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Olfactory processing, sex effects and heterogeneity in schizophrenia

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ABSTRACT

Introduction: Smell identification deficits are associated with negative symptoms in schizophrenia, particularly in males. Far less information is known about the relationship of odor detection sensitivity (acuity) and negative symptoms in schizophrenia, and currently there is a dearth in sex-stratified research specifically examining odor sensitivity and smell identification.
Methods: Fifty-eight individuals with schizophrenia and 42 healthy comparison subjects were assessed on tests of odor sensitivity, smell identification and cognition. Negative symptoms were assessed with the Positive and Negative Syndrome Scale and the Schedule for the Deficit Syndrome.
Results: In healthy males, increased odor detection sensitivity predicted better smell identification scores. In contrast, male schizophrenia patients showed a significant inverse relationship, in which increased odor sensitivity predicted lower smell identification scores. Odor sensitivity and smell identification were unrelated in both schizophrenia and healthy females. Olfactory processing was strongly linked to negative symptoms, but the relationships differed by sex. Emotional expression deficits were related to odor detection hypersensitivity in female patients, whereas smell identification deficits predicted these emotional deficits in male cases.
Conclusion: Sex differences in olfactory functioning were identified in healthy subjects and in schizophrenia patients. Smell identification was related to negative symptoms in males with schizophrenia, whereas odor detection sensitivity predicted these features in females. Sex differences should be considered in future analyses that employ odor stimuli for neuropsychiatric research.

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1. Introduction

Schizophrenia is a severe neuropsychiatric syndrome that affects about 1% of the population (National Institute of Mental Health, 2011). Its features include psychosis, socio-emotional deficits and cognitive impairments. Illness onset, typically in young adulthood, is defined by the emergence of psychotic symptoms such as hallucinations, delusions and disorganized thought or behavior. The "negative" symptoms, such as low social interest and motivation and impairments in emotional expression, are typically present and often precede the onset of psychosis. These symptoms are poorly responsive to existing treatments, associated with cognitive deficits, and account for the greatest amount of lifetime disability in the disease (Erhart et al., 2006). Smell identification deficits are associated with negative symptoms, particularly in male patients, and may significantly contribute to social drive abnormalities present in these individuals (Malaspina and Coleman, 2003). Less is known about odor detection sensitivity (acuity) and negative symptoms in schizophrenia, and the influence of gender. Sex-stratified analyses that specifically examine different components of olfactory processing and negative symptomatology may be crucial to improve the understanding of the causes for social function deficits in these individuals, and guide the development of new person-targeted treatment.

Neuroscience research is increasingly emphasizing the crucial importance of sex based differences in human brain function (Cahill, 2006; Beery and Zucker, 2011). Sexually dimorphic features are widely recognized in schizophrenia as well (Leung and Chue, 2000), and the failure to account for these dimorphic features may underlie some of the roadblocks that have been encountered in etiological research and treatment studies. On average, males have an earlier mean age of onset, more negative symptoms and greater cognitive deficits; females have more mood symptoms, better premorbid functioning and a better outcome than men (see Canuso and Pandina, 2007). Protective effects of female gonadal hormones have been hypothesized to explain some of these sex differences (Goldstein et al., 2002).

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Olfactory signals are implicated in social, sexual and other goal-directed behaviors in most species. Recently, Keller and Vosshall (2004) demonstrated that odor detection acuity is strongly influenced by higher level processing, even though it can be considered to be a peripheral system. Moreover, in mammals, the relationship of olfactory cues with social behavior is sexually dimorphic (Segovia and Guillamon, 1996). Human females, for example, have a slight advantage for detecting odors and performing central olfactory tasks (Doty and Cameron, 2009). Deficits in smell identification, considered to be connected to central olfactory mechanisms, are widely reported in schizophrenia (see Atanasova et al., 2008) and have been associated with negative symptoms (Brewer et al., 1996; Malaspina et al., 2002; Malaspina and Coleman, 2003; Corcoran et al., 2005). Although informative, smell identification assessment may not provide a full picture of the olfaction abnormalities in schizophrenia. In fact, a number of studies have shown that smell identification deficits can exist in people with intact olfactory sensitivity (Kopala et al., 1989; Kopala et al., 1993; Striebel et al., 1999). Few studies have examined odor detection sensitivity in schizophrenia and the results have been inconsistent (reviewed in Atanasova et al., 2008). Additionally, most psychiatric research examining social behavior and olfaction does not consider sex differences. This is surprising as early research by Kopala et al. (1989), and more recently by Seidman et al. (1997), suggests that male schizophrenia patients differ in olfactory processing compared to their female counterparts and healthy controls.

We addressed this limitation in the field by examining the relationship between two widely used "peripheral" and "central" olfactory metrics, a detection sensitivity test for phenyl ethyl alcohol (PEA) and a smell identification test, in male and female patients with schizophrenia and healthy control subjects. We also investigated the affect of negative symptoms on this relationship. Based on previous literature (e.g. Kopala et al., 1989; Seidman et al., 1997), we expected to find olfactory deficits in male schizophrenia patients as compared to female patients and control subjects. We also expected to demonstrate gender differences related to peripheral versus central olfactory processing and the relationship with negative symptoms in those with schizophrenia.

2. Methods

2.1. Participants

Fifty-eight individuals diagnosed with DSM-IV schizophrenia or schizoaffective disorder were recruited from inpatient and outpatient research and clinical units at the New York State Psychiatric Institute. Forty-two healthy comparison subjects were recruited from medical center postings and internet advertisements. Subjects were excluded who were psychiatrically unstable; pregnant; currently dependent on alcohol or other substances, on steroidal contraceptives or allergy medications; or who had a history of epilepsy, rhinoplasty or a major head injury requiring medical treatment. Patients were on stable medication regimens for at least one month and were clinically stable. All procedures were carried out by trained mental health professionals; their training entailed initial calibrations for validity, followed by regular tests of inter-rater reliability. The study was approved by the local Institutional Review Board and all subjects signed informed consent.

2.2. Measures

2.2.1. Diagnosis

The Diagnostic Interview for Genetic Studies (DIGS; Nurnberger et al., 1994) was used to determine the current and lifetime psychiatric diagnoses for all cases and controls. The inter-rater reliability was kappa = .95 for DSM-IV diagnosis and kappa = .80 for individual symptoms.

2.2.2. Negative symptoms

Current (state) negative symptoms were assessed with the negative subscale items from the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987), which include blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation and stereotyped thinking (Kay et al., 1987). Additionally, we also used a more recent factor analytic derived PANSS negative subscale comprised of lack of spontaneity, blunted affect, emotional withdrawal, poor rapport, apathetic social withdrawal, mannerisms and posturing, motor retardation, uncooperativeness, disturbance of volition, and poor impulse control (White et al., 1997).

Enduring (trait) negative symptoms were assessed with the Schedule for the Deficit Syndrome,(Kirkpatrick et al., 1989; Kirkpatrick et al., 1993) including restricted affect, diminished emotional range, poverty of speech, curbing of interests, diminished sense of purpose and diminished social drive.

2.2.3. Olfaction

Odor detection sensitivity was assessed with the Smell Threshold Test (STT) (Sensonics Inc.) for phenyl ethyl alcohol (PEA). A higher score corresponds to a stronger concentration required for odor detection (less sensitive acuity). The test was applied to the right and left nostril. Smell identification was assessed with the University of Pennsylvania Smell Identification Test (UPSIT; Doty et al., 1984), a 40-item scratch-and-sniff forced multiple choice test of odor identification.

2.2.4. Cognitive function

The Wechsler Adult Intelligence Scale (WAIS-III; Wechsler, 1997) was used to assess Verbal, Performance, and Full Scale IQ.

2.3. Data analysis

Data were entered and verified using the SIR Database Management Software (SIR 2002, SIR Pty Ltd). SPSS (PASW Statistics 17) was used for analyses. Descriptive statistics (means and standard deviations) and distributions of all measures were examined, whether continuous or categorical to identify key features (e.g. non-normal distribution, outliers, skewness) that might impact inferential methods. The demographic characteristics, age, education, WAIS Full Scale, Verbal and Performance IQs were assessed using univariate and multivariate ANOVA to examine effects of group membership (schizophrenia patients versus normal controls) and sex (male versus female) and to test for interaction between group and sex. Analyses of the olfaction scores (mean odor threshold, smell identification) were performed using univariate ANOVAs to assess the main effects of diagnostic group and sex and their interaction. Correlation coefficients were calculated between the measures of olfaction and those of the schizophrenia patients' symptoms. Testing of odor detection threshold (acuity) was applied to the right and left nostril; however, preliminary analyses of our results indicated only small differences between them, so the data for both sides were combined into a mean odor threshold. Clinical symptoms were not reported by the normal controls, as expected. As an integrative analysis to identify independent and salient associations between the two different olfactory measures and the symptom measures, we performed multiple regression analyses. The general regression model included either olfactory measure as the dependent variable, followed by the other olfactory measure at the first step, then age, age at illness onset, followed by the forward stepping of the symptom measures with the probability to enter set at $p<.10$. Separate regression analyses were performed for PANSS negative symptoms and deficit syndrome symptoms. Where appropriate multivariate tests were used to account for multiple comparisons; however Bonferroni

correction was not applied to correlation coefficients due to the unique features of the associations.

3. Results

3.1. Demographics

Study participants included 58 patients with DSM-IV schizophrenia or schizoaffective disorder (males/females: 31/27) and 42 healthy comparison subjects (males/females: 18/24). There were no significant differences in the distributions of age or ethnicity between patients and controls or for gender (Table 1). Patients had significantly less education than controls, although females were more educated than males in both groups. The male and female cases did not differ in age of illness onset. The WAIS-III Verbal IQ scores differed across diagnosis with the healthy controls exhibiting higher scores than the patients; however, there were no significant effects for Performance and Full Scale IQs. As for smoking, 31.3% of the patients and 16.2% of the healthy controls were current smokers, and 68.7% of the patients and 83.8% of the healthy controls reported that either never smoked or were former smokers. Significantly more patients were current smokers than the controls ($\chi^2 = 6.55$, df = 1, p = .011).

3.2. Olfactory processing

3.2.1. Odor detection sensitivity

Table 1 compares the measurements of olfaction between patients and controls and between the sexes and Fig. 1a illustrates these graphically. A lower threshold for odor sensitivity indicates that odor detection occurred at lower concentrations, indicative of more sensitive acuity. There were no significant diagnosis, gender or interaction effects for odor threshold. However, the Levene's test of equality of variances indicated that the schizophrenia patients exhibited a wider variation of thresholds than the controls, consistent with more heterogeneity (F = 3.50, df = 3/76, p = .019, [Fig. 1a]). This appears to be predominantly due to the female patients. Among all subjects, schizophrenia patients had both the highest percentage with less sensitive acuity (odor detection thresholds in upper quartile, cut point ≥3.614, seen in 34.8% of cases vs. 11.8% of controls), and the highest proportion with more sensitive acuity (odor detection scores in the lowest quartile, cut point ≤−5.45, seen in 28.3% of cases vs. 20.6% of controls). In female patients and controls, odor acuity became less sensitive with age (r = .499, n = 17, p = .041 and r = .442, n = 23, p = .034, respectively) with no comparable blunting of odor threshold observed with age in the males.

3.2.2. Smell identification

There was a significant gender effect in smell identification scores with females showing better identification than the males, however, post hoc tests did not reveal significant gender differences within the diagnostic groups (Table 1 and Fig. 1a). There was no significant group difference in overall accuracy, and the smell identification scores were uncorrelated with age in any group (correlation coefficients ranged from −.236 in female controls to .002 in male patients).

3.2.3. Relationships between odor detection sensitivity and smell identification

The scatter plots and correlations between the two olfactory measurements are depicted in the lower part of Fig. 1b (Note: the Y-axis scales for smell threshold move from less sensitive acuity to more sensitive acuity). The healthy males exhibited a significant association between their odor detection threshold and smell identification (r = .515, p = .041); those with more sensitive odor acuity correctly identified more of the 40 odor/items on the smell identification test. Odor sensitivity and smell identification were not significantly associated in male (r = −.27, p = .218) or female schizophrenia patients (r = −.12, p = .596), or the female controls (r = .066, p = .800). A comparison of the correlations between the male patients and controls, using Fisher's r to z transformation, revealed that they differed significantly (chi-square = 5.66, df = 1, p = .018). Moreover, the relationship in the males with schizophrenia was in the reverse direction as that of the healthy males such that those with a more sensitive acuity correctly named fewer smell items. In a subsequent multiple regression analysis controlling for relevant schizophrenia symptoms (*vide infra*) this reverse correlation of more sensitive acuity being related to lower smell

Table 1
Demographic, olfactory and cognitive measures in healthy controls and schizophrenia patients, by sex. Test statistic: Analysis of variance (ANOVA).

	Healthy controls		Schizophrenia patients		Statistics					
	Males N = 18	Females N = 24	Males N = 31	Females N = 27	Diagnosis		Gender		Diag./Gen.	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	F	p	F	p	F	p
Age (U)	29.5 (8.3)	34.5 (13.2)	32.3 (10.0)	33.0 (11.0)	0.10	.756	1.90	.172	1.11	.295
Onset age	–	–	22.2 (6.8)	25.2 (7.0)	t-test = 1.59, p = .118					
Education (category) (U)	4.4 (.92)	5.0 (.78)	3.2 (1.6)	4.1 (1.3)	17.8	.001*	8.46	.005*	0.51	.477
Smell identification	N = 17	N = 20	N = 28	N = 26						
SIT (U)	31.5 (3.6)	33.5 (4.4)	30.4 (4.0)	32.2 (4.4)	1.75	.189	4.58	.035*	0.01	.919
Odor threshold	N = 17	N = 17	N = 23	N = 23						
Multivariate Wilks' lambda for right and left smell thresholds					0.18	.834	1.77	.177	0.86	.427
Right smell threshold	−4.62 (1.4)	−4.83 (1.6)	−4.20 (1.4)	−5.43 (2.2)	0.06	.809	3.46	.067	1.73	.193
Left smell threshold	−4.64 (1.6)	−4.71 (1.1)	−4.21 (1.7)	−4.88 (2.7)	0.09	.767	0.70	.405	0.47	.497
Mean smell threshold (U)	−4.63 (1.5)	−4.77 (.98)	−4.29 (1.4)	−5.16 (2.2)	0.00	.957	1.87	.175	0.98	.325
WAIS IQ indices	N = 17	N = 14	N = 25	N = 22						
Multivariate Wilks' lambda for WAIS IQ indices					2.15	.124	0.01	.991	2.84	.065
Verbal IQ	110.4 (13.1)	106.4 (12.9)	99.8 (16.2)	103.7 (13.6)	4.01	.049*	0.00	.989	1.40	.239
Performance IQ	97.8 (12.6)	99.9 (14.3)	97.0 (19.2)	94.1 (12.7)	0.89	.350	0.01	.915	0.49	.487
Full Scale IQ (U)	105.2 (12.3)	103.4 (12.1)	98.6 (17.9)	99.6 (12.7)	2.41	.125	0.01	.907	0.18	.672

* Indicates significance, (U) = univariate ANOVA.

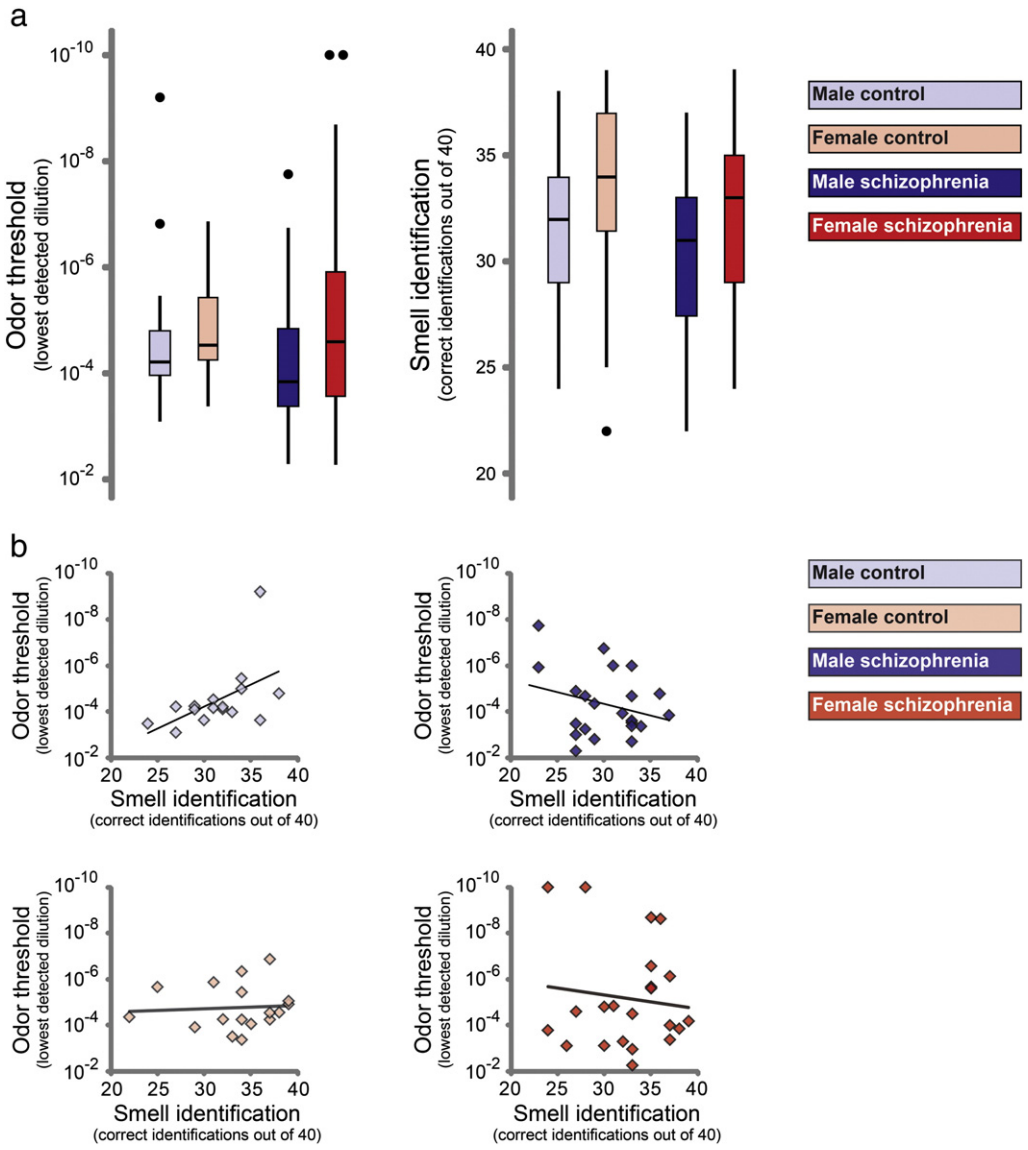

Fig. 1. Odor thresholds and smell identification in patients with schizophrenia and controls. (a) The lowest dilution of phenyl ethyl alcohol that was detected by male and female patients with schizophrenia and healthy controls (left) and the number of odors out of 40 that they could correctly identify in a 40-item scratch-and-sniff multiple choice test (SIT) (right) are shown (horizontal black line on each bar indicates median, boxed regions indicate 25%–75% quantiles, whiskers indicate 10–90% quantiles). (b) Both measures of olfactory function are shown for each subject. Note the much higher variability in the odor threshold in patients (right).

identification scores became significant in the male patients. Odor threshold and smell identification in the female patients, remained uncorrelated, as in the female controls (*vide infra*).

3.3. Negative symptoms

There were no significant differences on PANSS total scores between the male and female schizophrenia patients (multivariate Wilks' lambda: $F=0.19$, $df=3/50$, $p=.906$), for the negative symptom subscale (14.3 (6.1) versus 13.2 (5.6), $F=0.51$, $p=.477$), or other subscales that are not the focus of this report; positive symptoms (12.7 (6.2) versus 12.2 (7.9), $F=0.05$, $p=.830$) and general psychopathology (27.2 (11.2) versus 25.6 (9.3), $F=0.31$, $p=.580$).

The relationship between negative symptoms and olfaction sensitivity and identification was first analyzed on a factor level, using both the previously described standard PANSS negative subscale (Kay et al., 1987) and the modified PANSS negative subscale (White et al., 1997). Only male patients showed a significant correlation between reduction in smell identification and increased level of negative symptoms ($r=-.51$, $p=.008$ for both the standard and the modified negative subscale). There were no significant correlations between smell sensitivity and any of the negative subscales for either gender. We next analyzed the relationship between olfaction and individual negative symptoms (Fig. 2).

3.3.1. Odor sensitivity and symptoms (Fig. 2a)

To simplify the interpretation of the correlations and multiple regression analyses, we transformed the odor detection thresholds into absolute values. In so doing higher odor thresholds correspond to more sensitive acuity. Less sensitive acuity was significantly associated in males with decreased spontaneity ($r=-.493$, $p=.020$), and in females with increased social withdrawal ($r=-.449$, $p=.041$). To the contrary, more sensitive acuity predicted trait deficit symptoms

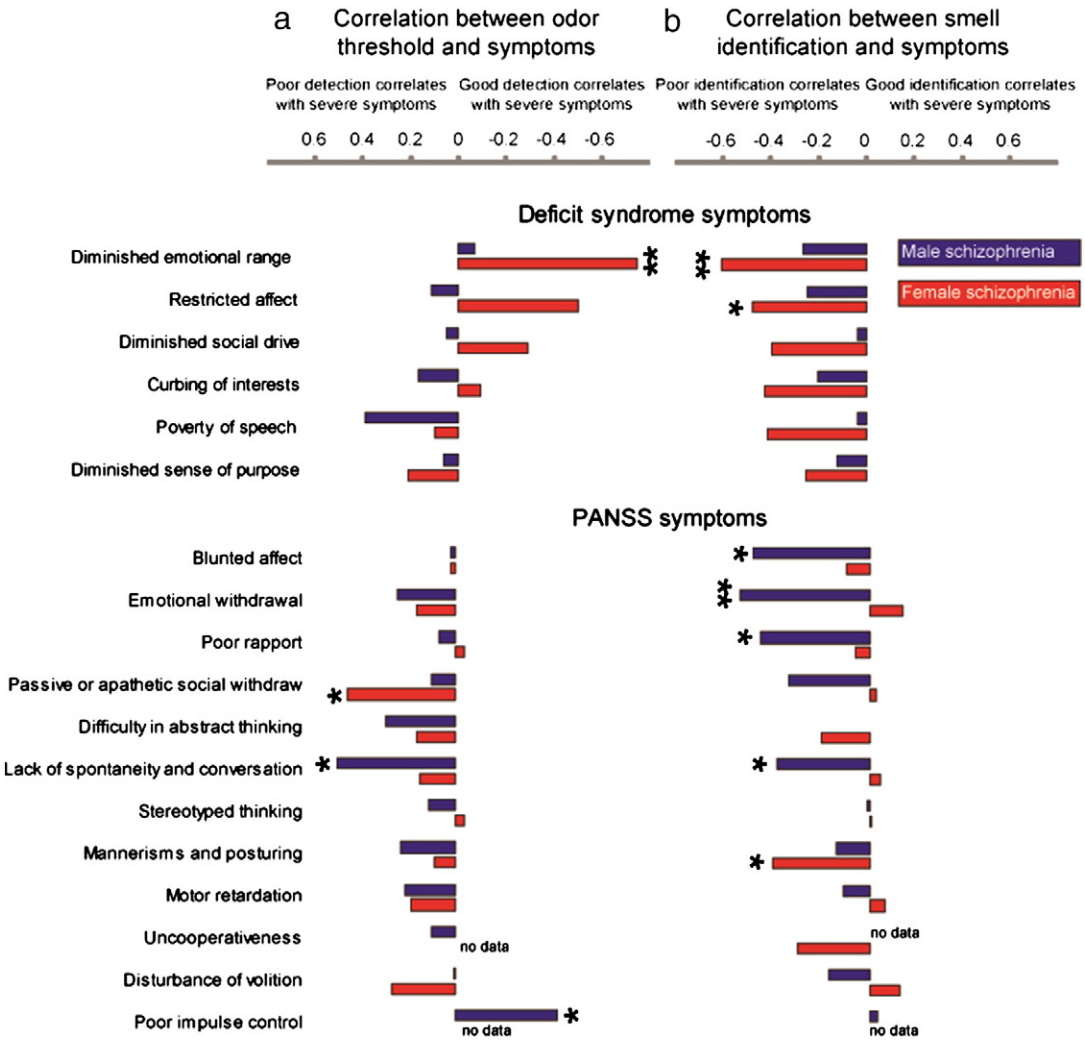

Fig. 2. Correlations between measures of olfaction and symptoms in patients with schizophrenia. The correlation coefficient between the lowest dilution of phenyl ethyl alcohol that was detected (a) or the number of odors out of 40 that they could correctly identify in a 40-item scratch-and-sniff multiple choice test (b) and schizophrenia symptoms are shown. The correlation coefficients for male and female patients are shown (**p<0.01, *p<0.05; bars to the left indicate cases in which poor olfactory function correlates with severe symptoms whereas bars to the right indicate cases in which good olfactory function correlates with severe symptoms; "no data" indicates cases in which there was insufficient data to calculate a correlation coefficient).

in females only, including diminished emotional range ($r = .750$, $p = .002$) and a trend for restricted affect ($r = .503$, $p = .067$).

We next examined which negative symptoms were related to odor threshold sensitivity using multiple regression models that included smell identification scores, age and onset age as control measures. For the PANSS symptoms in males (state measures), more sensitive odor acuity was associated with blunted affect ($t = 4.00$, $p = .002$) and lower smell identification scores ($t = -3.17$, $p = .007$); to the contrary, less sensitive odor acuity was related to lack of spontaneity, a symptom related to avolition ($t = -5.23$, $p < .001$). For the male patients, none of the deficit syndrome traits were significantly associated with odor threshold. In females, odor sensitivity was unrelated to smell identification or any PANSS negative symptoms, but it was associated with deficit syndrome traits. More sensitive odor acuity was associated with diminished emotional range ($t = 3.60$, $p = .009$), but less sensitive acuity was associated with increased poverty of speech ($t = -2.80$, $p = .026$).

3.3.2. Smell identification and symptoms (Fig. 2b)

For the male patients, smell identification deficits were significantly related to four of the seven PANSS negative symptom items (i.e. lower smell identification scores with greater negative symptoms): blunted affect ($r = -.493$, $p = .010$), emotional withdrawal ($r = -.545$, $p = .004$), poor rapport ($r = -.460$, $p = .018$), and lack of spontaneity ($r = -.392$, $p = .047$), as was the overall PANSS negative factor ($r = -.509$, $p = .008$). The female patients exhibited no associations with the PANSS state symptom items, but lower smell identification scores were associated with restricted affect ($r = -.479$, $p = .052$) and diminished emotional range ($r = -.609$, $p = .009$). Smell identification was not significantly associated with either of these in the male patients (respectively, $r = -.248$, $p = .266$ and $r = -.273$, $p = .218$).

Finally, we examined which negative symptoms were related to smell identification ability using multivariate regression models that included odor detection sensitivity, age and onset age as control measures. In the males with schizophrenia, better smell identification was related to less severe emotional withdrawal ($t = -2.89$, $p = .011$) and more sensitive odor acuity ($t = -2.42$, $p = .029$); the opposite relationship as was seen in the healthy males. Conversely in female cases, better smell identification was related to more severe emotional withdrawal ($t = 2.19$, $p = .046$), along with younger age ($t = -2.83$, $p = .013$) and later age of illness onset ($t = 2.25$, $p = .041$). For the females with schizophrenia, smell identification and sensitivity were again unrelated ($t = .81$, $p = .430$). No deficit syndrome traits were significantly associated to smell identification among either female or male schizophrenia patients.

4. Discussion

We identified robust sex differences in olfactory processing in both individuals with schizophrenia and healthy comparison subjects. The differences include the association, or lack thereof, between the sensitivity for detecting the test odor and smell identification ability. Healthy males showed a strong positive correlation between increasing acuity and better smell identification scores. Conversely, greater odor sensitivity predicted worse smell identification ability for males with schizophrenia in multiple regressions. However, neither female patients nor healthy females showed any relationship between odor detection sensitivity and smell identification, even though these female patients and controls had a slight advantage on both olfactory tasks, as is commonly reported (Doty and Cameron, 2009).

There was a female sex specific relationship for olfaction and negative symptoms in schizophrenia, whereby increased sensitivity for odor detection was strongly correlated with diminished emotional expression. We demonstrated a distinct male specific relationship for smell identification deficits and PANSS negative symptoms, which is consistent with the literature (Atanasova et al., 2008), with significant findings for blunted affect, emotional withdrawal, poor rapport, and lack of spontaneity/flow of conversation.

Since odor sensitivity and smell identification were significantly associated in males, we also used multiple regression to identify the specific symptoms linked to each olfactory test. In males, controlling for acuity showed that emotional withdrawal was uniquely associated with smell identification. Controlling for smell identification showed a more complex pattern for odor detection threshold, as blunted affect was linked to more sensitive acuity and lack of spontaneity was linked to less sensitive acuity. Comparably in females, controlled analyses showed diminished emotional range linked with very sensitive acuity and poverty of speech with less sensitive acuity. We earlier found that smell identification deficits were associated with social drive in a study that combined male and female cases and did not adjust for odor sensitivity. In the current analyses, smell identification was only associated with social drive factors in the male cases. After accounting for odor detection sensitivity, smell identification predicted expressive negative symptoms in male and female cases. It is of note that females only showed this association with respect to the enduring and severe “trait” negative symptoms of the deficit syndrome. This likely speaks to the sex differences in negative symptom expression that are well described in the disease.

The finding that both high and low odor sensitivity predicted different domains of negative symptoms is consistent with latent heterogeneity. Of further interest, factor analytic studies of negative symptoms consistently identify only two domains of symptoms: expressive deficits, which include emotion, linguistic and paralinguistic expressions, and avolition or asociality for daily-life activities (reviewed in Blanchard and Cohen, 2006; Messinger et al., 2011). In both males and females with schizophrenia in this study, more sensitive acuity tapped items related to emotional expression; diminished emotional range in females and flat affect in males. In contrast, less sensitive accuracy predicted asociality/avolition items: social withdrawal in females and decreased spontaneity in males. These findings bolster the hypothesis that deficits in expressiveness and avolition are non-overlapping domains of negative symptoms by showing that they are differentially associated with odor detection acuity.

The experience of symptoms in schizophrenia is described as “flooding” by intense sensory stimuli (Swerdlow and Geyer, 1998) that secondarily causes emotional blunting, which is consistent with our findings linking hyperosmia to emotional expression deficits. This sensory overload may be a result of deficient central inhibition, or “gating” of stimuli (see Tregellas et al., 2007). Odor sensitivity is known to be modulated by central mechanisms (Mainland et al., 2002) which could malfunction in schizophrenia. Such a failure might explain why more sensitive acuity predicted worse smell identification in males with schizophrenia, in direct contradistinction from healthy males. On the other hand, in the alternate setting of diminished olfactory input, elements of volition and sociality appear to be compromised in the patients. This observation would be particularly intriguing if social signaling molecules are shown to drive aspects of motivated behavior in humans. If so, then olfactory dysfunction might play a key pathogenic role in explaining this core disease feature.

In males, detecting and processing odor appear to be directly linked, whereas the modulation of odor sensitivity in female patients may be under different constraints. A role for odor processing in mate selection and child rearing by females may underlie both an olfactory advantage and a more enigmatic modulation of odor threshold. Sex differences in olfaction are of obvious importance in reproduction, since olfaction is the trigger for mating in many mammals and is supremely important in maternal behavior. It is plausible that females engage more memory and emotion in processing odor stimuli than males, leading to a more nuanced, top-down modulation of odor threshold. Sex differences in evaluating sexual attractiveness might also extend to evaluating olfactory signals. Human females, therefore, may employ cognitive processing and judgments of a man's status in evaluating his sexual attractiveness that males do not employ when evaluating female attractiveness (Rupp et al., 2009). Indeed sex differences are reported in the neural underpinnings of human olfaction (Frasnelli et al., 2009), including in the gray matter density of olfactory structures (Garcia-Falgueras et al., 2006). Since the orbitofrontal region that is activated by olfactory tasks (Savic, 2002) is consistently larger in females (Gur et al., 2002; Garcia-Falgueras et al., 2006; Luders et al., 2009) and is known to participate in the human sex differences for social and emotional capacities that favor females (Rupp, 2010), it may also contribute to a greater high level modulation of odor acuity in females.

These data extend the story of human sex differences in olfactory processing. They suggest that the detection of odors and the central processing of odors are less directly linked in females than in males, perhaps due to finer intervening cognitive processes or menstrual influences in females. Other clues to differential modulation of olfactory function are the sex differences in which types of symptoms relate to olfaction: only PANSS (state) negative symptom items in males and only deficit syndrome (trait) symptoms in females. Another sex specific effect was that younger age and later age of illness onset predicted better smell identification in females.

The wider variability of odor threshold in females with schizophrenia in this study may shed light on some of the contradictory findings on odor detection acuity from earlier studies (Atanasova et al., 2008). Most studies assess smell identification without testing odor threshold, as we did in an earlier patient cohort (Malaspina and Coleman, 2003). These have underestimated the relationship of olfactory processing abnormalities with schizophrenia symptoms for females. In addition, studies that combine male and female schizophrenia patients can obscure the sex specific findings.

These current findings come with possible limitations and should be considered to be preliminary. Although the schizophrenia patients and the comparison subjects were matched on age, ethnicity, gender, and cognition, the patients were less educated than controls. Given the comparable intelligence scores of the groups, we ascribed this difference to features of the illness, such as avolition or other symptoms. As these were key study outcomes, we did not adjust the analyses for education; although doing so did not substantially alter the results (data not shown but available upon request). Smell identification scores and mean sensitivity did not distinguish between the schizophrenia and control groups. Rather, our correlation and regression analyses focused on the sex differences in relationship of these measures and their associations with illness features. Deficits in smell identification and alterations in odor threshold are

useful tools for conducting sex-specific analyses in schizophrenia but are not necessarily tests for the disease. Another limitation is that we only used phenyl ethyl alcohol to test the threshold for odor detection sensitivity. Although there is a strong inter-odorant threshold correlation in humans (Hasin-Brumshtein et al., 2009), other odorants should be examined in future studies. It should be noted that our cases were all on stable medications and in a stable clinical state. Although there is no evidence linking medication status to performance on smell identification (Coleman et al., 2002), there is a report of a medication treatment effect on asymmetrical olfactory thresholds in schizophrenia (Purdon and Flor-Henry, 2000). These analyses did not separately consider right and left nostril thresholds, as this information converges at the anterior olfactory nucleus (Kikuta et al., 2008) and event related potential studies of central olfactory processing have not revealed main effects for right versus left nostril odor presentations (Olofsson et al., 2006; Stuck et al., 2006). We also did not control for menstrual cycle, which might underlie the sex differences linking threshold to smell identification, but would not explain the differential relationships of odor threshold and smell identification to symptoms in men and women with schizophrenia. Finally, some results of the controlled regression analyses were counterintuitive, which perhaps is a result of heterogeneity in physiological subtypes within our subject sample.

In summary, this study showed that the relationship between odor detection sensitivity and smell identification ability is sexually dimorphic; that negative symptoms are related to more sensitive odor detection in females, but to smell identification deficits in males; that odor threshold values are variable in schizophrenia; that very sensitive and insensitive acuity differentially tap the negative symptom domains of emotional expression and avolition/asociality, respectively; and that smell identification is better in younger females who have a later age of illness onset.

Olfaction is a promising probe for the social and emotional symptoms of schizophrenia but sex specific processing must be considered in these studies. Sex differences clearly underlie social and emotional functioning in humans and should be analyzed in neuropsychiatric research investigating these domains.

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Contributors

Drs. Malaspina, Bruder and R. Goetz, and Mrs. D. Goetz were involved in the design and writing of the study protocol. Drs. Malaspina, R. Goetz, Keller and Antonius, and Mrs. Messinger managed literature reviews and/or statistical analyses pertaining to the study. Drs. Malaspina, R. Goetz, Antonius, Opler, Harlap, and Harkavy-Friedman, and Mrs. Messinger and D. Goetz were involved in the writing of various drafts and the final manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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Nothing to report.

References

Atanasova, B., Graux, J., El Hage, W., Hommet, C., Camus, V., Belzung, C., 2008. Olfaction: a potential cognitive marker of psychiatric disorders. Neurosci. Biobehav. Rev. 32, 1315–1325.

Beery, A.K., Zucker, I., 2011. Sex bias in neuroscience and biomedical research. Neurosci. Biobehav. Rev. 35, 565–572.

Blanchard, J.J., Cohen, A.S., 2006. The structure of negative symptoms within schizophrenia: implications for assessment. Schizophr. Bull. 32, 238–245.

Brewer, W.J., Edwards, J., Anderson, V., Robinson, T., Pantelis, C., 1996. Neuropsychological, olfactory, and hygiene deficits in men with negative symptom schizophrenia. Biol. Psychiatry 40, 1021–1031.

Cahill, L., 2006. Why sex matters for neuroscience. Nat. Rev. Neurosci. 7, 477–484.

Canuso, C.M., Pandina, G., 2007. Gender and schizophrenia. Psychopharmacol. Bull. 40, 178–190.

Coleman, E., Goetz, R.R., Leitman, D., Yale, S., Stanford, A., Gorman, J.M., et al., 2002. Odor identification impairments in schizophrenia: relationship with demographic measures, clinical variables, and diagnostic subtypes. CNS Spectr. 7, 43–48.

Corcoran, C., Whitaker, A., Coleman, E., Fried, J., Feldman, J., Goudsmit, N., et al., 2005. Olfactory deficits, cognition and negative symptoms in early onset psychosis. Schizophr. Res. 80, 283–293.

Doty, R.L., Cameron, E.L., 2009. Sex differences and reproductive hormone influences on human odor perception. Physiol. Behav. 97, 213–228.

Doty, R.L., Shaman, P., Dann, M., 1984. Development of the University of Pennsylvania Smell Identification Test: a standardized microencapsulated test of olfactory function. Physiol. Behav. 32, 489–502.

Erhart, S.M., Marder, S.R., Carpenter, W.T., 2006. Treatment of schizophrenia negative symptoms: future prospects. Schizophr. Bull. 32, 234–237.

Frasnelli, J., Charbonneau, G., Collignon, O., Lepore, F., 2009. Odor localization and sniffing. Chem. Senses 34, 139–144.

Garcia-Falgueras, A., Junque, C., Gimenez, M., Caldu, X., Segovia, S., Guillamon, A., 2006. Sex differences in the human olfactory system. Brain Res. 1116, 103–111.

Goldstein, J.M., Seidman, L.J., O'Brien, L.M., Horton, N.J., Kennedy, D.N., Makris, N., et al., 2002. Impact of normal sexual dimorphisms on sex differences in structural brain abnormalities in schizophrenia assessed by magnetic resonance imaging. Arch. Gen. Psychiatry 59, 154–164.

Gur, R.C., Gunning-Dixon, F., Bilker, W.B., Gur, R.E., 2002. Sex differences in temporo-limbic and frontal brain volumes of healthy adults. Cereb. Cortex 12, 998–1003.

Hasin-Brumshtein, Y., Lancet, D., Olender, T., 2009. Human olfaction: from genomic variation to phenotypic diversity. Trends Genet. 25, 178–184.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276.

Keller, A., Vosshall, L.B., 2004. Human olfactory psychophysics. Curr. Biol. 14, R875–R878.

Kikuta, S., Kashiwadani, H., Mori, K., 2008. Compensatory rapid switching of binasal inputs in the olfactory cortex. J. Neurosci. 28, 11989–11997.

Kirkpatrick, B., Buchanan, R.W., McKenney, P.D., Alphs, L.D., Carpenter Jr., W.T., 1989. The Schedule for the Deficit Syndrome: an instrument for research in schizophrenia. Psychiatry Res. 30, 119–123.

Kirkpatrick, B., Buchanan, R.W., Breier, A., Carpenter Jr., W.T., 1993. Case identification and stability of the deficit syndrome of schizophrenia. Psychiatry Res. 47, 47–56.

Kopala, L., Clark, C., Hurwitz, T.A., 1989. Sex differences in olfactory function in schizophrenia. Am. J. Psychiatry 146, 1320–1322.

Kopala, L.C., Clark, C., Hurwitz, T., 1993. Olfactory deficits in neuroleptic naive patients with schizophrenia. Schizophr. Res. 8, 245–250.

Leung, A., Chue, P., 2000. Sex differences in schizophrenia, a review of the literature. Acta Psychiatr. Scand. Suppl. 401, 3–38.

Luders, E., Gaser, C., Narr, K.L., Toga, A.W., 2009. Why sex matters: brain size independent differences in gray matter distributions between men and women. J. Neurosci. 29, 14265–14270.

Mainland, J.D., Bremner, E.A., Young, N., Johnson, B.N., Khan, R.M., Bensafi, M., et al., 2002. Olfactory plasticity: one nostril knows what the other learns. Nature 419, 802.

Malaspina, D., Coleman, E., 2003. Olfaction and social drive in schizophrenia. Arch. Gen. Psychiatry 60, 578–584.

Malaspina, D., Coleman, E., Goetz, R.R., Harkavy-Friedman, J., Corcoran, C., Amador, X., et al., 2002. Odor identification, eye tracking and deficit syndrome schizophrenia. Biol. Psychiatry 51, 809–815.

Messinger, J.W., Tremeau, F., Antonius, D., Mendelsohn, E., Prudent, V., Stanford, A.D., et al., 2011. Avolition and expressive deficits capture negative symptom phenomenology: implications for DSM-5 and schizophrenia research. Clin. Psychol. Rev. 31, 161–168.

National Institute of Mental Health, 2011. What is Schizophrenia. . (Retrieved 06/11) http://www.nimh.nih.gov/health/publications/schizophrenia/what-is-schizophrenia.shtml.

Nurnberger Jr., J.I., Blehar, M.C., Kaufmann, C.A., York-Cooler, C., Simpson, S.G., Harkavy-Friedman, J., et al., 1994. Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative. Arch. Gen. Psychiatry 51, 849–859 (discussion 863–864).

Olofsson, J.K., Broman, D.A., Gilbert, P.E., Dean, P., Nordin, S., Murphy, C., 2006. Laterality of the olfactory event-related potential response. Chem. Senses 31, 699–704.

Purdon, S.E., Flor-Henry, P., 2000. Asymmetrical olfactory acuity and neuroleptic treatment in schizophrenia. Schizophr. Res. 44, 221–232.

Rupp, C.I., 2010. Olfactory function and schizophrenia: an update. Curr. Opin. Psychiatry 23, 97–102.

Rupp, H.A., James, T.W., Ketterson, E.D., Sengelaub, D.R., Janssen, E., Heiman, J.R., 2009. Neural activation in women in response to masculinized male faces: mediation by hormones and psychosexual factors. Evol. Human Behav. 30, 1–10.

Savic, I., 2002. Imaging of brain activation by odorants in humans. Curr. Opin. Neurobiol. 12, 455–461.

Segovia, S., Guillamon, A., 1996. Searching for sex differences in the vomeronasal pathway. Horm. Behav. 30, 618–626.

Seidman, L.J., Goldstein, J.M., Goodman, J.M., Koren, D., Turner, W.M., Faraone, S.V., Tsuang, M.T., 1997. Sex differences in olfactory identification and Wisconsin Card Sorting performance in schizophrenia: relationship to attention and verbal ability. Biol. Psychiatry 42, 104–115.

Striebel, K.M., Beyerstein, B., Remick, R.A., Kopala, L., Honer, W.G., 1999. Olfactory identification and psychosis. Biol. Psychiatry 45, 1419–1425.

Stuck, B.A., Frey, S., Freiburg, C., Hormann, K., Zahnert, T., Hummel, T., 2006. Chemosensory event-related potentials in relation to side of stimulation, age, sex, and stimulus concentration. Clin. Neurophysiol. 117, 1367–1375.

Swerdlow, N.R., Geyer, M.A., 1998. Using an animal model of deficient sensorimotor gating to study the pathophysiology and new treatments of schizophrenia. Schizophr. Bull. 24, 285–301.
Tregellas, J.R., Davalos, D.B., Rojas, D.C., Waldo, M.C., Gibson, L., Wylie, K., et al., 2007. Increased hemodynamic response in the hippocampus, thalamus and prefrontal cortex during abnormal sensory gating in schizophrenia. Schizophr. Res. 92, 262–272.
Wechsler, D., 1997. WAIS-III Administration and Scoring Manual. The Psychological Corporation, San Antonio, TX.
White, L., Harvey, P.D., Opler, L., Lindenmayer, J.P., 1997. Empirical assessment of the factorial structure of clinical symptoms in schizophrenia. A multisite, multimodel evaluation of the factorial structure of the Positive and Negative Syndrome Scale. The PANSS Study Group. Psychopathology 30, 263–274.