Article

# Impairment of Odor Hedonics in Men With Schizophrenia

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**Objective:** Olfactory deficits in patients with schizophrenia, including those of odor identification, detection threshold sensitivity, discrimination, and memory, have been well described. Deficits in emotional perception, processing, and experience have also been reported, with anhedonia being one of the core features. While anatomical connections testify to the relationship between olfaction and emotion, there has been little investigation of the hedonic properties of odors in schizophrenia. This study examined intensity and hedonic judgments in patients with schizophrenia to determine whether these functions were differentially impaired.

**Method:** Suprathreshold scaling of odor intensity and pleasantness was acquired by using the Suprathreshold Amyl Acetate Odor Intensity and Odor Pleasantness Rating Test given to 30 patients (15 men and 15 women) with a DSM-IV diagnosis of schizophrenia and 30 age- and sex-matched healthy comparison subjects.

**Results:** Despite virtually identical ratings of odor intensity, male patients were impaired in the assignment of odor pleasantness to amyl acetate. This gender-specific diagnostic group difference was not explained by variability in symptom severity or negative/positive symptoms. The impact of smoking status and general cognitive impairment on this deficit was also insignificant.

**Conclusions:** Findings reveal a gender-specific disruption in the ability to attribute appropriate hedonic valence to odors in male patients with schizophrenia. This difficulty in identifying the hedonic valence of odors, despite intact intensity ratings, is consistent with clinical observations of anhedonia and points to a neural substrate that might contribute to the emotional disturbances seen in patients with schizophrenia.

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Deficits in emotional perception and processing have been well described in patients with schizophrenia (1–3). Impairments in olfactory perception and processing have also been identified, with deficits in identification, detection threshold sensitivity, memory, and discrimination being reported (4–9). Olfaction has been associated with emotions and emotionally laden memory, with evidence of overlapping limbic system structures (10, 11) and similar right hemisphere dominance for both olfactory and emotional stimulus processing (12, 13). Given the configuration and relevance of the underlying neural substrate, and the evidence of performance deficits in patients with schizophrenia, psychophysical probes of the olfactory system may hold special promise for understanding the pathophysiology of schizophrenia. They may elucidate limbic system dysfunction, which is thought to be responsible for the well-known deficits in emotional reactivity, responsiveness, and anhedonia observed in schizophrenia. Despite this relationship between olfactory and emotion brain systems, there has been little direct investigation of this aspect of olfactory function in patients with schizophrenia.

Recently, Crespo-Facorro and colleagues (14) found that schizophrenia patients subjectively experienced an unpleasant odor in a manner similar to healthy volunteers but demonstrated impairment in the experience of a pleasant odor. Analysis of odor-evoked regional cerebral blood flow data revealed a failure to activate limbic/paralimbic regions during the experience of unpleasant odors, recruiting a compensatory set of frontal cortical regions instead. In another study by Hudry et al. (15), patient ratings of odor intensity, pleasantness, familiarity, and edibility across 12 different odors showed deficits in ratings for pleasantness, familiarity, edibility, and identification against the background of intact intensity ratings. Both studies, however, used disparate odors to probe the hedonic aspects of odor processing, which may have introduced confounding effects of different chemical makeup and trigeminal contributions among the target odorants.

A number of psychological attributes can be assigned to odors, including strength, pleasantness, and quality (16). Studies in healthy people that have used intensity and pleasantness ratings of some olfactory stimuli (e.g., amyl acetate, furfural), showed that pleasantness ratings are highest (i.e., most pleasant) at weak concentrations and decline progressively (i.e., become more unpleasant) as odorant concentration increases (17, 18). Tests based upon such scales allow for probing bipolar dimensions of pleasantness using a single odor, avoiding potential confounds posed by using disparate pleasant and unpleasant

odors that might bring other confounding aspects into the evaluation process (e.g., basal intensity, familiarity, or chemical composition differences).

To examine potential disruption in odor hedonics in patients with schizophrenia, odor intensity and pleasantness were assessed with the Suprathreshold Amyl Acetate Odor Intensity and Odor Pleasantness Rating Test (16), which was given to a group of male and female patients with schizophrenia and a group of healthy subjects comparable in age and gender distribution.

## Method

### *Participants*

Thirty patients with a diagnosis of schizophrenia (15 men and 15 women) and 30 healthy volunteers (11 men and 19 women) were recruited from the Schizophrenia Research Center at the University of Pennsylvania Medical Center, Philadelphia. Demographic and patient clinical data are presented in Table 1. There were no differences between the schizophrenia and healthy comparison groups in the percentage of male and female participants ($\chi^2$=1.08, df=1, p=0.30), mean age (F=0.55, df=1, 58, p=0.46), or handedness ($\chi^2$=0.22, df=1, p=0.64). As expected, patients had lower educational attainment than did the healthy comparison subjects (F=25.1, df=1, 58, p<0.001). Because schizophrenia adversely affects educational attainment, however, maternal and paternal education provides the most appropriate estimate of pre-illness educational expectation (19). Mean parental (maternal and paternal) education did not differ between patients and healthy comparison subjects (Wilks's lambda=0.99, df=2, 57, p=0.71). Patients with schizophrenia were heavier smokers than were the healthy comparison subjects (F=4.91, df=1, 58, p=0.03), smoking an average of 0.51 packs of cigarettes a day as opposed to 0.14 packs daily in healthy comparison subjects.

All subjects underwent a psychiatric interview (Structured Clinical Interview for DSM-IV, patient or nonpatient edition) (20, 21) and a physical examination that included routine laboratory tests. Every participant was administered the Mini-Mental State Examination (MMSE) (22) to assess global cognitive status. Symptom ratings for the patients were assessed with the Brief Psychiatric Rating Scale (BPRS) (23), the Scale for Assessment of Negative Symptoms (SANS) (24), and Scale for Assessment of Positive Symptoms (SAPS) (25). Ratings were completed by investigators trained to a criterion reliability of 0.90 (intraclass correlation). Healthy comparison subjects received the Structured Clinical Interview for DSM-IV Personality Disorders (26). All patients met DSM-IV criteria for schizophrenia, with no other concurrent diagnoses. Comparison subjects were free of any axis I diagnosis, axis II cluster A (i.e., schizoptypal, schizoid, or paranoid) personality disorder, and family history of psychiatric illness.

Subjects were excluded if they had a history of neurological disorder, including head trauma with loss of consciousness, history of substance abuse or dependence (as assessed by history, record review, and serum toxicology), any medical condition that might alter cerebral functioning, a recent respiratory infection, or any other condition that could affect olfactory functioning (e.g., common cold or allergies). The patients were all stable outpatients at time of testing. Twenty-eight patients were receiving atypical antipsychotic medications, and two were unmedicated at the time of testing. After complete description of the study to the subjects, written informed consent was obtained.

**TABLE 1. Demographic and Clinical Characteristics of Healthy Subjects and Patients With Schizophrenia Recruited for a Study of Odor Hedonics**

| Characteristic | Healthy Subjects (N=30) | | Patients With Schizophrenia (N=30) | |
|---|---|---|---|---|
| | N | % | N | % |
| Sex | | | | |
| Men | 11 | 36.7 | 15 | 50.0 |
| Women | 19 | 63.3 | 15 | 50.0 |
| Handedness | | | | |
| Right | 27 | 90.0 | 28 | 93.3 |
| Left | 3 | 10.0 | 2 | 6.7 |
| | Mean | SD | Mean | SD |
| Age (years) | 35.8 | 15.5 | 33.4 | 8.8 |
| Education (years) | 15.7 | 1.7 | 13.1[a] | 2.3 |
| Parental education (years) | 14.3 | 2.8 | 13.9 | 2.7 |
| Smoking (pack-years) | 2.1 | 6.8 | 9.6[b] | 17.4 |
| MMSE score | 29.5 | 0.50 | 28.8[c] | 1.2 |
| BPRS (total score) | — | — | 32.5 | 8.4 |
| SANS (total score) | — | — | 33.5 | 21.3 |
| SAPS (total score) | — | — | 17.8 | 14.5 |
| Duration of illness (years) | | | 7.6 | 6.6 |

[a] Significant between-group difference (F=25.10, df=1, 58, p<0.001).
[b] Significant between-group difference (F=4.91, df=1, 58, p<0.03).
[c] Significant between-group difference (F=10.36, df=1, 58, p<0.003).

### *Ratings of Odor Intensity and Pleasantness*

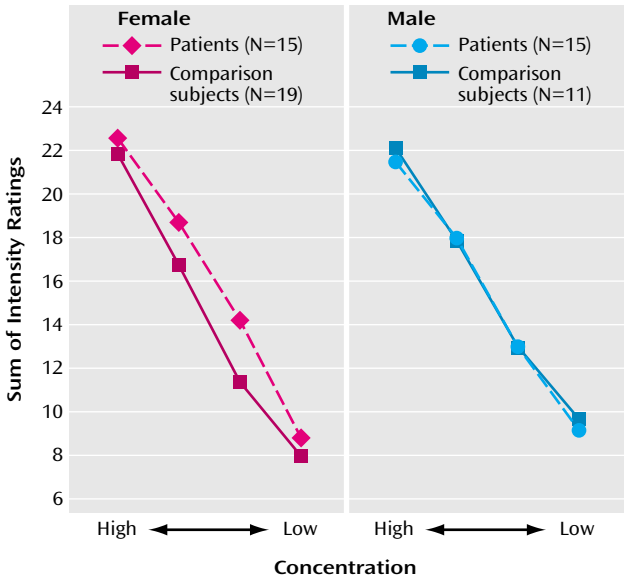
Odor intensity and pleasantness were assessed by using a slightly modified version of the hedonic test described by Doty et al. (16). In this task, 100-ml glass sniff bottles containing four different suprathreshold concentrations (–1.00, –2.00, –3.00, and –4.00 log vol/vol) of amyl acetate diluted in USP grade light mineral oil were presented to each subject. For each trial, one 100-ml glass sniff bottle was opened by a trained technician, who then placed it over each subject's nares in a standardized manner, and recorded the answer following the subject's response. All tests were administered birhinally (i.e., both nostrils simultaneously). The subject smelled the amyl acetate odor and rated the perceived intensity and pleasantness of the odor on separate 5-point category scales. The scales used to assess odor intensity and pleasantness were adaptations of the Self-Assessment Manikin developed by Lang and colleagues (27, 28). The Self-Assessment Manikin has been used effectively to measure emotional responses in a variety of situations, including reactions to pictures (29), images (30), sounds (31), and painful stimuli (32). No feedback was provided to the subjects as to the accuracy of their responses.

Each of the four stimulus concentrations were presented five times in counterbalanced order, for a total of 20 trials in each rating condition. The sum of the intensity and pleasantness ratings at each concentration step served as the dependent measures. The test-retest reliability of intensity and pleasantness measures derived from this type of test are typically greater than 0.75 (16).

### *Statistical Analysis*

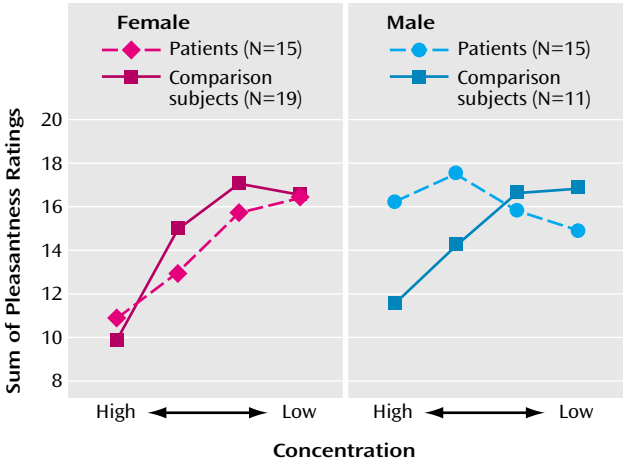
Repeated-measures multivariate analyses of covariance (MANCOVAs) were conducted, with overall odor intensity and pleasantness ratings as the dependent measures, group (patient versus healthy comparison subject) and sex as the between-subject factors, and concentration step (–1.00, –2.00, –3.00, and –4.00 log vol/vol) as the repeated-measures factor. While the effects of smoking on other olfactory psychophysical measures have been shown to be negligible in patients with schizophrenia (4, 5), the effect of smoking on intensity and pleasantness ratings of olfactory stimuli is unknown. We therefore included smoking status, as indi-

**FIGURE 1. Odor Intensity Ratings by Gender for Different Suprathreshold Concentrations[a] of Amyl Acetate in Healthy Subjects and Patients With Schizophrenia**




[a] Four concentrations (from highest to lowest: –1.00, –2.00, –3.00, and –4.00 log vol/vol) were presented to subjects five times in counterbalanced order for a total of 20 trials.

**FIGURE 2. Odor Pleasantness Ratings by Gender for Different Suprathreshold Concentrations[a] of Amyl Acetate in Healthy Subjects and Patients With Schizophrenia**




[a] Four concentrations (from highest to lowest: –1.00, –2.00, –3.00, and –4.00 log vol/vol) were presented to subjects five times in counterbalanced order for a total of 20 trials.

cated by number of packs smoked per year, as a covariate in all analyses. Significant MANCOVA effects were followed by univariate analyses examining pairwise group contrasts on the individual measures.

## Results

### *Odor Intensity Ratings*

Patients and comparison subjects did not differ in their intensity ratings of the different concentrations of amyl acetate, with no main effects of diagnosis or sex or a diagnosis-by-sex interaction being observed (Figure 1). Consistent with the finding of similar intensity ratings, both patients and comparison subjects demonstrated a significant within-subject effect for concentration, with weak odors being rated as less intense and stronger odors being rated as more intense ($F=377.4$, $df=3, 168$, $p<0.001$). These data indicate that both groups were able to accurately discern the intensity of the four different concentrations of amyl acetate.

### *Odor Pleasantness Ratings*

In contrast to the findings for intensity ratings, a significant diagnosis-by-sex-by-concentration interaction was noted for pleasantness judgments ($F=3.5$, $df=3, 168$, $p<0.02$), with male patients showing significant impairment in their pleasantness ratings relative to both healthy comparison subjects and women with schizophrenia (Figure 2).

As can be seen in the left panel of Figure 2, female patients with schizophrenia showed a parallel change in pleasantness ratings over decreasing concentration sets (i.e., weaker concentrations being rated more pleasant), quite similar to the pattern seen in healthy female and male subjects. In contrast, male patients with schizophrenia showed a marked disruption of pleasantness ratings, tending to rate even very strong concentrations as pleasant (right panel, Figure 2). It is notable that compared with the pattern seen in healthy men, as the concentrations weakened men with schizophrenia actually tended to rate these odors as less pleasant. This abnormality in pleasantness ratings could not be explained by reduced odor perception, since patients and comparison subjects did not differ with regard to basic intensity ratings, and all odors were presented at suprathreshold levels.

To ascertain whether the observed sex difference in pleasantness ratings among patients might be explained by differences in general cognitive status or clinical symptoms, an examination of MMSE scores, overall severity of psychiatric symptoms, and degree of negative and positive symptoms was carried out. Male and female patients did not differ with regard to MMSE scores ($F=0.60$, $df=1, 28$, $p=0.45$), with both men (mean=28.6, SD=1.1) and women (mean=29.0, SD=1.2) showing very mild cognitive decrements. Male patients also did not differ from female patients in total BPRS ($F=1.5$, $df=1, 23$, $p=0.23$), SANS ($F=2.0$, $df=1, 27$, $p=0.17$), or SAPS ($F=0.19$, $df=1, 27$, $p=0.67$) scores. Follow-up MANCOVAs of pleasantness ratings between men and women with schizophrenia in which MMSE, BPRS, SANS, and SAPS scores were used as covariates did not alter the observed sex differences in the ability to attach appropriate valence to odors, nor were significant correlations observed between the slopes of intensity and pleasantness ratings and SANS scores in male or female patients.

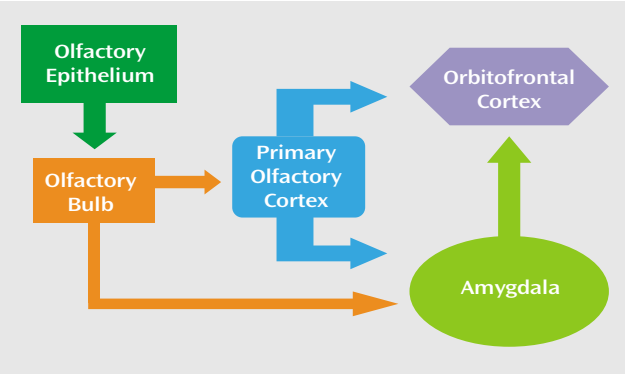
## Discussion

These data provide evidence for an abnormality in the ability to process the hedonic properties of odors in patients with schizophrenia. Specifically, men with schizophrenia demonstrated a significant disruption in their ability to attach the appropriate hedonic valence to a pleasant odor, despite giving intensity ratings that were in the normal range. This behavioral response is consistent with the clinical observation that patients with schizophrenia frequently experience anhedonia and that male patients tend to show a greater burden of deficit with regard to such symptoms (33, 34). By using a single odorant that varied in pleasantness by intensity, we minimized potential confounds in these ratings due to differences in odor composition and other qualitative characteristics (e.g., familiarity).

Our findings are compatible with those of Crespo-Facorro et al. (14), who reported significant deficits in attributing the appropriate hedonic valence to pleasant stimuli. While they did not specifically address sex differences, we note that their study included only two female subjects. This observation lends indirect support for the current finding that men with schizophrenia have deficits in the ability to attach appropriate hedonic valence to pleasant odors. In the only other study of olfactory hedonics in schizophrenia, Hudry et al. (15) also found deficits in odor pleasantness, familiarity, edibility, and identification in schizophrenia. However, while male patients were more impaired in odor familiarity judgments, they did not differ from female patients in pleasantness scores, in contrast to our study. A possible reason for the differences in our findings with those of Hudry et al. is the method used to assess pleasantness. In the Hudry et al. study, pleasantness scores were an average of ratings given to a number of different odor types, perhaps introducing confounding effects of differences in familiarity, pleasantness, and chemical composition of the target odors. Taken all together, these studies and ours document a disruption of odor hedonics in patients with schizophrenia and that such deficits occur independent of odor intensity.

While previous studies of odor identification, detection threshold sensitivity, memory, and discrimination in schizophrenia have generally not supported a diagnosis-specific sex difference in olfactory abilities (see reference 5 for a meta-analytic review), there are compelling reasons to expect such differences in patients suffering from schizophrenia. Clinically, sex differences have been reported in schizophrenia, with women having a later onset, milder course, and more affective symptoms (35–37). With regard to olfaction in schizophrenia, Kopala and Clark (38) have detailed a model where such potential sex differences in olfactory abilities are modulated by estrogen in olfactory-related brain regions. Indeed, in the brains of both men and women, estrogen α and β receptors and progesterone, androgen, and prolactin receptors are widely distributed in a number of extrahypothalamic basal forebrain sites including the amygdala, lateral septum, bed nucleus of the stria terminalis, nucleus of the diagonal band, basal nucleus of Meynert, periaqueductal gray matter, and islands of Calleja (39). These brain areas are intimately involved in olfactory processing and underscore how hormonal differences or disruption may influence the interplay among olfactory, emotional, and cognitive processes (5, 40, 41). Tasks of odor hedonics may uniquely tap the convergence of emotional and olfactory processing units. Further studies detailing the relationship of hormonal factors to olfactory functions are clearly needed.

**FIGURE 3. Major Efferent Connections of the Main Olfactory System**




In humans, a strong and relatively consistent activation of the right orbitofrontal cortex by olfactory stimuli has been observed (42, 43), and involvement of the amygdala has also been described in olfactory stimulation tasks (44). There is also considerable evidence that the amygdala and the orbitofrontal cortex play a role in mediating emotional experience and expression (45–47). Within this general framework, the connectivity of the amygdala and orbitofrontal cortex is consonant with a role for these regions in the processing of information concerning the emotional and motivational significance of olfactory cues (48–53).

In a study of temporolimbic and neocortical gray and white matter volumes in patients with schizophrenia, Gur and colleagues (54) found significant sex differences in amygdala volumes. Specifically, while 8% of male patients showed a decrease in volume, 10.5% of female patients showed an increased volume in these structures. It may be the initial processing of the olfactory stimulus at the level of the amygdala that is disrupted in male patients, preventing or degrading further processing in orbitofrontal regions (Figure 3). Support for this hypothesis can be seen in cerebral imaging studies in healthy subjects where increased blood flow in the amygdala in response to unpleasant odors has been demonstrated (44). In addition, a study by Hudry and colleagues (55) also demonstrated that pleasantness ratings on olfactory tests are significantly reduced in patients whose seizures originate in the amygdala and hippocampus.

A few limitations should be noted. First, a single odor was used for the intensity and pleasantness ratings. Whether the observed diagnosis-specific sex difference in hedonic attribution can be generalized to other odorant types remains to be examined empirically. The current design, however, used a single odor that had been shown to vary in hedonic properties with changes in intensity in healthy volunteers. The advantage of this test paradigm is that it avoids potentially confounding differences caused by using two different odorants that might have divergent chemical composition and odor qualities (e.g., vanillin versus skatole). Second, while intensity ratings did not differ between subjects, suprathreshold intensity ratings are sometimes less sensitive to alterations in odor perception (56), suggesting that more work may be needed on this point. Third, our patient group included young adults with mild to moderate symptoms and without comorbidity. The generalizability of findings to older adults with a broader range of symptoms merits further study. Last, the precise anatomic and physiologic mechanisms underlying this deficit are not yet clear. Relating odor pleasantness and intensity ratings to MRI volumetric measures or functional imaging assessments (e.g., PET, fMRI) of amygdala and orbitofrontal regions will also help to discern whether there is a structural or physiologic component to the observed psychophysical deficit.

In summary, these data support a significant deficit in hedonic processing of odors in men with schizophrenia and suggest a significant disruption in olfactory-limbic brain regions responsible for attaching emotional valence to sensory stimuli. This impairment in hedonic ratings cannot be explained by poorer odor perception, since both patients and comparison subjects did not differ with regard to basic intensity ratings, and all odors were presented at suprathreshold levels. Future studies examining the underlying structural and physiological etiologies/mechanisms for these impairments will be important in furthering our understanding of this phenomenon.

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