum of total letters and numbers correct	13.25 (3.70)	16.41 (3.71)	−0.85
Auditory-verbal Learning/Memory	HVLT	Total words learned (HVLT Learning)	22.24 (4.96)	26.28 (4.96)	−0.81
		Delayed word recall (HVLT delay)	7.17 (2.43)	9.38 (2.43)	−0.91
Visuospatial Learning/Memory	BVMT	Total figures learned (BVMT Learning)	23.43 (6.19)	28.04 (6.19)	−0.75
		Delayed figure recall (BVMT delay)	8.98 (2.17)	10.61 (2.17)	−0.75
Ideational Fluency	CIFA-VF	Letter-guided verbal fluency	25.92 (8.86)	32.89 (8.86)	−0.79
		Category-guided verbal fluency	40.17 (11.23)	48.89 (11.23)	−0.78
	CIFA-DF	Novel designs produced	12.36 (6.62)	17.85 (6.62)	−0.83
Executive Functioning	MWCST	Number of category sorts	5.00 (1.16)	5.70 (1.16)	−0.60
		Number of perseverative errors	4.89 (4.44)[a]	2.46 (4.44)[a]	−0.55

Note. Sniffin' Sticks Odor Identification and Discrimination Identification Test (SS-OIT and SS-ODT; Hummel et al., 1997; Kobal et al., 1996), Grooved Pegboard Test (GPB; Klove, 1963), Salthouse Perceptual Comparison Test (PCT; Salthouse, 1996), Digit Span Forward and Backward (DS; Wechsler, 1956), Brief Test of Attention (BTA; Schretlen, 1989), Hopkins Verbal Learning Test – Revised (HVLT; Brandt, 2001), Brief Visuospatial Memory Test – Revised (BVMT; Benedict, 1997), Verbal Fluency (VF) and Design Fluency (DF) subtests of the Calibrated Ideational Fluency Assessment (CIFA; Schretlen & Vannorsdall, 2010), Modified Wisconsin Card Sorting Test (MWCST; Nelson, 1976)

[†]Mean raw scores and standard deviations presented are the estimated marginal means after adjusting for age, sex, and education

[‡]Cohen's *d*

[a]Larger scores denote poorer performances

[b]Olfactory scores were adjusted for the amount of cigarettes per day in addition to age, sex, and education.

Table 3

Correlations between olfactory and cognitive measures for healthy controls and schizophrenia

	Controls		SZ+ Patients	
Cognitive Variables	**Odor Discrimination**	**Odor Identification**	**Odor Discrimination**	**Odor Identification**
GPB	−0.24	**−0.3** **	−0.01	**−0.36** **b
PCT-Letters	0.14	−0.6	0.04	0.10
PCT-Patterns	**0.27** *	0.02	0.12	0.15
DS	0.14	0.11	0.11	**0.33** *
BTA	0.10	0.06	0.19	**0.30** *
HVLT Learning	0.15	0.05	0.22	**0.29** *
HVLT Delay	0.09	0.04	0.**32** *	**0.29** *
BVMT Learning	0.04	0.10	0.06	0.19
BVMT Delay	−0.16	−0.04	0.20	0.09
CIFA-VF Letters	0.13	−0.03	−0.02	0.27
CIFA-VF Category	0.19	0.08	−0.04	0.10
CIFA-DF	0.05	0.01	0.13	0.13
MWCST Categories	−0.02	−0.11	**0.35** **b	0.23
MWCST Perseverations	−0.04	−0.02	**−0.46** ***b	−0.25

Note: Using procedures detailed by Uitenbroek (1997), we maintained an experiment-wise significance level of $p<.05$ using a partial Bonferroni correction in which we accounted for the average correlation among cognitive variables. The average Pearson r among these variables was 0.28 for controls and 0.38 for patients with first episode psychosis. The partial Bonferroni-corrected p value that defined significance was <0.0076 for controls and <0.0099 for patients with SZ+

* $p<.05$

** $p<.01$

*** $p<.005$

b correlations surviving partial Bonferonni correction

Table 4

Confusion matrix of the original and predicted classifications calculated by the linear discriminant analysis

		Predicted Group Membership[†]			
		Healthy Controls		SZ+ Patients	
		n	%	*n*	%
Original Group Membership	Healthy Controls	52	82.5%	11	17.5%
	SZ+ patients	16	25.4%	47	74.6%

[†]78.6% of all cases were classified correctly; *Note.* The classification rate marginally improves to 79.4% when adjusting for the accurate classification of a healthy control that later converted to schizophrenia at their one-year follow-up visit.