

Odor Hedonic Capacity and Anhedonia in Schizophrenia and Unaffected First-Degree Relatives of Schizophrenia Patients

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Objective: There is increasing evidence that schizophrenia patients have difficulties in the hedonic appraisal of odors. In a prior study, we assessed olfactory hedonic perception birhinally and found that males with schizophrenia failed to attach the appropriate hedonic valence to a pleasant odor, despite correctly perceiving changes in odor intensity. Female patients, in contrast, exhibited normal responses. The current study extends this work by examining odor valence processing in unaffected first-degree relatives of schizophrenia patients, to determine the extent to which this abnormality may be genetically mediated. We also examine odor valence processing unirhinally, rather than birhinally, to probe possible lateralized differences in patients' hedonic processing deficits. **Method:** Individuals with schizophrenia ($n = 54$), first-degree unaffected family members ($n = 22$), and demographically matched controls ($n = 45$) were administered the Suprathreshold Amyl Acetate Odor Intensity and Odor Pleasantness Rating Test. **Results:** In contrast to family members and controls, both male and female schizophrenia probands undervalued the hedonic characteristics of amyl acetate at lower concentrations and overvalued its pleasantness at concentrations perceived as unpleasant by both controls and relatives. These patient-specific differences could not be explained by differences in smoking habit, medication use, or subjective ratings of odor intensity. However, they were associated with increased levels of anhedonia/asociality and negative symptomatology. **Conclusions:** Our findings suggest that both male and female schizophrenia patients have difficulties in the unirhinal appraisal of hedonic valence. Normal responses in unaffected first-degree relatives suggest that this is an environmentally, rather than genetically, mediated abnormality denoting negative symptomatology.

Key words: smell/olfactory/valence processing/pleasantness/emotion/olfaction

Introduction

Anhedonia, the decreased capacity to experience pleasure, is an enduring and treatment-resistant negative symptom in the presentation of schizophrenia.^{1,2} Increased social anhedonia is thought to be a marker of transition to psychosis³ and, in patients, is associated with poor premorbid adjustment, decreased social functioning, and poor long-term outcome.^{4,5} Therefore, understanding the neural correlates of anhedonia may contribute to elucidating the pathophysiology of schizophrenia and help identify first-episode patients and at-risk individuals early in the course of illness.

Among neurobehavioral probes of hedonic capacity, olfactory measures may have a unique advantage owing to direct and reciprocal connections between brain regions modulating olfaction and emotion processing, including the orbitofrontal cortex (OFC), amygdala, and hippocampus. In schizophrenia, structural and functional abnormalities in the olfactory-orbitofrontal circuitry have been consistently observed (for a review, see Turetsky et al⁶), and reduced activity in the OFC and putamen/ventral striatum is inversely associated with anhedonia in patients.⁷ Behaviorally, increased olfactory anhedonia is associated with a higher level of negative symptoms^{8,9} and is more profound in patients with deficit syndrome schizophrenia.¹⁰ Taken together, these data suggest that similar neural circuitry may underlie odor hedonic processing and trait anhedonia.

Current reports on olfactory anhedonia have indicated that patients have difficulties in the appraisal of odor valence despite intact intensity perception,^{11,12} though how these abnormalities manifest have varied across studies. Several reports have noted attenuated pleasantness ratings for pleasant but not unpleasant odors in patients.^{11–13} (Note: Data from the Hudry et al¹² report

were reanalyzed separately for pleasant and unpleasant odor valences, and results were reported in Plailly et al.¹³). Conversely, others have reported increased pleasantness ratings in patients^{8,14} or pleasantness ratings restricted to the higher end of the pleasantness spectrum in contrast to more variability observed in controls.⁹ While these studies collectively noted disruptions in odor hedonic processing, the use of disparate odors with varying chemical compositions, trigeminal contributions, and dimensions of edibility, familiarity, and pleasantness, may have introduced potential confounds into the analysis. In an attempt to minimize these confounds, our group ascertained pleasantness and intensity ratings following birhinal presentation of 1 odor, amyl acetate, at 4 suprathreshold concentrations.¹⁵ While groups did not differ in their appreciation of intensity differences across odor concentrations, healthy individuals rated amyl acetate as more pleasant at weaker concentrations and increasingly unpleasant as the concentration increased. Female patients showed a pattern of ratings that was similar to controls, whereas male patients rated the odor as significantly more pleasant at higher concentrations. Sexually dimorphic pleasantness ratings are consistent with reports that male patients experience more enduring negative symptoms, earlier illness onset, and decreased social, cognitive, and premorbid functioning compared with their female counterparts (for a review, see Leung et al.¹⁶).

Despite the growing body of literature on olfactory hedonic processing in schizophrenia, no studies have examined possible odor hedonic disturbance in unaffected family members of patients. Given the familial basis for increased social anhedonia^{17,18} and olfactory impairments,^{19,20} the aim of the current study was to examine odor valence processing in relatives of schizophrenia patients. We also sought to extend prior work by assessing odor valence processing unirhinally (separately for each nostril), as opposed to birhinally as we did in our previous study.¹⁵ Unirhinal odor presentation allows the examination of potentially important lateralized differences in hedonic processing. It also enables us to assess hedonic processing in the absence of birhinal facilitation, whereby olfactory performance is enhanced through secondary integration of left and right nostril inputs.

Methods

Participants

Participants in the current study were recruited to the University of Pennsylvania Medical Center into 1 of 3 groups as follows: (1) schizophrenia probands ($n = 54$) who met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) diagnosis of schizophrenia, (2) healthy comparison subjects ($n = 45$), and (3) first-degree unaffected family members

of individuals with schizophrenia ($n = 22$). Participants underwent a standard clinical assessment using the *Structured Clinical Interview for DSM-IV Axis I Disorders, Patient or Nonpatient Edition* (SCID²¹) by trained master's level clinicians, as well as a detailed medical history including a physical examination and laboratory testing by a licensed psychiatrist (C.G.K., R.E.G., and B.I.T.). Diagnoses were established by consensus conference of psychologists and psychiatrists using best estimate DSM-IV-TR²² diagnoses for schizophrenia. A trained diagnostician rated patients on the Brief Psychiatric Rating Scale (BPRS²³), the Scales for Assessment of Negative Symptoms (SANS²⁴) and Positive Symptoms (SAPS²⁵), as well as the Hamilton Psychiatric Rating Scale for Depression (HAM-D²⁶). Family members and controls were also assessed for a DSM-IV Axis II disorder with the *Structured Clinical Interview for DSM-IV Axis II Disorders* (SCID-II²⁷) in order to rule out the presence of an Axis I disorder. Raters were trained to a criterion reliability of .90 (intraclass correlation). Individuals were excluded from participation from all groups based on a lack of proficiency in English, history of neurological disorder, loss of consciousness, head trauma, current substance abuse (determined by a urine drug screen), mental retardation, past substance dependence, and the presence of a medical condition that could alter cerebral or olfactory functioning (eg, an upper respiratory infection, common cold, or allergy).

Unaffected family members were first-degree relatives (father, mother, offspring, or full sibling) of an individual affected with the sole diagnosis of schizophrenia. The cohort of unaffected first-degree relatives represented 6 parents, 15 siblings, and 1 offspring. Healthy participants and family members were screened for any current or past history of a DSM-IV Axis I or Axis II Disorder using the SCID—Nonpatient Edition. After providing a complete description of the study to participants, written informed consent was obtained from all participants. All study procedures were approved by the University of Pennsylvania Institutional Review Board and complied with the Declaration of Helsinki's ethical standards in the treatment of human research participants.

The 3 groups did not differ with regard to 'age' ($F_{2,118} = 1.50, P = .23$), 'sex composition' ($\chi^2 = 1.81, df = 2, P = .40$), 'handedness' ($\chi^2 = 3.96, df = 4, P = .41$), or 'ethnicity' ($\chi^2 = 8.26, df = 6, P = .22$). Overall group differences in educational attainment were statistically significant ($F_{2,118} = 4.97, P = .01$). Healthy comparison subjects had more years of education than patients ($F_{1,118} = 9.66, P = .002$), while differences between healthy controls and family members were not statistically significant ($F_{1,118} = 0.41, P = .52$). Patients and family members did not differ significantly with regard to educational attainment ($F_{1,118} = 3.20, P = .08$). Conversely, groups did not differ with regard to parental education (Wilks' $F_{4,170} = 1.30, P = .27$). Overall

Table 1. Demographic and Clinical Characteristics

Characteristics	Schizophrenia Probands (<i>n</i> = 54)			Family Members (<i>n</i> = 22)			Control Group (<i>n</i> = 45)		
	Mean	SD	% (<i>N</i>)	Mean	SD	% (<i>N</i>)	Mean	SD	% (<i>N</i>)
Age (years)	40.69	8.89		45.68	16.00		40.89	13.03	
Sex									
Males			57.4 (31)			40.9 (9)			55.6 (25)
Females			42.6 (23)			59.1 (13)			44.4 (20)
Ethnicity									
Caucasian			27.8 (15)			40.9 (9)			51.1 (23)
African-American			68.5 (37)			59.1 (13)			42.2 (19)
Latino-American			1.9 (1)			0 (0)			4.4 (2)
Asian-American			1.9 (1)			0 (0)			2.2 (1)
Education level* (years)	12.57	2.08		12.95	2.26		14.04	2.66	
Mother's education (years)	12.19	2.60		11.47	2.94		13.32	2.03	
Father's education (years)	12.15	3.76		11.71	4.36		12.69	2.76	
Pack-days*	0.34	0.48		0.30	0.41		0.09	0.20	
Illness duration (years)	16.89	9.50							
Age of onset (years)	22.76	7.71							
BPRS ²³ total score	29.42	8.01							
SANS ²⁴ total score	26.98	15.78							
SAPS ²⁵ total score	21.62	15.77							
HAM-D ²⁶ total score	6.22	6.88							
Chlorpromazine equivalents	353.79	491.13							

Note: BPRS, Brief Psychiatric Rating Scale; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; HAM-D, Hamilton Psychiatric Rating Scale for Depression.

*Significant group difference ($P = .01$).

group differences in 'smoking' (measured as packs per day) were statistically significant ($F_{2,111} = 5.03$, $P = .01$). Patients smoked significantly more than the healthy comparison subjects ($F_{1,111} = 9.55$, $P = .003$) but the same as family members ($F_{1,111} = 0.14$, $P = .71$). Differences between family members and controls trended toward significance ($F_{1,111} = 3.59$, $P = .06$).

Of the patients with schizophrenia, 8 individuals were unmedicated and 46 were on a regimen of antipsychotic medications (11 were on first-generation antipsychotics and 35 were on second-generation antipsychotics). Medication dosages were converted to chlorpromazine equivalents using published reference tables.²⁸ Means and standard deviations for sample demographic and clinical data are provided in table 1.

Suprathreshold Amyl Acetate Odor Intensity and Odor Pleasantness Rating Test

Measures of odor intensity and pleasantness were assessed using the Suprathreshold Amyl Acetate Odor Intensity and Odor Pleasantness Rating Test,¹⁵ a modified version of a hedonic task created by Doty et al.²⁹ Subjects were presented with 100-ml glass containers with 4 suprathreshold concentrations (-1.00 , -2.00 , -3.00 , and -4.00 log vol/vol, from strong to weak intensity) of amyl acetate, with United States Pharmacopeia grade light mineral oil as the diluent. Odor concentrations

were administered unilaterally (ie separately to each nostril). The individual's contralateral nostril was occluded with Durapore tape (3M Corporation, Minneapolis, Minnesota) in order to minimize retronasal airflow.³⁰ Standardized administration was completed by a trained technician that opened each glass bottle, held it under the unoccluded nostril, and acquired intensity and pleasantness ratings on separate 5-point scales for each odor presentation. The scales used to assess odor intensity and pleasantness were adaptations of the Self-Assessment Manikin (developed by Lang et al³¹). The 4 odor concentrations were presented 5 times in a counterbalanced order to each nostril, for a total of 20 trials in each rating condition. Previous research has suggested a test-retest reliability of 0.75 or greater for similar tasks.²⁹

Data Analysis

Primary data analysis was performed in STATISTICA (Statsoft Inc., Tulsa, Oklahoma). Overall group differences in age, education, smoking, and parental education were assessed using an ANOVA. Pearson chi-squares were used to determine group differences for sex, handedness, and ethnicity. A MANCOVA was conducted separately for intensity and pleasantness ratings. Left and right nostril ratings across the 4 concentrations (-1.00 , -2.00 , -3.00 , and -4.00 log vol/vol) were repeated measure factors, with group and sex as between-subject

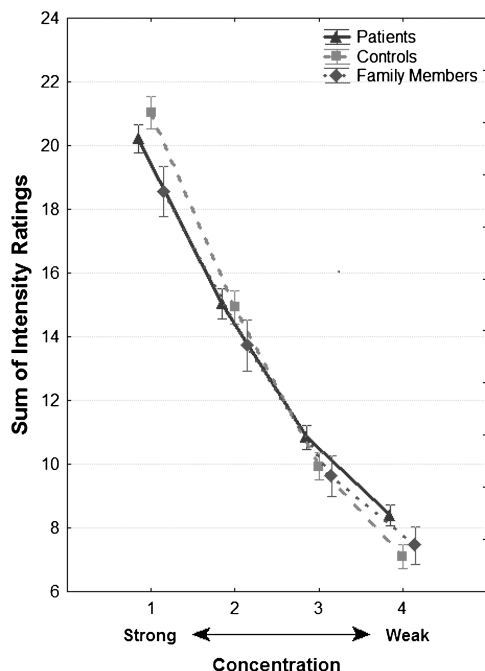


Fig. 1. Odor intensity ratings (\pm SE) for suprathreshold concentrations of amyl acetate in patients with schizophrenia, first-degree unaffected relatives, and healthy comparison subjects. *Note:* Participants were presented with 4 odor concentrations (from strongest to weakest: -1.00 , -2.00 , -3.00 , and -4.00 log vol/vol) to each nostril 5 times in counterbalanced order for a total of 40 trials

factors. Smoking (packs/day) was included as a covariate in all analyses. Post hoc univariate analyses were conducted for significant effects by examining pairwise group contrasts on individual measures.

In order to account for the potential impact of differences in intensity perception on hedonic ratings, group differences were also examined using the Generalized Linear Latent and Mixed Models algorithm implemented in Stata 9.0 (StataCorp., College Station, Texas), with subject as a random-effects factor. Group (patient/relative/control), nostril, odor concentration, and sex were included as fixed-effects predictors of response. Individual intensity ratings and smoking were included as covariates in the analysis. Significance levels were assessed using the Wald test statistic with χ^2 distribution.

Within the patient group, relationships between pleasantness ratings and clinical assessments (duration of illness, age of onset, negative and positive symptoms, and chlorpromazine equivalents) were measured using Pearson's correlations (r).

Results

Intensity Ratings

Analysis of intensity ratings revealed a significant main effect of concentration ($F_{3,321} = 426.94$, $P < .0001$) with all participants rating stronger concentrations as more intense than adjacent weaker concentrations (all

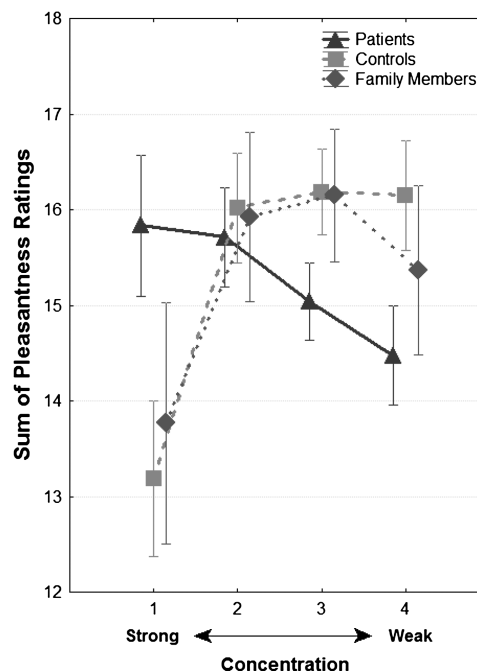


Fig. 2. Odor pleasantness ratings (\pm SE) for suprathreshold concentrations of amyl acetate in patients with schizophrenia, first-degree unaffected relatives, and healthy comparison subjects. *Note:* Participants were presented with 4 odor concentrations (from strongest to weakest: -1.00 , -2.00 , -3.00 , and -4.00 log vol/vol) to each nostril 5 times in counterbalanced order for a total of 40 trial

P 's $< .0001$). No effect of nostril ($F_{1,107} = 0.01$, $P = .94$), sex ($F_{1,107} = 0.03$, $P = .87$), or group-by-sex interaction ($F_{2,107} = 1.39$, $P = .25$) was observed.

However, a significant group-by-concentration interaction ($F_{6,321} = 2.51$, $P = .02$) was noted. In paired contrasts, this interaction was significant for both patients vs controls ($F_{3,273} = 3.25$, $P = .02$) and family members vs controls ($F_{3,168} = 4.67$, $P = .004$) but not for patients vs family members ($F_{3,198} = 0.21$, $P = .89$). As illustrated in figure 1, control subjects rated the strongest (1.00 log vol/vol) concentration as more intense and the weakest (-4.00 log vol/vol) concentration as less intense than patients and family members.

Pleasantness Ratings

A statistically significant group-by-concentration interaction was observed ($F_{6,321} = 3.35$, $P = .003$). In paired contrasts, this interaction was significant only for patients vs controls ($F_{3,273} = 5.85$, $P < .001$), although there was also a trend toward significance ($F_{3,198} = 2.43$, $P = .06$) for patients vs family members. Family members and controls were indistinguishable ($F_{3,168} = 0.07$, $P = .98$). As seen in figure 2, controls and family members showed parallel changes in odor pleasantness ratings, with the strongest odor concentration being rated as the least pleasant. Schizophrenia patients, in contrast, showed a linear increase in pleasantness ratings with increasing odor concentration; they rated weaker odors as less pleasant and

the strongest odor as more pleasant than both controls and family members. The statistically significant concentration-by-group interaction persisted after included intensity ratings as a covariate ($\chi^2 = 41.88$, $df = 3$, $P < .0001$), and intensity ratings did not significantly predict pleasantness ratings ($Z = 1.06$, $P = .29$).

When comparing valence ratings between the strongest and weakest concentration within each group, healthy controls had significantly higher pleasantness ratings for the weakest compared with the strongest concentration ($F_{1,107} = 5.93$, $P = .01$). Neither patients ($F_{1,107} = 1.39$, $P = .24$) nor family members ($F_{1,107} = 1.15$, $P = .28$) exhibited a significant difference between the ratings for the strongest and weakest concentrations. Family members' ratings were in the same direction as controls, while patients' ratings were in the opposite direction.

In addition, a main effect of nostril ($F_{1,107} = 4.13$, $P = .03$) and a significant nostril-by-concentration interaction ($F_{3,321} = 3.96$, $P = .01$) were observed. Individuals across all groups reported significantly higher pleasantness ratings for odors presented to the left nostril, and this was especially true at the lower odor concentrations which were rated the most pleasant. A main effect of sex was also observed across all odor concentrations such that females, regardless of group status, rated odors as more pleasant than males ($F_{1,107} = 4.873$, $P = .03$). Contrary to our previous results using birhinal stimulation (Moberg et al¹⁵), sex did not modify or interact with the observed group differences in pleasantness ratings across odor concentrations.

Pleasantness Ratings and Illness Characteristics

In patients, an inverse relationship was observed between SANS total score (sum of all items) and left nostril pleasantness ratings, such that patients with higher negative symptoms reported lower left nostril ratings of pleasantness for the 2 weakest concentrations (-3.00 log vol/vol: $r = -.37$, $P = .01$ and -4.00 log vol/vol: $r = -.44$, $P = .002$). In particular, the SANS anhedonia/asociality subscale (calculated as the sum of all anhedonia/asociality items) was inversely associated with left nostril ratings for the 3 weaker concentrations (-2.00 log vol/vol: $r = -.40$, $P < .01$; -3.00 log vol/vol: $r = -.33$, $P = .02$; and -4.00 log vol/vol: $r = -.32$, $P = .03$). After controlling for HAM-D total scores, correlations between the SANS anhedonia/asociality subscale and left nostril hedonic ratings for all odor concentrations were statistically significant (-1.00 log vol/vol: $r = -.34$, $P = .05$; -2.00 log vol/vol: $r = -.50$, $P = .002$; -3.00 log vol/vol: $r = -.44$, $P = .01$; and -4.00 log vol/vol: $r = -.34$, $P = .05$). Overall associations between SANS indices and odor valence ratings are presented in table 2.

For the SAPS, a significant association was observed between the SAPS Bizarre Behavior subscale and right nostril pleasantness ratings of the strongest odor concentration (-1.00 log vol/vol: $r = .30$, $P = .04$),

such that patients with more bizarre symptomatology rated these odors as more pleasant (ie, more abnormal in comparison with controls). Similarly, the SAPS Positive Formal Thought Disorder subscale was positively associated with right nostril pleasantness ratings for the 2 strongest odors (-1.00 log vol/vol: $r = .31$, $P = .03$ and -2.00 log vol/vol: $r = .43$, $P < .01$). Pleasantness ratings in the patient group were not significantly associated with age, education, illness duration, age of onset, HAM-D scores, or BPRS scores (all P 's $> .09$). Furthermore, the SANS symptoms subscales, including the SANS anhedonia subscale, were not associated with HAM-D scores, nor were total SANS scores (all P 's $> .13$).

Patients were further subdivided according to medication status. Unmedicated and medicated patients did not differ significantly with respect to ratings of either pleasantness or intensity (all P 's $> .10$). Further subdividing medicated patients into those taking first-generation antipsychotics and those taking second-generation antipsychotic medications similarly revealed no significant main effects or interactions (all P 's $> .20$). Finally, no relationships were observed between chlorpromazine equivalent dosage and ratings of pleasantness (all P 's $> .42$).

Discussion

In the current study, we extend prior research on olfactory anhedonia in schizophrenia by examining unirhinal hedonic and intensity ratings in males and females with schizophrenia, as well as unaffected first-degree family members. Our results indicate, first, that both male and female patients demonstrate abnormalities in perceived olfactory hedonic valence. Specifically, patients undervalued the pleasantness of amyl acetate at low concentrations and did not appreciate its increasing unpleasantness at high concentrations, as experienced by healthy control subjects. This finding replicates our previous results for male patients.¹⁵ However, in contrast to our previous finding that female patients had normal hedonic valence perception, the female patients in the current study also experienced a disturbance in the appreciation of hedonic valence. One notable explanation for this discrepancy in findings between the current and prior study was the method of odor presentation. Compared with Moberg's¹⁵ study, the current study employed unirhinal assessment whereby each nostril was tested in isolation. While few studies have compared differences between unirhinal and birhinal assessment, at least 1 study noted that the female advantage for birhinal odor identification disappears during unirhinal testing.³² As birhinal odor assessment is thought to involve interhemispheric facilitation compared with unirhinal conditions,^{30,33} it is possible that unirhinal testing suppressed the compensation of the contralateral hemisphere, and without this advantage female patients exhibited the same hedonic disturbance as male patients. Further research directly

Table 2. Correlations Between Odor Valence Ratings and Negative Symptoms in Schizophrenia

	Valence Ratings							
	Right Nostril				Left Nostril			
	Odor Concentration (log vol/vol)				Odor Concentration (log vol/vol)			
	Strong	↔	Weak		Strong	↔	Weak	
SANS ²⁴ Indices	-1.00	-2.00	-3.00	-4.00	-1.00	-2.00	-3.00	-4.00
Total score	.04	-.04	-.22	-.23	.07	-.25	-.37**	-.44**
Affective flattening	-.12	-.15	-.19	-.19	.03	-.22	-.27	-.24
Alogia	.14	-.03	-.05	-.03	.11	-.05	-.27	-.29*
Avolition-apathy	.20	.16	-.06	-.17	.16	.00	-.08	-.21
Anhedonia-asociality	-.03	-.06	-.16	-.16	-.15	-.40**	-.33*	-.32*
Attention	.06	.03	-.23	-.18	.18	-.02	-.21	-.43**

Note: SANS, Scale for the Assessment of Negative Symptoms. Values are Pearson correlations.

*Statistically significant $P < .05$; ** $P < .01$.

comparing birhinal and unirhinal conditions with measures for interhemispheric transfer times could help elucidate these differences.

The unaffected family members of schizophrenia patients, in contrast, did not show any disruption in odor hedonic perception. This was unexpected because previous investigations have noted both increased anhedonia¹⁸ and deficits in olfactory task performance in family members with schizophrenia.^{19,20} In addition, significant associations between physical anhedonia and neuropsychological probes of executive function have been noted in unaffected siblings of schizophrenia patients.³⁴ Given these findings, we anticipated that family members would also exhibit a disturbance in attaching hedonic valence to odors. However, the current literature on heritability for olfactory ability is complex because heritability may vary depending on the olfactory task type and odorants assessed. Finkel and colleagues³⁵ noted modest heritability for odor identification and odor intensity perception but found that ratings for the perceived pleasantness of odorants did not show significant genetic mediation in a non-clinical sample. Knaapila et al³⁶ reported that both intensity and pleasantness perception are predominantly environmentally mediated, with minimal genetic contribution. Still others have noted that heritability of hedonic perception may depend on the nature and chemical composition of the particular odorant being assessed because hedonic perception of certain odorants (eg, androstenone, cinnamon) appear to be genetically mediated.^{37,38} Our findings suggest, though, that the odor hedonic abnormalities associated with schizophrenia are not genetically mediated but rather represent a functional deterioration associated with the illness state.

Patients' abnormal pleasantness ratings could not be attributed to their inability to perceive the odors. Although we observed a statistically significant group difference in

odor intensity ratings, the pattern of results was not consistent with decreased patient intensity perception. Rather, control subjects rated the strongest odor concentration as more intense and the weakest odor concentration as less intense. This suggests that control subjects used a greater range in their attribution of odor intensity but were not actually better at perceiving the odors. All groups showed a robust relationship between odor concentrations and intensity ratings, suggesting intact appreciation for basic intensity differences across adjacent concentrations. In addition, intensity ratings were not a significant predictor of pleasantness ratings, and controlling for individual intensity ratings for corresponding pleasantness ratings did not alter the effects.

Patient hedonic ratings were also not associated with antipsychotic medication dosage, illness duration, age of onset, depressive symptomatology, or current smoking behavior. However, a significant relationship was observed between pleasantness perception and anhedonia such that patients with higher levels of anhedonia/asociality showed a blunted perception of amyl acetate pleasantness, specifically at those concentrations that were perceived as most pleasant by control subjects. This association remained significant after controlling for current level of depressive symptomatology, suggesting a relationship between trait anhedonia/asociality and impaired odor valence processing. In contrast, increased disorganization (bizarre behavior and positive thought disorder) was associated with blunted appreciation of amyl acetate unpleasantness at the high concentrations that were perceived by controls as most unpleasant. The association between negative symptoms and impaired odor identification has been noted repeatedly.^{39,40} A prior study by Malaspina and Coleman⁴¹ noted a significant relationship between smell identification deficits and diminished social drive in schizophrenia patients. These data provide a logical

and anticipated extension of this relationship into the domain of olfactory hedonic perception. However, the association between disorganized symptoms and impaired unpleasantness perception is not one that was either expected or readily understood. We did previously observe an association between disorganized symptoms and impaired odor identification.⁴² More recently, a study by Strauss et al¹⁰ noted that Nondéficit Syndrome patients (ie, those with positive, but not enduring negative, symptoms) showed a similar selective impairment in judging unpleasant odors to be less unpleasant compared with controls, whereas déficit syndrome (ie, primary and enduring negative symptoms) patients also underrated the pleasantness of pleasant odors. Collectively, these findings suggest that negative symptoms of anhedonia/asociality and positive symptoms of disorganization are independently associated with the perception of opposing valence characteristics in schizophrenia. Further studies comparing patient groups within these symptoms clusters are needed to elucidate the complexity of odor hedonic perception in schizophrenia.

This relationship between anhedonia and olfactory hedonic déficits was limited to odor presentations to the left nostril. This is consistent with the overall effect we observed in which all subjects tended to rate odors as more pleasant when presented to the left, rather than the right, nostril. While the neural basis for odor hedonic abnormalities is unclear, odor valence processing in healthy people, particularly for pleasant odors, has shown left hemisphere dominance.⁴³ In schizophrenia, reduced hedonic ratings for pleasant odors has been associated with decreased activation in left temporo-limbic and left orbital olfactory regions¹³ and increased physical anhedonia has been linked with decreased activation in the amygdala.⁴⁴ The authors of the latter report note that aberrant amygdala activation results in a failure to mark the salience of pleasant events. If one were to extrapolate these findings to the current analysis, it is possible that aberrant processing in OFC and amygdala networks results in reduced representation of affective value and a failure to signify the pleasantness of amyl acetate as salient. Further investigation of aberrant processing in these brain regions as neural correlates of anhedonia is warranted.

Prior laboratory studies in schizophrenia using olfactory stimuli have repeatedly noted abnormalities in valence ratings,^{8–13,15} while studies examining subjective ratings of stimuli from other modalities (eg, pictures, film clips) have not consistently elicited patient-control differences in subjective hedonic reactions (for a review, see Cohen and Minor⁴⁵). It is possible that the relative integration that exists between olfactory and limbic circuitry, coupled with the evolutionary salience of olfaction to social behavior, makes olfactory stimuli especially sensitive probes of hedonic perception. While this is of course speculative, there is evidence for an evolutionary

role of olfactory cues in directing humans toward food, identifying mates and offspring, and signaling threat or danger. Furthermore, olfaction is distinct from other senses because only 1 synapse lies between olfactory receptors and olfactory cortex, providing a direct pathway between the sensory environment and cortex, bypassing the thalamus. Therefore, olfactory probes may offer a unique advantage over other forms of emotional stimuli when probing emotional disturbance and hedonic capacity in schizophrenia.

Limitations of this study include the use of a single odor to ascertain intensity and pleasantness ratings. While the use of 1 odor remedies the potential confound of using disparate odors that differ with respect to chemical makeup and odor dimensions (eg, familiarity, edibility, intensity), it does not allow for generalizability to other classes of odorants or for an examination of genetic mediation across different odor classes. Second, we characterized anhedonia in schizophrenia using a subscale of the SANS. The use of multiple measures of anhedonia, including those that distinguish between social and physical anhedonia (eg, Chapman Scales⁴⁶), or anticipatory and consummatory pleasure (eg, Temporal Experience of Pleasure Scale⁴⁷), and relating these measures to odor hedonic capacity would help to elucidate what aspects of anhedonia are associated with odor hedonic capacity in schizophrenia. Though we observed no significant effect of medication status or type of antipsychotic agent used on odor hedonic ratings, our analysis was likely underpowered given the relatively small number of patients within each subgroup. Therefore, these results must be interpreted with caution given the possibility for false-negative findings. Future studies examining odor valence processing in larger groups of medicated and unmedicated patients are warranted. Similarly, the first-degree family member cohort was considerably smaller than the patient and control group. This limited our ability to examine differences in odor hedonic ratings by degree of relationship (eg, sibling vs parent vs offspring) and resulted in a higher degree of variability in their hedonic responses. Thus, follow-up studies on odor hedonic abnormalities in larger family member groups would be especially useful in understanding how odor valence perception is influenced by degree of genetic relationship to schizophrenia probands.

Our findings indicate that individuals with schizophrenia experience difficulty when assigning valence characteristics to amyl acetate and this difficulty is related at opposing ends of the spectrum, to increased anhedonia and increased disorganization. In contrast to our prior report,¹⁵ female patients showed a similar abnormality to male patients when hedonic ratings were elicited during unirrinal odor presentation. Unaffected family members of schizophrenia patients did not show a disruption in valence appreciation for amyl acetate, which suggests that this disruption represents an

environmentally mediated abnormality. Anhedonia is a treatment-resistant and enduring feature of schizophrenia that is associated with poor functional outcome in patients and individuals at-risk for psychosis. New treatments that target anhedonia in schizophrenia are underway,⁴⁸ and thus, behavioral measures that have predictive value in identifying those at risk for anhedonia are necessary. The use of olfaction as a probe of hedonic capacity is a novel and promising avenue to explore anhedonia in schizophrenia and could be especially useful in identifying people at-risk for anhedonia and in need of targeted intervention for poor social, emotional, and functional outcomes.

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