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Sex Differences in Hedonic Judgement of Odors in Schizophrenia Cases and Healthy Controls

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Abstract

The neurocircuitries subserving affective and olfactory processes overlap, are sexually dimorphic, and show disruptions in schizophrenia, suggesting their intersection may be a window on the core process producing psychosis. This study investigated diagnostic and sex differences in hedonic judgments of odors and smell identification in 26 schizophrenia cases and 27 healthy controls. Associations between olfaction measures and psychiatric symptoms were also examined. Cases and controls had similar identification accuracy of unpleasant odors, but cases were significantly less accurate in naming pleasant odors. In cases, greater negative symptom severity was related to abnormal hedonic judgments; specifically, higher pleasantness ratings for unpleasant odors and higher unpleasantness ratings for pleasant odors. Greater positive symptom severity was associated with higher pleasantness and unpleasantness ratings for neutral odors. Regarding sex differences, male cases and female controls rated pleasant odors as significantly more unpleasant than male controls. Correlations between depression severity and pleasantness ratings of neutral odors were in opposite directions in male and female cases. These results suggest that a normal sexual dimorphism in the circuitry for hedonic odor judgments may interact with schizophrenia

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Conflict of Interest

The authors report no financial conflicts of interest.

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pathology, supporting the utility of olfactory hedonics as a sex-specific biomarker of this pathology.

1. Introduction

Deficits in emotion processing are a central feature of schizophrenia, yet the relation to schizophrenia pathology remains poorly understood. The limbic system and the central circuitry of emotion processing is closely connected to olfaction circuitry, and olfactory-evoked memories induce stronger affective responses than those evoked by verbal and visual stimuli (Herz, 1998; Willander and Larsson, 2007). Impaired smell identification accuracy is consistently reported in schizophrenia (reviewed in Moberg et al., 2014); however, findings on hedonic judgment of odor are more variable. Some studies report similar odor pleasantness ratings for schizophrenia cases and healthy participants (Clepce et al., 2013; Rupp et al., 2005), while others find that cases rate odors as more pleasant (Cumming et al., 2011; Doop and Park, 2006) or less pleasant (Crespo-Facorro et al., 2001; Hudry et al., 2002; Moberg et al., 2003; Plailly et al., 2006).

Negative symptoms, which categorize the social and emotional impairments of schizophrenia, appear to be associated with smell identification deficits (Brewer et al., 1996; Doop and Park, 2006), specifically avolition (Malaspina and Coleman, 2003). Less is known about the relation between negative symptoms and olfactory hedonics. One study found an association between negative symptoms and reduced range of pleasantness ratings (Doop and Park, 2006), while in another study, negative symptoms were unrelated to odor valance ratings (Kamath et al., 2013). Similarly, a study that examined olfactory hedonics in the deficit syndrome (a form of schizophrenia with primary severe and chronic negative symptoms), found that both deficit syndrome and other cases rated unpleasant odors as less unpleasant than healthy participants, but the deficit syndrome cases also rated pleasant odors as less pleasant than other cases and healthy participants (Strauss et al., 2010).

Differences in symptom profiles could contribute to discrepant findings regarding olfactory hedonics. Sex differences may also be involved as some of the neural structures associated with human olfaction are sexually dimorphic. In healthy females, higher gray matter concentrations are found in the orbitofrontal cortex (implicated in cognitive processes such as decision-making), while healthy males demonstrate more gray matter in the entorhinal cortex, which receives direct input from the olfactory bulb and is associated with memory (GarciaFalgueras et al., 2006). Consistent with higher neural regions subserving olfaction in healthy females, they have better smell identification accuracy than males (Doty et al., 1985), with similar findings are reported in some schizophrenia studies (Coleman et al., 2002; Kopala et al., 1989; Seidman et al., 1997).

Sex has been largely overlooked in studies of olfactory hedonics in schizophrenia, despite sex differences reported in neural activation during hedonic evaluation of odor in healthy individuals and the consistent sex differences in the disease. One study found that while judging the pleasantness of odors, healthy females activated their left orbitofrontal cortex and bilateral insula while only the bilateral insula was activated in healthy males (Royet et al., 2003). Of the few studies considering sex differences in olfactory hedonics among

schizophrenia cases, one found that male cases, but not female cases, were impaired in odor pleasantness ratings (Moberg et al., 2003). Others have reported impaired odor hedonic evaluation in both male and female cases (Hudry et al., 2002), and that sex was unrelated to odor valance ratings in schizophrenia (Kamath et al., 2013). We previously found smell identification impairment was related to negative symptoms predominantly in male cases (Malaspina et al., 2012a), but no study has examined whether sex differences influence the associations between hedonic judgement of odors and negative symptoms.

Another limitation in the field is the type of scale used to assess odor valance, as most studies assess pleasantness and unpleasantness in a single (bipolar) scale that places “extremely unpleasant” or the equivalent at one end, and “extremely pleasant” or equivalent at the other end. This is problematic, as several affective models demonstrate that that positive and negative affect are not at the opposite ends of one spectrum, but are instead separate interactive systems (Cacioppo et al., 1999). Approach motivation is facilitated by the appetitive nature of positivity, whereas avoidance results from threat activated by negativity. When these separate constructs are simultaneously activated, it produces ambivalence (Trémeau et al. 2009) that can mistakenly appear as neutrality on a bipolar rating scale (Larsen et al., 2004). Thus, bipolar scales may not capture the nuances of affective appraisals as scores in the middle may or may not represent a neutral affective response, making the score difficult to interpret. This is particularly important for schizophrenia research, as it has been hypothesized that avolition may result from impaired ability to generate behavioral motivation from pleasurable experiences (Heerey and Gold, 2007); thus, accurate assessment of positivity and negativity are essential for studies relating affective processes with avolition in schizophrenia. Only one previous study in schizophrenia utilized separate unipolar odor pleasantness and unpleasantness rating scales, although only results of the pleasantness ratings were reported (Auster et al., 2014).

The present study addressed these gaps by employing separate unipolar valance rating scales for odor pleasantness and unpleasantness with respect to sex differences in hedonic judgment of odors in schizophrenia cases and healthy participants. We hypothesized that cases would rate odors as less pleasant and more unpleasant than healthy participants, with male cases demonstrating the greatest decrement in olfactory hedonic ratings. Associations between ratings of olfactory pleasantness and unpleasantness, smell identification accuracy, and psychiatric symptoms were also investigated.

2. Methods

2.1. Participants

Study participants included 26 cases diagnosed with DSM-IV schizophrenia ($n=22$) or schizoaffective disorder ($n=4$) and 27 healthy participants. Cases were referred to the study by outpatient clinicians at a large Northeastern urban medical center and healthy participants were recruited via internet postings on [Craigslist.org](https://www.craigslist.org). Local Institutional Review Boards approved the study and all participants provided informed consent. Exclusion criteria for all participants included English language capacity and healthy participants were also excluded for having any DSM-IV diagnosis within two years of the study or having any personal or family history of psychosis. Participants with allergies, illness, or other conditions that might

temporarily affect olfactory function were not eligible to participate in the olfactory assessments until their condition cleared. To reduce fatigue, participants attended multiple data collection sessions; diagnosis and psychiatric symptoms were assessed first, followed by the olfaction assessments.

2.2. Measures

2.2.1. Diagnosis and symptoms—The *Diagnostic Interview for Genetic Studies* (DIGS; Nurnberger et al., 1994) was used to assess lifetime and current DSM-IV AXIS-I psychiatric diagnoses. Current psychiatric symptoms were assessed with the *Structured Clinical Interview for the Positive and Negative Syndrome Scale* (SCI-PANSS; Opler et al., 1992) and the associated 30-item PANSS Rating Scale (Kay et al., 2006), which yields positive, negative and general psychopathology subscales. Symptoms of mania, depression, and anxiety were respectively rated using the 11-item *Young Mania Rating Scale* (YMRS; Young et al., 1978), 24-item *Hamilton Depression Inventory* (HAM-D; Hamilton, 1960), and 14-item *Hamilton Anxiety Inventory* (HAM-A; Hamilton, 1959). All clinical assessments were conducted by interviewers with a master's or doctoral degree in psychology, who were trained to maintain a reliability criterion of at least 0.70. Final clinical diagnoses involved a consensus conference of two or more doctoral level research clinicians (M.D. or Ph.D.) and the interviewer.

2.2.2. Olfaction—Smell identification was assessed with the *Sniffin' Sticks Identification* test (Burghart Instruments, Wedel, Germany), a 16-item forced multiple-choice smell identification test that utilizes pen-like devices to deliver common odorants such as orange, peppermint, and fish. Using normative data (Hummel et al., 1997) based on a bipolar hedonic rating scale of -50 (unpleasant) to +50 (pleasant), we categorized odors with mean pleasantness scores in the top third of the rating scale (>16.67) as „pleasant,” odors with mean scores in the middle third (16.67 to +16.67) as „neutral,” and odors with mean scores in the bottom third (<-16.67) as „unpleasant.” This resulted in eight pleasant, five neutral, and three unpleasant odors. We then summed the number of correct responses for each valence category and computed a total identification accuracy score for all 16 odorants.

During the administration of the Sniffin' Sticks test, olfactory hedonic ratings were collected utilizing the two five-point Likert scales assessing odor pleasantness and unpleasantness. Responses across all 16 odors were summed to yield a total pleasantness score and total unpleasantness score. Pleasantness and unpleasant ratings were also summed to yield separate scales for the pleasant, neutral, and unpleasant odors, categorized as described above. Due to low reliability (Chronbach's $\alpha < 0.070$), the unpleasantness ratings for neutral odors scale was excluded from the analyses.

2.3. Data analysis

SPSS (version 17.0) was used for data analysis. Independent samples t-tests and chisquares were used to test for differences between schizophrenia cases and healthy participants in demographic characteristics. Two (case, control) x 2 (male, female) analysis of variance (ANOVA) was used to examine group and sex differences in overall performance (across all

16 odors) on the olfaction measures. For the first ANOVA, total odor identification accuracy was the dependent variable. The dependent variables for the second and third ANOVAs were total pleasantness scores and total unpleasantness scores, respectively.

To investigate group and sex differences in smell identification accuracy and hedonic ratings across the three odor valence categories we ran three 2 (case, control) by 2 (male, female) multivariate analysis of covariances (MANOVAs). Smell identification accuracy for pleasant, unpleasant, and neutral odors were the dependent variables for the first MANOVA, pleasantness scores for pleasant, unpleasant, and neutral odors were the dependent variables for the second, and unpleasantness scores for pleasant and unpleasant odors were the dependent variables for the third. Due to the small sample size, Spearman correlations were computed to examine associations between the olfaction measures and psychiatric symptoms. In exploratory analyses, we examined these associations separately by sex, and a freely available online utility (Preacher, 2002) was used for the Fisher's r -to- z transformation test to examine sex differences in correlations that were significant for at least one of the sexes. For all analyses, cut-offs of $p < 0.05$ were considered significant and p values < 0.07 were deemed to be trends.

3. Results

3.1. Demographics

Demographic data for each group are presented in Table 1. The case and control groups were matched for sex and race/ethnicity. The schizophrenia group was older and less educated than healthy participants, although none of the olfaction measures were related to age (r 's ranged from -0.202 to 0.174). Smoking status was also not associated with smell identification accuracy or hedonic judgment of odor (r 's ranged from -0.168 to 0.317).

3.2. Smell identification

Mean smell identification accuracy percentages for all odors and for the separate hedonic valence categories are presented for schizophrenia cases and healthy participants in Figure 1. Cases had significantly lower overall smell identification accuracy compared to healthy participants ($F(1,48)=5.352$, $p=.025$, partial $\eta^2=.100$). Results of the MANOVA analysis showed a main effect for group in identification of pleasant, unpleasant, and neutral odors (Wilks' Lambda= 0.813 , $F(3,46)=3.520$, $p=0.022$, partial $\eta^2=0.187$), but no effect for sex (Wilks' Lambda= 0.925 , $F(3,46)=1.249$, $p=0.303$, partial $\eta^2=0.075$), or group x sex interaction (Wilks' Lambda= 0.964 , $F(3,46)=0.576$, $p=0.634$, partial $\eta^2=0.036$). Follow-up univariate testing showed a significant between-subjects group effect for pleasant odors ($F(1,48)=7.139$, $p=0.010$, partial $\eta^2=0.129$), indicating that cases were less accurate than healthy controls in their identification of pleasant odors. There was a similar trend level effect for neutral odors ($F(1,48)=3.578$, $p=0.065$, partial $\eta^2=0.069$), but the groups did not differ in identification accuracy for unpleasant odors ($F(1,48)=0.230$, $p=0.0634$, partial $\eta^2=0.005$).

3.3. Hedonic ratings

Figure 2 presents the total mean pleasantness and unpleasantness ratings and separate mean pleasantness and unpleasantness ratings for the odor valance categories for each group by sex. Cases and healthy participants did not differ in total mean pleasantness ratings ($F(1,48)=0.832$, $p=0.366$, partial $\eta^2=0.017$), or unpleasantness ratings ($F(1,48)=0.227$, $p=0.636$, partial $\eta^2=0.005$). The multivariate analysis for pleasantness ratings showed no main effects for group (Wilks' Lambda=0.968, $F(3,46)=0.510$, $p=0.677$, partial $\eta^2=0.032$), sex (Wilks' Lambda=0.985, $F(3,46)=0.238$, $p=0.870$, partial $\eta^2=0.015$), or group x sex interaction (Wilks' Lambda=0.924, $F(3,46)=1.269$, $p=0.296$, partial $\eta^2=0.076$). For unpleasantness ratings, there were no main effects for group (Wilks' Lambda=0.944, $F(2,47)=1.387$, $p=0.260$, partial $\eta^2=0.056$) or sex (Wilks' Lambda=0.985, $F(2,47)=0.363$, $p=0.698$, partial $\eta^2=0.076$), but there was a significant group x sex interaction (Wilks' Lambda=0.847, $F(3,46)=2.768$, $p=0.052$, partial $\eta^2=0.153$). Follow-up univariate testing indicated that there was a significant between-subjects group x sex interaction for unpleasantness ratings of pleasant odors $F(1,48)=7.561$, $p=0.008$, partial $\eta^2=0.136$, and pairwise comparisons indicated that male cases ($F(1,48)=11.013$, $p=0.002$, partial $\eta^2=0.187$) and healthy females ($F(1,48)=5.529$, $p=0.023$, partial $\eta^2=0.103$) rated pleasant odors as more unpleasant than healthy males.

3.4. Correlations between smell identification and hedonic ratings

Pleasantness and unpleasantness ratings were unassociated with smell identification accuracy in cases or healthy participants (Table 2). However, when examined in sex-stratified analyses, sex differences emerged. In female cases, better smell identification accuracy was associated with lower unpleasantness ratings of all odors, which significantly differed from associations in the opposite direction in male cases and healthy females. Better smell identification accuracy was associated with lower unpleasantness ratings of unpleasant odors in female cases and higher unpleasantness ratings of unpleasant odors in male cases. Again, the correlation in female cases significantly differed from male cases and healthy females. There were no sex differences for the healthy participants and controlling for age did not alter these results.

3.5. Correlations between olfaction measures and psychiatric symptoms

Associations between the olfaction measures and PANSS symptoms were only explored in the cases and are displayed in Table 3. The PANSS scales were not associated with smell identification accuracy. Higher negative symptom severity was associated with higher pleasantness ratings of unpleasant odors and higher unpleasantness ratings of pleasant odors. Higher positive symptom severity was correlated with lower pleasantness ratings of neutral odors. More general psychopathology was associated with increased pleasantness ratings of unpleasant odors. When correlations between PANSS symptoms and the olfaction measures were examined separately by sex, all significant correlations were in the same direction in males and females and did not significantly differ, suggesting no sex-specific effects.

We also examined associations between the olfaction measures and depression, mania, anxiety, and anhedonia in cases (see Tables 3). Anxiety predicted better overall smell identification accuracy, particularly for neutral and pleasant odors. Depression was also

associated with better identification accuracy of neutral odors. In contrast, mania, was related to lower pleasantness ratings for neutral odors.

When stratified by sex, depression was associated with lower pleasantness ratings for neutral odors in female cases, which was opposite and significantly differed from male cases ($z=2.251$, $p=.024$). All other significant correlations did not significantly differ.

3.6 Descriptive analysis of individual odor ratings.

Finally, we explored whether odor valance ratings across the groups and sexes were consistent with normative ratings. Pleasantness and unpleasantness rating means and standard deviations for each of the 16 odors are displayed in Table 4. We considered odors with a mean pleasantness rating of > 2 (corresponding to “pleasant” or higher) and a mean unpleasantness rating of < 1 (indicating the odor was rated either “not unpleasant” or “a little unpleasant”) to be categorized as “pleasant.” Odors were categorized as “neutral” if they had mean pleasantness and unpleasantness ratings < 2 . Finally, odors with a mean pleasantness rating of < 1 (indicating the odor was rated either “not pleasant” or “a little pleasant”) and a mean unpleasantness rating of > 2 (corresponding to unpleasant or higher) were categorized as “unpleasant.”

Pleasant Odors.—Of the eight odors categorized as pleasant by normative data, healthy controls had mean ratings of seven and schizophrenia cases had mean ratings of five in the pleasant range. Both groups rated anise in the neutral range, while cases also rated peppermint and orange as neutral. However, there was more divergence across the sexes. Healthy males and females both rated six odors as pleasant, but the males rated anise and lemon as neutral whereas females had neutral ratings for anise and cinnamon. Female cases also rated six of the odors as pleasant and had neutral ratings for orange and anise. In contrast, male cases rated only three odors as pleasant, notably all fruits, while ratings for cinnamon, orange, peppermint, pineapple, and anise were in the neutral range.

Neutral Odors.—Schizophrenia cases and healthy controls rated four of the five neutral odors as neutral, and one (rose) as pleasant. Ratings were consistent across the sexes, with the exception of cloves, which healthy females rated in the neutral range.

Unpleasant Odors.—Both groups rated only one of the three odors (fish) as unpleasant, with garlic and turpentine rated as neutral. Healthy males also had mean ratings in the unpleasant range for garlic and in the neutral range for turpentine, while the opposite was true in healthy females and male cases. Female cases had mean ratings of both garlic and turpentine in the neutral range.

4. Discussion

The results of this study showed deficient smell identification in schizophrenia for pleasant odors, and neutral odors to a lesser extent, but intact naming of unpleasant odors. Male cases and female controls also rated pleasant odors as less unpleasant than healthy males, while no differences were observed between female cases and their healthy counterparts. More severe negative symptoms in cases predicted impaired affective appraisal of both pleasant and

unpleasant odors, whereas psychotic symptom severity was associated with impairment in the appraisal of neutral odors. Finally, converse associations for depression severity and olfactory hedonics in male and female cases also support sex differences in the underpinnings of pleasurable experiences in schizophrenia.

4.1. Smell identification

Our findings of impaired smell identification accuracy for pleasant and neutral, but not unpleasant odors are consistent the results of most studies on smell identification and odor valance in schizophrenia (Kamath et al., 2011a; Kamath et al., 2011b, Kamath et al., 2013). Conflicting findings by Strauss and colleagues (2010), showed cases with the primary and chronic negative symptoms of the deficit syndrome were significantly impaired in identifying pleasant and unpleasant odors. This discrepancy could be explained by methodological differences as odors were only categorized as pleasant and unpleasant without a neutral category. We did not find the association between smell identification accuracy and negative symptoms reported in several other samples (Brewer et al., 2001; Malaspina et al., 2002; Moberg et al., 2006); however, the small sample size and/or the relatively lower negative symptom severity across the stable outpatient cases who participated in the present study may account for our different result.

With respect to mood, better smell identification accuracy, specifically for neutral odors, was associated with increased depression. Previous research suggests that smell identification ability is preserved in individuals with major depression (reviewed in Naudin and Atanasova, 2014) and it is possible that impaired reward circuitry predisposing for depressive symptomatology may be somehow protective of smell identification ability for non-affective stimuli. This is consistent with a study that found similar pleasantness and unpleasantness ratings of affective visual stimuli cases and healthy participants, but an impairment in translating the affective information into motivated behavior (Trémeau et al., 2010). The present finding of an association between better smell identification accuracy and increased anxiety is also consistent with our study in a different sample showing that better smell identification in schizophrenia predicted more social anxiety but less negative symptoms, particularly less anhedonia (Cieslak et al., 2015).

4.2. Ratings of odor pleasantness and unpleasantness

We found no group differences in ratings of odor pleasantness and unpleasantness, nor any relation between these ratings and smell identification accuracy. However, sex effects did emerge. Male cases with schizophrenia rated pleasant odors as more unpleasant than the healthy males, while female cases and healthy participants had similar pleasantness ratings. This is consistent with the results of a study in which males with schizophrenia had abnormal patterns of pleasantness ratings of amyl acetate at various concentrations in comparison to male healthy participants (Moberg et al., 2003). While their methodology differs from this report, both studies support impaired odor hedonic ratings in schizophrenia male, but not females. There is evidence that persons with schizophrenia experience increased negative affect in response to verbal, visual, and gustatory stimuli (reviewed in Cohen and Minor, 2010). However, the present findings, in conjunction with a recent report of increased unpleasant emotion in response to emotionally evocative film clips in females

(Mote et al., 2014), suggest that affective response abnormalities in schizophrenia may be more nuanced with sex specific effects for different sensory stimuli. These differences highlight the importance of conducting sex specific analyses in future research.

Female cases who perceived unpleasant and pleasant odors as less unpleasant demonstrated better identification accuracy, suggesting better accuracy with less negative emotional reactivity. By contrast, male cases, and to a lesser extent healthy females, who had better smell identification accuracy rated unpleasant odors as more unpleasant, suggesting better accuracy with increased negative emotional reactivity. This divergence may be the result of evolutionary sensory advantages that females developed for childbearing or sensitivity for food toxicity, or related to increased levels of hypervigilance and social fear in males with schizophrenia (Cieslak et al., 2015). Still, these theories do not explain why female cases would also differ from healthy females.

We found that results for male cases were more consistent with female healthy participants. This is not a unique result as there is converging evidence for a reversal of the normal sexual dimorphism in schizophrenia, particularly in limbic structures (Gur et al., 2004; Goldstein et al., 2002) and related functions (Strauss et al, 2015) and we have previously reported associations between impaired smell identification and slower processing speed in female cases (Malaspina et al. 2012b) and with negative symptoms in male cases (Malaspina et al. 2012a). These findings, in conjunction with the present results, suggest that females with schizophrenia may fail to activate cognitive processes mediated by orbitofrontal circuitry, while males with schizophrenia may be deficient in affective processes mediated by limbic circuitry. Sex stratification of data analysis in schizophrenia research is of the utmost importance for advancing our understanding of these differences, as well as other sexually dimorphic aspects of the disease.

Notably, the male and female healthy participants also showed sex-differences in unpleasantness ratings of pleasant odors. This finding is consistent differences reported for specific odorants such as pyridine (Olofsson and Nordin, 2004) and breath odor (Doty, 1982), although other studies on affective response to odor in healthy samples do not report sex differences (Ferdenzi et al., 2013; Thuerauf et al., 2009). Healthy males and females have also shown sex differences in responses to visual emotional stimuli via emotional expressivity (Kring and Gordon, 1998), self-reported ratings of valance (Bradley et al., 2001; Deng et al., 2016), and psychophysiology (Kring and Gordon, 1998; Bradley et al. 2001; Fernandez, et al., 2012). Neuroimaging studies likewise show sex differences in neural response patterns during visual emotional tasks (Wager et al 2003; Schienle et al, 2005; Domes et al., 2010). More research is needed to disentangle how hedonic evaluation of odor relates to affective appraisal of other sensory stimuli in healthy individuals and in schizophrenia, as differences may provide a window into neural connectivity abnormalities and suggest targets for future treatments to remediate emotion deficits in schizophrenia.

Important findings regarding associations with symptoms also emerged. Our finding that cases with more severe negative symptoms rated unpleasant odors as more pleasant and pleasant odors as more unpleasant was not unexpected, as impairment in emotional processes contribute prominently to negative symptoms, most notably flat affect and

avolition (reviewed in Messinger et al., 2011). Alternatively, the results could be interpreted as a consequence of random responding due to motivational deficits (Trémeau et al., 2010). We also found that cases with increased positive symptoms rated neutral odors as less pleasant, which is consistent with the theory that individuals with schizophrenia attach more significance to meaningless stimuli (Venables, 1963), resulting in heightened vigilance and the development of delusions.

Interestingly, cases with more mania symptoms found neutral odors to be less pleasant, suggesting a reduction in positive affect during mania. This was unexpected given that positive (euphoric) affect is typically associated with mania. There is some evidence of heightened amygdala response to a facial emotion labeling paradigm in bipolar mania (Foland et al., 2008) and it is possible that cases with subclinical mania symptoms might experience a similar heightened fear response to non-affective stimuli increasing negative affect. Consistent with this hypothesis, a recent study that both individuals with bipolar disorder and with schizophrenia report increased negative affect compared to healthy participants, and that negative affect in these disorders predicts social function (Grove et al., 2016). Similarly, we previously found associations between diminished odor detection sensitivity for phenyl ethyl alcohol (a neutral odor), mania and greater social anxiety in individuals with bipolar disorder (Hardy et al., 2012). Further clarification of these associations may come from a recent finding in which healthy individuals who underwent anxiety induction rated neutral odors as more unpleasant, took longer to detect neutral odors, and showed greater neural response in the orbitofrontal cortex and pregenual anterior cingulate cortex, regions implicated in olfaction and emotion, respectively (Krusemark et al., 2013). It may be that more anxiety during mania results in greater negative affective evaluation of non-affective stimuli and diminished odor sensitivity.

4.3. Limitations

There are several limitations to the present study that could have impacted the results. First, the groups were not matched for age or education. However, age was not significantly associated with any of the variables and the discrepancy in years of education is consistent with the literature and is likely a result of the disease (Resnick, 1992), thus we did not match for education as doing so would eliminate some of the disease specific variability across the groups (Meehl, 1970). Another limitation of the study is the small sample size and reduced power, particularly for the sex analyses. As such, replication of these preliminary findings in larger samples is needed. Additionally, our patient sample was comprised of non-institutionalized, relatively stable individuals with schizophrenia who were motivated to participate in a research study, and able to attend multiple data collection sessions. This is not characteristic of the large majority of individuals with schizophrenia and therefore the generalizability of our results to more symptomatic lower-functioning patients warrants future study. We were also unable to look at whether menstrual cycle affected our findings in females, and future studies are encouraged to address this question. Although the psychometric literature (e.g. Worthington and Whittaker, 2006) generally considers three-item scales to be acceptable, scales with fewer items are susceptible to lower reliability; thus, the inclusion of only three unpleasant odors in the present study may limit the

reliability of this scale. Finally, as valance was not equally distributed across the Sniffin[®] Sticks battery we were unable to compare within group differences by valance.

4.4. Conclusion

In summary, the present study highlights the importance of considering sex in schizophrenia research. While sex differences were not observed in healthy participants, important sex differences were observed in cases. Female cases also differed from healthy females, further supporting a reversal of the normal sexual dimorphism in schizophrenia. Human sexual dimorphism in the circuitry for hedonic judgments may interact with schizophrenia pathology, and hedonic judgement of odors may have utility as a sex-specific biomarker of this pathology. Stratification by sex in schizophrenia research continues to be critical to ensure that important sex-specific findings are not obscured, and to facilitate further understanding of disease heterogeneity. Additionally, our findings lend further support for a relation between negative symptoms and impairment in hedonic response to odor, and suggest that psychosis and mood separately influence olfaction. Future studies on olfaction should assess both mood and psychotic symptoms to further elucidate the independent contribution of each. Finally, to further our understanding of affective processing impairments in schizophrenia, future studies should examine relations between affective appraisal of odor and other sensory stimuli in healthy populations as well as schizophrenia.

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Highlights

- This study examined sex differences in olfactory hedonics in schizophrenia.
- Male schizophrenia cases and female controls rated pleasant odors as more unpleasant than male controls.
- Negative symptom severity was associated with hedonic ratings of pleasant and unpleasant odors.
- Positive symptom severity was associated with hedonic ratings of neutral odors.
- Correlations between depression and pleasantness ratings for neutral odors differed by sex.

Figure 1.
Mean percent of correctly identified odors in schizophrenia cases (SCZ) and healthy participants (HP).

Figure 2.
Mean pleasantness and unpleasantness odor ratings for schizophrenia cases (SCZ) and healthy participants (HP).

Table 1.

Demographic information for schizophrenia cases and healthy participants.

	<u>Healthy Participants</u>			<u>Schizophrenia Cases</u>			<i>t</i>	<i>p</i>
	<i>N</i>	<i>M</i>	(<i>SD</i>)	<i>N</i>	<i>M</i>	(<i>SD</i>)		
Age	27	37.30	(12.28)	26	45.42	(7.92)	-2.87	0.006**
Education	27	15.11	(1.50)	26	13.00	(2.12)	4.17	0.000**
PANSS								
Positive	-	-	-	24	14.75	(6.23)		
Negative	-	-	-	24	13.92	(4.32)		
General Psychopathology	-	-	-	24	29.04	(8.12)		
HAM-D	-	-	-	24	11.20	(10.23)		
HAM-A	-	-	-	24	8.06	(7.28)		
YMRS	-	-	-	24	7.14	(6.52)		
	<i>n</i>	<i>%</i>		<i>n</i>	<i>%</i>		<i>χ²</i>	<i>p</i>
Gender (Male/Female)	16/11	56/44		16/10	64/36		0.29	0.865
Racial/Ethnic Background							5.16	0.161
Caucasian	11	41		5	19			
Hispanic	5	18		4	15			
Black/African American	10	37		17	66			
More than one race	1	4		0	0			

*
 $p < 0.05$ **
 $p < 0.01$

Spearman correlations between pleasantness and unpleasantness ratings and overall smell identification accuracy, and correlation coefficient comparisons for schizophrenia cases (SCZ) and healthy participants (HP), by group and sex.

Table 2.

	HP				SCZ				Correlation Comparison ^d			
	Male N = 16		Female N = 11		Male N = 26		Female N = 16		All HP:SCZ		HP Male: Female	
	rho	rho	rho	rho	rho	rho	rho	rho	z	z	z	z
Pleasantness Ratings												
All Odors	-0.184	-0.097	-0.220	-0.112	-0.094	-0.112	-0.129	-0.32	-0.32	0.28	-0.04	0.04
Pleasant Odors	-0.046	0.134	-0.238	-0.184	-0.090	-0.184	0.025	0.15	0.15	0.84	-0.45	0.82
Neutral Odors	-0.209	-0.226	-0.173	-0.005	-0.031	-0.005	-0.096	-0.62	-0.62	-0.12	0.20	-0.57
Unpleasant Odors	-0.122	-0.029	-0.218	-0.170	-0.229	-0.170	-0.436	0.38	0.38	0.43	0.63	0.36
Unpleasantness Ratings												
All Odors	0.033	-0.018	0.137	0.252	-0.104	0.252	-0.706 *	0.47	0.47	-0.35	2.43 *	-0.70
Pleasant Odors	-0.041	-0.223	0.350	0.074	-0.191	0.074	-0.635 *	-0.52	-0.52	-1.32	1.76	-0.77
Unpleasant Odors	0.108	0.117	0.295	0.563 *	0.266	0.563 *	-0.713 *	-0.56	-0.56	-0.52	3.27 **	-1.33

*
 $p<0.05$

**
 $p<0.01$

_yTest of difference between correlations using Fisher's r -to- z transformation (Preacher, 2002)

Table 3.

Spearman correlations between olfaction measures and psychiatric symptoms for all schizophrenia cases, and by sex.

	All Odors			Pleasant Odors			Unpleasant Odors			Neutral Odors		
	All	Male <i>N</i> = 16	Female <i>N</i> = 10	All	Male <i>N</i> = 16	Female <i>N</i> = 10	All	Male <i>N</i> = 16	Female <i>N</i> = 10	All	Male <i>N</i> = 16	Female <i>N</i> = 10
	rho	rho	rho	rho	rho	rho	rho	rho	rho	rho	rho	rho
Smell Identification												
PANSS Positive	-0.242	-0.179	-0.270	-0.317	-0.389	-0.163	-0.006	-0.014	0.000	-0.050	0.105	-0.192
PANSS Negative	-0.293	-0.127	-0.642 [*]	-0.228	-0.204	-0.378	-0.136	0.091	-0.394	-0.158	-0.153	-0.284
PANSS Gen Psych	0.094	0.140	-0.013	0.086	0.048	0.110	-0.071	-0.086	-0.178	0.350	0.554 [*]	0.151
HAM-D	0.339	0.537 [*]	0.012	0.204	0.466	-0.226	0.281	0.270	0.213	0.422 [*]	0.686 ^{**}	0.156
HAM-A	0.507 ^{**}	0.574 [*]	0.424	0.463 [*]	0.585 [*]	0.330	0.148	0.208	0.000	0.487 [*]	0.608 [*]	0.225
YMRS	-0.140	-0.094	-0.248	-0.242	-0.287	-0.299	0.054	0.099	-0.072	-0.028	0.120	-0.258
Odor Pleasantness Ratings												
PANSS Positive	-0.294	-0.170	-0.340	-0.252	-0.180	-0.144	0.195	0.095	0.315	-0.469 [*]	-0.269	-0.644 [*]
PANSS Negative	-0.089	0.270	-0.246	-0.198	0.163	-0.285	0.504 [*]	0.423	0.600	-0.170	0.163	-0.414
PANSS Gen Psych	-0.034	0.296	-0.309	-0.175	-0.022	-0.198	0.422 [*]	0.439	0.473	-0.079	0.262	-0.442
HAM-D	-0.140	0.333	-0.622 ⁺	-0.133	0.232	-0.492	0.230	0.264	0.233	-0.170	0.236	-0.690 [*]
HAM-A	0.037	0.266	-0.256	0.097	0.203	-0.146	-0.063	0.041	-0.220	0.047	0.235	-0.317
YMRS	-0.374	-0.365	-0.285	-0.292	-0.265	-0.269	-0.131	-0.301	0.179	-0.447 [*]	-0.426	-0.419
Odor Unpleasantness Ratings												
Positive	0.284	0.132	0.376	0.140	0.265	-0.043	0.022	-0.146	0.448			
PANSS Negative	0.252	-0.001	0.472	0.498 [*]	0.479	0.508	0.002	-0.195	0.356	---	---	---
PANSS Gen Psych	0.140	0.055	-0.003	0.339	0.384	0.130	-0.056	-0.117	-0.048	---	---	---
HAM-D	0.316	0.299	0.340	0.105	0.340	-0.111	0.325	0.253	0.400	---	---	---
HAM-A	0.221	0.280	0.170	0.045	0.107	0.074	0.238	0.336	-0.159	---	---	---
YMRS	0.567 ^{**}	0.448	0.749 [*]	0.281	0.298	0.292	0.309	0.214	0.620 ⁺	---	---	---

⁺
p < 0.07

^{*}
p < 0.05

^{**}
p < 0.01

Table 4.

Mean pleasantness and unpleasantness ratings of the 16 odors for schizophrenia cases (SCZ) and healthy participants (HP), by group and sex.

		Healthy Controls			Schizophrenia Cases		
		All N=17	Male N=16	Female N=11	All N=26	Male N=16	Female N=10
		M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
Apple	PL	2.35 (1.02)	2.27 (1.03)	2.45 (1.04)	2.27 (1.08)	2.25 (1.07)	2.30 (1.16)
	UnPL	0.15 (0.37)	0.20 (0.41)	0.09 (0.30)	0.23 (0.51)	0.19 (0.54)	0.30 (0.48)
Banana	PL	2.58 (0.90)	2.47 (0.99)	2.73 (0.79)	2.27 (1.08)	2.25 (1.00)	2.30 (1.25)
	UnPL	0.12 (0.33)	0.13 (0.35)	0.09 (0.30)	0.19 (0.40)	0.25 (0.45)	0.10 (0.32)
Cinnamon	PL	2.00 (1.17)	2.20 (0.78)	1.73 (1.56)	2.00 (1.13)	1.81 (1.17)	2.30 (1.06)
	UnPL	0.38 (0.64)	0.27 (0.59)	0.55 (0.69)	0.54 (0.71)	0.69 (0.79)	0.30 (0.48)
Lemon	PL	2.00 (1.06)	1.93 (0.80)	2.09 (1.38)	2.19 (1.02)	2.19 (0.91)	2.20 (1.23)
	UnPL	0.23 (0.43)	0.20 (0.41)	0.27 (0.47)	0.23 (0.51)	0.31 (0.60)	0.10 (0.32)
Orange	PL	2.19 (1.02)	2.27 (0.88)	2.09 (1.22)	1.81 (0.94)	1.75 (0.78)	1.90 (1.20)
	UnPL	0.19 (0.63)	0.07 (0.26)	0.36 (0.92)	0.38 (0.70)	0.44 (0.73)	0.30 (0.68)
Peppermint	PL	2.31 (1.01)	2.47 (0.74)	2.09 (1.30)	1.85 (1.85)	1.62 (0.96)	2.20 (1.03)
	UnPL	0.27 (0.67)	0.13 (0.35)	0.45 (0.93)	0.58 (0.99)	0.69 (1.01)	0.40 (0.97)
Pineapple	PL	2.65 (0.89)	2.53 (0.74)	2.82 (1.08)	2.23 (1.07)	1.94 (1.06)	2.70 (0.95)
	UnPL	0.08 (0.27)	0.07 (0.26)	0.09 (0.30)	0.12 (0.43)	0.13 (0.50)	0.10 (0.32)
Rose	PL	2.35 (1.13)	2.27 (1.10)	2.45 (1.21)	2.15 (1.12)	2.00 (1.10)	2.40 (1.17)
	UnPL	0.27 (0.45)	0.40 (0.51)	0.09 (0.30)	0.27 (0.67)	0.38 (0.81)	0.10 (0.32)
Anise	PL	1.58 (1.03)	1.80 (0.78)	1.27 (1.27)	1.12 (0.91)	1.13 (1.09)	1.10 (0.57)
	UnPL	0.54 (1.10)	0.13 (0.35)	1.09 (1.51)	0.77 (0.91)	0.81 (0.91)	0.70 (0.95)
Cloves	PL	1.69 (1.16)	1.47 (1.06)	2.00 (1.27)	1.27 (1.04)	1.38 (1.20)	1.10 (0.74)
	UnPL	0.50 (0.07)	0.53 (0.74)	0.45 (0.69)	1.00 (1.23)	1.19 (1.47)	0.70 (0.68)
Coffee	PL	1.69 (1.32)	1.60 (1.12)	1.82 (1.60)	1.31 (1.29)	1.44 (1.21)	1.10 (1.45)
	UnPL	0.69 (1.16)	0.60 (1.21)	0.82 (1.25)	0.88 (0.99)	0.69 (0.87)	1.20 (1.14)
Leather	PL	0.85 (1.08)	1.13 (1.25)	0.45 (0.69)	1.27 (1.31)	1.44 (1.21)	1.00 (1.49)
	UnPL	1.08 (1.02)	0.93 (0.80)	1.27 (1.27)	0.96 (1.15)	0.81 (1.11)	1.20 (1.23)
Liquorice	PL	1.38 (1.06)	1.47 (1.06)	1.27 (1.10)	1.46 (1.24)	1.25 (1.13)	1.80 (1.40)
	UnPL	0.92 (1.39)	0.73 (1.39)	1.18 (1.40)	0.62 (0.70)	0.75 (0.76)	0.40 (0.52)
Fish	PL	0.19 (0.80)	0.07 (0.26)	0.36 (1.21)	0.35 (0.89)	0.56 (1.09)	0.00 (0.00)
	UnPL	2.81 (1.13)	2.87 (1.06)	2.73 (1.27)	2.50 (1.14)	2.44 (1.26)	2.60 (0.97)
Garlic	PL	0.88 (1.34)	0.73 (1.16)	1.09 (1.59)	0.50 (0.86)	0.56 (0.81)	0.40 (0.97)
	UnPL	1.69 (1.20)	2.00 (1.25)	1.27 (1.01)	1.69 (1.05)	1.63 (1.27)	1.80 (0.63)
Turpentine	PL	0.50 (0.86)	0.60 (0.99)	0.36 (0.67)	0.62 (0.75)	0.63 (0.81)	0.60 (0.70)
	UnPL	1.81 (1.20)	1.67 (1.18)	2.00 (1.27)	1.81 (1.13)	2.00 (1.27)	1.50 (0.85)

PL = Pleasantness rating

UnPL = Unpleasantness rating

Yellow = Pleasant

Green = Neutral

Blue = Unpleasant

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