

Various Bilateral Olfactory Deficits in Male Patients With Schizophrenia

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Olfactory identification deficits in schizophrenia patients are well documented. Less is known about the functioning of other olfactory domains and the possibility of lateralized dysfunctions. Thirty male schizophrenia patients and 30 male healthy controls underwent unirhinal assessment of various olfactory domains: detection threshold (dimethyl disulfide, phenyl ethanol), quality discrimination, and odor ratings (familiarity, pleasantness, edibility, intensity) of pure chemicals (Munich Olfaction Test), as well as familiarity and edibility judgments and identification of everyday odors. Aside from impaired identification, patients showed impaired familiarity and edibility judgments of everyday odors. With regard to odor ratings of pure chemicals, group differences were observed only in pleasantness ratings, with higher ratings in patients. Furthermore, patients had reduced sensitivity with dimethyl disulfide and reduced quality discrimination compared with controls. Further analyses showed that identification deficits were not attributable to reduced sensitivity but may be associated with impairments in quality discrimination. Olfactory dysfunctions were found across both nostrils. Results suggest specific dysfunctions in olfactory processing in schizophrenia patients, including early stages of the odor identification process.

Keywords: Olfactory identification/olfactory sensitivity/olfactory discrimination/odor judgments/odor ratings/unirhinal

Introduction

Given that neuroanatomical regions, particularly prefrontal and medial-temporal regions (see Eslinger et al. 1982; Pantelis and Brewer 1995; Shipley and Ennis 1996; Christensen and Bilder 2000), involved in olfactory processing have also been implicated in the pathophysiology of schizophrenia, interest in olfactory processing in this disorder has grown in recent years (Moberg et al. 1999; Rupp 2003). Assessing olfactory functions may provide information regarding the integrity of these brain areas. Clinical relevance of assessing olfactory dysfunction,

furthermore, has been described in terms of the potential of a vulnerability marker that may be valuable for differential diagnosis (i.e., for differentiating between biologically distinct subtypes of this heterogeneous disorder). This seems supported by findings suggesting a possible genetic contribution to dysfunctional olfactory processing in schizophrenia, or psychosis, respectively (Kopala et al. 1991, 1998, 2001; Becker et al. 1993; Kwapil et al. 1996).

To date, the finding of reduced odor identification performance in patients with schizophrenia, mostly assessed with the University of Pennsylvania Smell Identification Test (UPSIT; Doty et al. 1984), is well documented (Hurwitz et al. 1988; Serby et al. 1990; Kopala et al. 1992, 1994, 1995; Wu et al. 1993; Houlihan et al. 1994; Malaspina et al. 1994; Brewer et al. 1996, 2001; Seidman et al. 1997; Moberg et al. 1997a, 1997b, 1999). Research suggests that identification deficits are not attributable to smoking (Kopala et al. 1992; Houlihan et al. 1994; Brewer et al. 1996), olfactory hallucinations (Kopala et al. 1992, 1994; Stedman and Clair 1998), or medication (Kopala et al. 1992; Wu et al. 1993; Brewer et al. 1996, 2001). Whether identification deficits are associated with negative symptoms is still controversial (Malaspina et al. 1994; Brewer et al. 1996, 2001; Good et al. 1998, 2002).

However, olfactory identification deficits are not specific to schizophrenia. They were seen in patients with affective and other forms of psychoses (Brewer et al. 2001), as well as in a wide variety of brain disorders and diseases (see Martzke et al. 1997; Doty 2001). Given the wide range of disorders accompanied by olfactory identification impairment, a single etiology seems unlikely, and the utility of this deficit as a marker for schizophrenia remains unclear.

Odor identification, as assessed in a multiple-choice test procedure (e.g., UPSIT), requires subjects to perceive, recognize, and select the name of the previously smelled odor from a list. The question of a cognitive basis for identification deficits in schizophrenia was first raised by Serby et al. (1990), who failed to find identification deficits in a yes/no identification task. Several other studies have since indicated a link between impairments in UPSIT performance and cognitive functions in schizophrenia (Brewer et al. 1996; Seidman et al. 1997; Purdon 1998; Stedman and Clair 1998; Good et al. 2002).

With regard to olfactory processing, odor identification requires accurate odor detection (sensitivity) and

quality discrimination. Moberg et al. (1999), in their meta-analyses on olfactory functions in schizophrenia, observed substantial olfactory deficits across all domains, including identification, memory, detection threshold, and discrimination. Unfortunately, none of these studies assessed the basic olfactory functions within a sample. The interpretation of data pertaining to more “secondary” or “higher order” olfactory processing (e.g., identification) is possible only within the context of available data about the integrity of the “primary” sensory systems (e.g., intact sensitivity) (Martzke et al. 1997), a premise routinely applied in other fields of neurobehavioral assessment. It may be worthwhile to note that the characterization as primary and secondary olfactory measures only maintains an appreciation for the latter’s (higher order) dependence upon the former (Martzke et al. 1997). This does not rule out an influence of central processes in all olfactory measures. Identification (higher order) in general requires accurate sensitivity and odor discrimination (both lower order), and discrimination requires accurate sensitivity but not necessarily identification or naming of an odor. Thus, a finding of reduced sensitivity potentially limits the significance of reported deficits in, for instance, identification (Martzke et al. 1997). Furthermore, in the meta-analyses of Moberg et al. (1999) the number of studies that used detection threshold and discrimination was extremely limited (four and two studies, respectively). Meanwhile, no further study has assessed misperception via discrimination, also described as a linking process between threshold and identification (de Wijk and Cain 1994), in schizophrenia. The findings concerning threshold are also controversial. Results range from hypersensitivity (Bradley 1984; Sirota et al. 1999) to intact sensitivity (Geddes et al. 1991; Kopala et al. 1992; Good et al. 1998; Striebel et al. 1999; Kohler et al. 2001) and hyposensitivity (Gross-Isseroff et al. 1987; Serby et al. 1990; Sirota et al. 1999).

Because the olfactory system is unique among the senses in that second order neurons send information directly, with primarily ipsilateral projections, unirhinal assessment of olfactory functions provides an interesting opportunity to probe for asymmetric neuropathology. The few studies that have investigated higher order identification have found poor performance across nostrils (Good et al. 1998; Kohler et al. 2001). Only analyses of post hoc defined subgroups (Good et al. 1998) revealed that unirhinally impaired patients were more likely to have a left (left < right) rather than a right (right < left) nostril disadvantage in identification (Good et al. 2002). A match-to-sample task also failed to demonstrate atypical asymmetry (Dunn and Weller 1989). Contrary to these findings, Purdon and Flor-Henry (2000) found an asymmetrical left nostril impairment in sensitivity in unmedicated patients.

In summary, the present study was undertaken to extend prior research by exploring various olfactory

domains unirhinally in a within-subjects experimental design. Following a multivariate approach to behavioral measurement in olfaction, we included tasks tapping basic olfactory domains such as sensitivity (detection threshold) and quality discrimination, odor identification, and ratings about odors such as familiarity, edibility, pleasantness, and intensity (Eslinger et al. 1982; Royet et al. 1999; Zald and Pardo 2000). We hypothesized that male schizophrenia patients would demonstrate deficits in olfactory domains aside from impaired higher order identification. The second aim was to assess whether the same patients would show abnormal patterns of laterality in these olfactory functions.

Methods

Subjects. Thirty male patients meeting *DSM-IV* criteria (American Psychiatric Association 1994) for schizophrenia and 30 male healthy controls with no history of central nervous system disease and a negative family history (among first degree relatives) of mental disorder participated in the study. The two groups were comparable in age and smoking status. Demographic and clinical characteristics of the sample are illustrated in table 1.

Two senior psychiatrists independently diagnosed all patients. Three were outpatients and the remaining 27 were inpatients treated at the Department of Psychiatry, Innsbruck Medical University. Controls were mainly recruited within the medical center and screened with a semistructured interview. Most of them were male nurses or other hospital staff. Exclusion criteria were (1) history of a psychiatric disorder (other than schizophrenia for the patient group), (2) history of a neurological disorder or head injury with loss of consciousness, (3) history of electroconvulsive therapy, (4) substance dependence or (recent) substance abuse (Rupp et al. 2003), (5) medical conditions that could alter cerebral functioning, and (6) other conditions known to affect olfactory functioning (e.g., upper respiratory tract infection). Psychiatrists (H.O., C.W.), who were blind to patients’ olfactory status, rated symptom severity using the Positive and Negative Syndrome Scale (PANSS; Kay et al. 1987). All subjects had an otorhinolaryngological (ENT) examination, including inspection of the outer nose, the nasal cavity, and the transnasal airflow. ENT findings were graded on a five-point scale (1 = no pathological finding, 2 = septum deviation, 3 = concha hyperplasia, 4 = moderate acute or chronic mucositis, and 5 = complete obstruction of the nasal cavity by acute or chronic paranasal sinuses, acute or chronic rhinitis, trauma, or tumor). Subjects rated 5 were not entered into the study. Handedness preference was assessed using the Edinburgh Handedness Inventory (EHI; Oldfield 1971). Subjects with a laterality quotient > 0.70 were classified as dextral. After complete description of the study to the subjects, written informed consent was obtained prior

Table I. Demographic and clinical characteristics

Variable	Patients (<i>n</i> = 30)				Controls (<i>n</i> = 30)				Analysis ¹		
	Mean	SD	Range	<i>n</i>	Mean	SD	Range	<i>n</i>	Value	<i>df</i>	<i>p</i>
Demographic variables											
Age	31.5	6.1	21–47		32.5	6.9	22–49		<i>t</i> = −0.633	58	<i>ns</i>
Education (yrs)	10.5	1.9	8–17		13.7	3.7	8–18		<i>t</i> = −4.321	58	<0.001
EHI (dextral)				24				25		1	<i>ns</i>
Tobacco smoking history											
Currently smoker (yes)				14				11		1	<i>ns</i>
Cigarettes (average no./day)	20.0	7.6	10–30		19.3	8.8	2–30		<i>t</i> = 0.222	23	<i>ns</i>
Duration of smoking (mos)	136.4	71.3	1–252		144.7	73.0	36–240		<i>t</i> = −0.288	23	<i>ns</i>
Personal psychiatric history											
Age at illness onset	22.4	5.3	14–37								
Duration of hospitalization (days)	18.4	14.1	3–57								
Number of hospitalizations	5.3	4.6	1–21								
Subtypes (<i>DSM-IV</i>)											
Paranoid/disorganized/residual				25/2/3							
Medication											
Antipsychotic (mg/day CPZE) ²	492.5	207.7	250–800								
Lifetime antipsychotic treatment (mos)	86.4	60.8	3–222								
PANSS scores											
PANSS positive	17.4	5.5	8–27								
PANSS negative	21.7	7.1	10–37								

Note.—CPZE = chlorpromazine equivalent; EHI = Edinburgh Handedness Inventory; *ns* = nonsignificant; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation.

¹*t* test, Fisher's exact test; *ns* (*p* > 0.05).

²*n* = 28 (2 patients were medication-free); CPZE doses (Riederer et al. 1998) wherever applicable (haloperidol [*n* = 4], clozapine [*n* = 10], and pimozide [*n* = 2]); the others received risperidone (*n* = 9), sertindole (*n* = 2), and zotepine (*n* = 1).

to participation. None of the subjects had previously undergone an olfactory assessment.

Olfactory Testing

Olfactory measures. Using a slightly modified version of the Munich Olfaction Test (MOT) (cf. Kruggel 1989, 1993; Diekmann et al. 1994; Hudson et al. 1994), we assessed the following olfactory domains: detection threshold (sensitivity), (quality) discrimination, and ratings of familiarity, pleasantness, and edibility. Modifications of the MOT consisted of an extra dilution step (detection threshold) and an additional intensity rating. Test and retest reliability for the threshold and discrimination have been described (threshold 0.92, discrimination 0.96; Kruggel 1989). Except for the detection threshold task (sodium tetraborate), the substances were diluted with diethyl phthalate and presented in concentrations sufficiently above threshold to be easily detected by normosmics.

All odors were presented in 250 mL polyethylene squeeze bottles with a flip-up spout equipped with an exchangeable handmade Teflon nosepiece that fit snugly into the subject's nostril, allowing testing of each nostril separately (Eskenazi et al. 1986; Laska and Hudson 1991; Cain et al. 1992; Martinez et al. 1993; Laska and Teubner 1999; Mohr et al. 2001).

The detection threshold task (sensitivity) consisted of a geometric dilution set of phenyl ethanol (pleasant; 1 g/L) and dimethyl disulfide (unpleasant; 0.2 g/L), successively diluted by factor 5. Thresholds were measured using an ascending triple-forced choice procedure, starting with the lowest concentration (no. 1). With variations (two vs. three alternatives; ascending vs. descending procedures), this kind of method of limits is widely used to establish thresholds in basic research (e.g., Laska and Hudson 1991; Laska and Teubner 1999; Lehrner et al. 1999), clinical research (e.g., Eskenazi et al. 1983, 1986; Cain et al. 1988; Jones-Gotman and Zatorre 1988; Zatorre and Jones-Gotman 1991; Martinez et al.

1993; Lehrner et al. 1997; Mohr et al. 2001), and research in schizophrenia (e.g., Serby et al. 1990; Striebel et al. 1999; Purdon and Flor-Henry 2000). In brief, three bottles were presented in random order, two containing the pure diluent and the third the odor at a certain dilution. Threshold was defined as the weakest concentration of solution for which the subject was able to select the odor-containing bottle correctly on two consecutive trials. If a subject failed on step no.7, they got the triplet with the stock solution bottles (no. 8; 5 g/L).

In the quality discrimination task, eight triplets of bottles were presented in random order, with two containing the same odor and the third a different one (citronellyl¹ nitrile vs. methylpyrrolidine, phenyl ethanol vs. dimethyl disulfide, pyridine vs. butanol, t-butylcyclohexyl acetate vs. cyclopentadecanone, 2-methyl-4-phenyl-2-butanol vs. dihydrorose oxide, eugenol vs. anethole, octyl acetate vs. decyl acetate, allylcapronat vs. amypropionate). Subjects had to determine which of the three bottles smelled different (Eskenazi et al. 1983; Martinez et al. 1993; Hummel et al. 1997; Laska and Teubner 1999; Mohr et al. 2001).

For the ratings of familiarity, pleasantness, edibility, and intensity, subjects were successively presented with eight odors (methyl cinnamate, methylpyrrolidine, cyclopentadecanone, (-)-carvone, pyridine, 5 α -androst-16-en-3-one, isoamyl acetate, eugenol) and asked to rate them using linear rating scales from -5 (extremely negative) to 5 (extremely positive) (e.g., Ayabe-Kanamura et al. 1998; Distel et al. 1999; Herz et al. 1999).

To assess olfactory identification, we employed commonly known everyday odors—real-world items. The reasons for this are manifold. First, identification deficits are well documented in schizophrenia employing the UPSIT, which has no adequate German version; because some of the odors and descriptors used in the test are nearly unknown in our culture, the test cannot be used without adaptation. Second, everyday odors, possibly achieving maximum ecological validity, are widely used in both basic and clinical research of identification (e.g., Larsson and Bäckman 1997; Lehrner et al. 1997, 1999; Ayabe-Kanamura et al. 1998; Cain et al. 1998; Distel et al. 1999; Lehrner and Deecke 2000). Furthermore, the use of everyday odors enables assessment of categorical identification of real-world items (e.g., edibility judgments) (Larsson 1997; Ayabe-Kanamura et al. 1998; Distel et al. 1999; Olsson and Fridén 2001). Categorical identification does not necessarily require the knowledge of odor names or precise identification (Schab 1991; Larsson 1997; Olsson and Fridén 2001). Finally, assessing odor identification by using squeeze bottles allows the subject to smell and select the response (name) simultaneously.

Identification was assessed using a multiple-forced-choice task format. Selection of odors (and descriptors)

mainly derived from research by Lehrner et al. (1997, 1999, 2000). In brief, subjects were required to identify the odor from sets of four alternative descriptors: chocolate (garlic, gasoline, cleaner), mustard (fish, tomato, mayonnaise), pencil shavings (marzipan, salami, detergent), coffee (tea, hazelnut, potato chips), cigarette butt (rubber, cigar, tobacco pipe), cinnamon (melon, blueberry, vanilla), peppermint (liquorice, beer, tar), and peanut (rye bread, wine, lemon).

Judgments for familiarity and edibility of everyday odors were assessed prior to identification (yes/no/don't know).

Identification and judgments of everyday odors were scored as accurate = 1 and incorrect = 0 (including a "don't know" answer). To minimize visual, acoustic, or proprioceptive cues in these tasks, everyday odors were secured in disposable teapot filter bags, and these were suspended inside the bottles (Ayabe-Kanamura et al. 1998).

Procedure. At the beginning of each test session, subjects were allowed time to familiarize themselves with the bottles and with the sampling technique. Olfactory measurements were performed separately for the left and right nostrils. The testing sequence was randomized by a predetermined order related to day and time of testing (10 a.m., 1 p.m., and 4 p.m.) and counterbalanced between groups: half of each group started with the right nostril (R-L) and half of each group with the left nostril (L-R). Individual testing lasted 1½ to 2 hours, including a break of about 10 minutes after the completion of the first nostril testing. Subjects were not given feedback on their performance. All subjects were told not to use perfumes or perfumed cosmetics on the day of olfactory testing. They were also instructed to eat nothing, to drink only water, and to refrain from smoking at least ½ hour before commencement of testing. Testing took place in a quiet, odorless, and well-ventilated room. Using a semi-structured interview at the end of a test session (Krugger 1993), we interviewed subjects about olfactory experiences, hallucinations, and changes they had experienced, either before or since illness onset.

Statistical Analyses. Data were analyzed using SPSS (version 11.0.1). Group comparisons with respect to demographic and clinical characteristics were evaluated by *t* tests or Fisher's exact test. To test our hypotheses and to assess the main effects of group (schizophrenia vs. controls) and the statistical interaction between group and tested side (left vs. right) on olfactory measures, data were analyzed using multiple analysis of variance (MANOVA). To limit the number of dependent variables considered in a single MANOVA, the total set of ten olfactory measures was divided into two subsets: olfactory performance (detection threshold, discrimination, identification, and edibility and familiarity judgments of everyday odors) and olfactory ratings (MOT; familiarity, pleasantness, edibility, and intensity), each of which was

¹The second substance listed in each grouping is the "odd" stimulus.

analyzed in a separate MANOVA (within-subjects factors side and olfactory measure, between-subjects factor group). If the main effect of group or the group-by-side interaction was found to be statistically significant, subsequent univariate analyses (repeated-measures analyses of variance [ANOVAs] with side as the within-subjects factor and group as the between-subjects factor) were performed. To facilitate the comparison of group effects across the individual olfactory measures, effect sizes were calculated as the difference between the mean scores in the patient group and the control group divided by the standard deviation of the measure in the control group.

To test for possible effects of age and smoking, MANOVAs as above with the additional covariates age and smoking were carried out; subsequent univariate analyses were performed if at least one of the covariates or its interaction with group showed a significant effect in the MANOVA. To check for group differences in performance over test sessions (first vs. second test session), MANOVAs as above (within-subjects factors session and olfactory measure, between-subjects factor group) were performed. Finally, we studied whether deficits in secondary (higher order) main olfactory domains (e.g., identification, discrimination) are merely a consequence of primary (lower order) olfactory deficits (e.g., threshold) or whether these deficits exist independently. This was performed by repeated-measures analyses of covariance (ANCOVAs) using the higher order olfactory measure of interest as the dependent variable and including the score of the lower order measure as a covariate (within-subjects factor side, between-subjects factor group).

Within patients, separate MANOVAs (within-subjects factors side and olfactory measure) with psychopathology ratings (PANSS positive, negative, and total) as covariates were performed. To compare patients with and without olfactory hallucinations (or deviant olfactory experiences), separate MANOVAs with the same within-subjects factors as above and olfactory hallucinations (or deviant olfactory experiences) as the between-subjects factor were performed.

Results

Subject Characteristics. Table 1 presents the demographic and clinical characteristics of all subjects. Patients and controls did not differ in terms of age and smoking characteristics. Controls had significantly higher levels of education, but all subjects had completed at least 8 years of grade school. There was no significant difference between groups in handedness preference (EHI), and no differences were observed with regard to the ENT examination (chi-square test; Fisher's exact test for comparison of groups divided into with and without [1] a pathological finding [2–4]).

At the time of assessment, half of the patient group suffered from olfactory hallucinations ($n = 4$) or deviant ol-

factory experiences ($n = 11$). Only 2 patients reported them to be pleasant, with 11 patients reporting unpleasant experiences. The rest (50%) definitively denied having olfactory hallucinations or deviant olfactory experiences. In terms of olfactory perception history, 5 patients associated a self-reported enhanced olfactory perception with the beginning of their illness, and 4 described a reduction, which most associated with medication intake ($n = 3$).

Olfactory Performance. The MANOVAs showed a significant effect of group on olfactory performance (detection threshold: phenyl ethanol, dimethyl disulfide; discrimination, identification, and edibility and familiarity judgments of everyday odors) (table 2). Subsequent repeated-measures ANOVAs revealed a significant effect of group in all olfactory measures except the detection threshold with phenyl ethanol. Patients showed a significantly higher threshold (lower sensitivity) with dimethyl disulfide and significantly lower mean scores in discrimination, identification, and correct edibility and familiarity judgments of everyday odors. The effect sizes for the group differences in these measures were moderately high, ranging from 0.65 (identification) to 1.08 (discrimination). No significant main effect of side, or group-by-side interaction, was observed.

A significant effect of age on olfactory performance was observed in the MANOVA; subsequent repeated-measures ANOVAs revealed an effect of age on discrimination, indicating a decrease with increasing age (de Wijk and Cain 1994; Hummel et al. 1997). No significant effect on olfactory performance was observed for the covariate smoking or for its interaction with group. The same held true by controlling for effects of education. MANOVAs controlling for effects of session showed a significant effect of session on olfactory performance ($F = 6.799$, $df = 6, 53$, $p < 0.001$); subsequent repeated-measures ANOVAs revealed a significant effect of session on identification ($F = 8.006$, $df = 1, 58$, $p = 0.006$) and correct judgments of edibility ($F = 8.778$, $df = 1, 58$, $p = 0.004$) and familiarity ($F = 18.265$, $df = 1, 58$, $p < 0.001$) of everyday odors, indicating an improvement from the first to the second nostril testing. However, as there was no significant interaction between session and group, the significant effect of group on these measures was not affected by this finding.

Repeated-measures ANCOVAs adding the olfactory measure to control for as a covariate demonstrated that the differences in discrimination and identification between groups remained significant even after controlling for detection thresholds (discrimination with phenyl ethanol: $F = 13.650$, $df = 1, 57$, $p < 0.001$; with dimethyl disulfide: $F = 10.646$, $df = 1, 57$, $p = 0.002$; identification with phenyl ethanol: $F = 5.099$, $df = 1, 57$, $p = 0.028$; with dimethyl disulfide: $F = 7.301$, $df = 1, 57$, $p = 0.009$). However, the significant group difference in identification

Table II. Olfactory measures

Variable ¹	Patients				Controls				Analysis ²						
	Left		Right		Left		Right		Effect size ³	Group			Group x Side		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		F	df	p	F	df	p
Olfactory performance ⁴										3.819	6, 52	0.003	1,397	6, 53	ns
Detection thresholds (MOT) (1–8)															
Phenyl ethanol	3.6	2.1	3.3	1.7	3.1	1.5	3.2	1.6	–0.25	1.048	1, 57	ns			
Dimethyl disulfide	3.9	1.7	3.4	1.8	2.7	1.6	3.0	1.6	–0.68	6.040	1, 57	0.017			
Discrimination (MOT) (0–8) ⁵	5.4	1.4	5.2	1.3	6.3	1.6	6.6	1.0	–1.08	20.021	1, 57	<0.001			
Identification (everyday odors) (0–8)	6.9	1.0	7.0	1.2	7.5	1.0	7.5	0.8	–0.65	5.260	1, 57	0.026			
Familiarity (everyday odors) (0–8)	6.8	1.2	7.1	1.4	7.4	0.8	7.5	0.6	–0.77	4.649	1, 57	0.035			
Edibility (everyday odors) (0–8)	5.9	1.6	6.2	1.3	6.8	1.1	6.7	1.2	–0.66	4.682	1, 57	0.035			
Olfactory ratings ⁶ (MOT) (–5 to 5)										3.995	4, 55	0.006	1,204	4, 55	ns
Familiarity	1.2	2.5	1.5	2.2	1.7	1.5	1.6	1.8	–0.23	0.331	1, 58	ns			
Pleasantness	0.4	1.3	0.5	1.0	–0.4	1.0	–0.3	1.2	0.84	9.054	1, 58	0.004			
Edibility	–1.4	2.0	–0.9	1.9	–1.9	1.7	–1.7	1.7	0.30	1.885	1, 58	ns			
Intensity	2.2	1.4	2.6	1.0	2.9	1.0	2.8	1.2	–0.24	2.565	1, 58	ns			

Note.—ANOVA = analysis of variance; MANOVA = multiple analysis of variance; MOT = Munich Olfaction Test; ns = nonsignificant; SD = standard deviation.

¹Possible score ranges in parentheses.

²Results of MANOVA and subsequent ANOVAs; ns ($p > 0.05$).

³Difference of the means of the two groups, divided by the SD of the control group (r and l pooled). In the first block (olfactory performance), the minus sign means that patients showed the poorer performance. In the second block, the minus sign indicates lower mean ratings in the patient group compared with controls.

⁴MANOVA (detection thresholds: phenyl ethanol and dimethyl disulfide, discrimination, identification, and familiarity and edibility judgments); significant effect of the covariate age ($F = 2.849$, $df = 6, 52$, $p = 0.018$).

⁵Significant effect of the covariate age ($F = 11.916$, $df = 1, 57$, $p = 0.001$).

⁶MANOVA (ratings of familiarity, pleasantness, edibility, and intensity).

disappeared after controlling for differences in quality discrimination ($F = 1.718$, $df = 1, 57$, $p > 0.1$).

Olfactory Ratings (MOT). The separate MANOVAs with the olfactory ratings (MOT; familiarity, pleasantness, edibility, and intensity) also showed a significant effect of group (table 2). Subsequent repeated-measures ANOVAs

revealed a significant effect of group for only the pleasantness ratings. Patients showed significantly higher pleasantness ratings than controls. No significant main effect of side, or group-by-side interaction, was observed.

No significant effect was found for age or smoking as covariates or for their interaction with group. MANOVAs controlling for effects of session showed a trend to-

ward an effect of session on olfactory ratings ($F = 2.533$, $df = 4, 55$, $p = 0.050$); subsequent repeated-measures ANOVAs revealed a significant effect of session on familiarity ($F = 6.525$, $df = 1, 58$, $p = 0.013$) and edibility ratings ($F = 7.991$, $df = 1, 58$, $p = 0.006$), indicating an increase in these ratings from the first to the second nostril testing. However, again no significant session-by-group interaction was observed.

Relation to Psychiatric Symptoms. MANOVAs (olfactory performance, olfactory ratings) with PANSS scores (positive, negative, and total) as covariates revealed no significant effect. Additional MANOVAs (olfactory performance, olfactory ratings) comparing patients with ($n = 15$) and without ($n = 15$) olfactory hallucinations or deviant olfactory experiences revealed no significant main effect of group or group-by-side interaction.

Discussion

To our knowledge, this is the first study investigating various olfactory domains unilaterally within a sample of male schizophrenia patients and healthy controls. The main findings of this study are (1) male patients with schizophrenia showed impaired identification of everyday odors, (2) these everyday odors were less familiar to patients, and (3) they judged everyday odors less correctly concerning edibility; (4) furthermore, the same patients showed reduced sensitivity with dimethyl disulfide and (5) impaired quality discrimination; (6) olfactory ratings of pure chemicals revealed higher pleasantness ratings in patients compared with controls; moreover, (7) no abnormal laterality in olfactory measures was found in patients. All observed olfactory dysfunctions were present bilaterally.

Results indicate that observed olfactory dysfunctions cannot be explained by the influence of smoking, olfactory hallucinations, or test sessions. No association was found between olfactory performance and psychiatric symptoms. With regard to medication, although a potential contribution from long-term antipsychotic treatment cannot be excluded (Moberg et al. 1997b), previous research has failed to indicate medication effects (Kopala et al. 1992; Wu et al. 1993; Moberg et al. 1999; Brewer et al. 2001). In addition, a potential detrimental effect of medication on sensitivity (Sirota et al. 1999) would have most likely reduced sensitivity for both odors, dimethyl disulfide and phenyl ethanol. Purdon and Flor-Henry (2000) have observed that an asymmetrical left nostril impairment in detection thresholds in patients dissipated with medication treatment. Therefore, our findings in a medicated sample, which do not provide evidence for any asymmetrical olfactory deficit, have to be interpreted with this fact in mind. In any case, the fact that we observed olfactory dysfunctions across both nostrils suggests dysfunctional processing of olfac-

tory brain regions in both hemispheres, at least in medicated patients with schizophrenia.

Our study replicates previous findings of impaired identification in schizophrenia patients (Hurwitz et al. 1988; Serby et al. 1990; Kopala et al. 1992, 1994, 1995; Wu et al. 1993; Houlihan et al. 1994; Malaspina et al. 1994; Brewer et al. 1996, 2001; Seidman et al. 1997; Moberg et al. 1997a, 1997b, 1999) and extends them, in so far as our results indicate that patients have reduced ability to identify everyday odors. Furthermore, as odor identification has been viewed as a continuum of informational specificity, ranging from nonverbal feelings of familiarity to specific object names (Schab 1991; Larsson 1997), impaired familiarity and edibility judgments in our patients suggest impaired semantic knowledge of everyday odors. Aside from implications for subjects' real-life experiences, these findings demonstrate that schizophrenia patients show dysfunctions in olfactory processing that do not necessarily require the knowledge of odor names or precise identification.

The hypothesis of dysfunctions in early stages of olfactory processing in schizophrenia patients is further supported by our findings of reduced sensitivity (dimethyl disulfide) and quality discrimination, which are in keeping with Moberg et al.'s (1999) meta-analysis. For the first time, the present study demonstrates sensitivity, discrimination, and identification deficits within the same patient sample. Identification and discrimination impairments cannot be explained by reduced sensitivity. Our results indicate that deficits in (verbal) identification may reflect impaired (nonverbal) quality discrimination. Although not completely devoid of cognitive demands, odor discrimination has been proposed to be a useful measure of alterations in olfactory functioning, if cognitive limitations are an issue (de Wijk and Cain 1994). We submit that verbal or semantic factors, previously observed to influence even discrimination performance (Savic and Berglund 2000), cannot explain our finding of reduced discrimination in patients. A semantic influence in olfaction refers to a subject's general knowledge of an odor and is usually expressed by odor identification and familiarity ratings (Schab 1991; Schab and Cain 1991; Larsson 1997; Savic and Berglund 2000). Because our (nonverbal) discrimination task used pure chemicals, which in general were not very familiar to either group, and furthermore, because patients and controls did not differ in familiarity and edibility ratings of these odors, it seems unlikely that semantic or verbal factors played a major role for discrimination deficits. Moreover, the finding of comparable performance in the detection threshold task with phenyl ethanol, using the same task format, also argues against the fact that the observed discrimination deficits in patients were due to cognitive impairment related to task complexity. As we found no effect of test session in these tasks, attentional problems due to test duration are also an unlikely explanation of

our findings. Thus, we suggest that schizophrenia patients suffer from an impairment of odor quality discrimination that could be related to misperception. Errors in identification seem to arise from such discrimination deficits, recently also observed in young male patients with schizophrenia (Rupp *et al.* 2000).

Our results argue against a generalized olfactory impairment. Dysfunctions seem specific to different types of olfactory processing. With regard to odor ratings, which some have suggested represent steps in the odor name identification process (Royet *et al.* 1999, 2001), we and others (Hudry *et al.* 2002; Moberg *et al.* 2003) found no impairments in intensity ratings. Of interest, in contrast to the everyday odors, pure chemicals were not perceived differently by patients and controls with regard to familiarity and edibility ratings, and patients showed higher pleasantness ratings. A possible explanation may be related to the familiarity of the odors used. Recently, Hudry *et al.* (2002) found lower pleasantness and disturbed edibility ratings of odors that also showed lower familiarity in schizophrenia patients compared with healthy controls. The level of familiarity may be regarded as a continuum covering the subject's implicit level of odor knowledge, with a high familiarity rating presumably reflecting more specific knowledge about an odor (e.g., about edibility) (Larsson 1997). Thus, it can be assumed that group differences in odor familiarity ratings should also have their expression in ratings such as edibility, as we have found for everyday odors. Aside from odor properties, another interesting aspect of odor pleasantness derives from a recent observation by Crespo-Facorro *et al.* (2001), who suggested that there may be an association between psychotic symptoms and unpleasantness of an unpleasant odor. We could not replicate this association, but differences in symptomatology between our sample and that reported by Hudry *et al.* (2002) could explain the divergent findings. More similar to our findings, higher pleasantness ratings were found in a psychosis-prone sample with high scores in physical anhedonia (Becker *et al.* 1993). Moreover, and consistent with our findings of higher pleasantness ratings in patients, a recent study by Moberg *et al.* (2003) observed that male schizophrenia patients tended to rate only low odor concentrations as less pleasant, while higher odor concentrations also showed higher pleasantness ratings. All evidence taken together, olfactory hedonic valence in schizophrenia merits further studies in more homogeneous patient samples and with a careful selection of odors and odor properties such as familiarity and (stimulus) intensity.

With regard to detection thresholds, our controversial observation concerning sensitivity reflects the existing literature (Gross-Isseroff *et al.* 1987; Serby *et al.* 1990; Geddes *et al.* 1991; Kopala *et al.* 1992; Good *et al.* 1998; Sirota *et al.* 1999; Striebel *et al.* 1999; Kohler *et al.* 2001). Because we found intact and reduced sensi-

tivity within a sample, and over both sessions, a detrimental effect of medication (Sirota *et al.* 1999) or cognitive impairment associated with task complexity seems an unlikely explanation. The most salient difference between the odors used in our study is their hedonic valence. So far, all studies including pleasantness ratings have observed disturbances in the hedonic experience of odors in patients with schizophrenia (Crespo-Facorro *et al.* 2001; Hudry *et al.* 2002; Moberg *et al.* 2003). It can be hypothesized that our finding of reduced sensitivity for dimethyl disulfide (unpleasant) but not for phenyl ethanol (pleasant) is related to the odors' hedonic valence, namely, the unpleasantness of dimethyl disulfide. Research using imaging technologies (Becker *et al.* 1993; Crespo-Facorro *et al.* 2001) revealed dysfunctions particularly in the processing of unpleasant stimuli. Becker *et al.* (1993) hypothesized that their finding of smallest olfactory event-related potential amplitudes in a psychosis-prone subgroup after stimulation with the unpleasant odor can be explained as a higher threshold for the perception of unpleasant odors.

The current knowledge about human olfaction suggests that functional olfactory processing depends upon many factors, including olfactory functions (tasks) and odor properties (e.g., familiarity, pleasantness) (Savic *et al.* 1997; Zald and Pardo 1997, 2000; Savic and Berglund 2000; Brand *et al.* 2001; Savic 2002; Anderson *et al.* 2003). Different olfactory functions (tasks) and odors may be processed, and therefore impaired, differently. Prefrontal cortical areas and medial-temporal, subcortical connections are associated with the pathophysiology of schizophrenia (Christensen and Bilder 2000). The investigation of functions such as olfactory function, which are mediated by these neuronal pathways, are thought to provide some clues as to the nature of this heterogeneous disorder (Pantelis and Brewer 1995). The functional localization of odor identification is poorly understood. Only a few research groups have used functional neuroimaging techniques in olfaction in schizophrenia (Clark *et al.* 1991, 2001; Wu *et al.* 1993; Malaspina *et al.* 1998; Crespo-Facorro *et al.* 2001), mostly correlating psychometric olfactory measures (identification) with functional indices. Given that disruption anywhere along the olfactory pathways and other mediating cognitive processes may result in odor identification deficits, it is not surprising that patients with a wide variety of diseases show such impairments (see Martzke *et al.* 1997; Doty 2001). To date, the utility of odor identification performance as a marker for schizophrenia (and, *i.e.*, to identify distinct subgroups of the disorder) remains unclear (e.g., Serby *et al.* 1996; Kopala *et al.* 2001). In addition, Moberg *et al.* (1997a) have reported that elderly patients with schizophrenia and Alzheimer's disease could not be distinguished by odor identification performance.

Our results demonstrate that deficits in olfactory processing in schizophrenia patients clearly go beyond higher

order identification deficits. There was no generalized impairment in olfaction, but patients showed various dysfunctions specific to olfactory tasks and possibly also related to odor properties. We suggest that impaired quality discrimination ability in schizophrenia patients is of particular interest, as nonverbal odor discrimination, primarily assumed to have its neural correlate in the orbitofrontal cortex (Tanabe et al. 1975; Potter and Butters 1980; Eslinger et al. 1982; Zatorre and Jones-Gotman 1991; Savic et al. 1997), is necessary to succeed in an odor identification task. We believe that investigating different types of olfactory functions in patients with schizophrenia represents an intriguing avenue for further exploration. Together with neuroimaging techniques this may provide valuable diagnostic and theoretical information concerning this heterogeneous disorder.

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