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Olfactory Functioning in Schizophrenia: Relationship to Clinical, Neuropsychological, and Volumetric MRI Measures

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Deficits in odor identification and detection threshold sensitivity have been observed in schizophrenia but their relationship to clinical, cognitive, and biologic measures have not been clearly established. Our objectives were to examine the relationship between measures of odor identification and detection threshold sensitivity and clinical, neuropsychological, and anatomic brain measures. Twenty-one patients with schizophrenia and 20 healthy controls were administered psychophysical tests of odor identification and detection threshold sensitivity to phenyl ethyl alcohol. In addition, clinical symptom ratings, neuropsychological measures of frontal and temporal lobe function and whole brain MRIs were concurrently obtained. Patients exhibited significant deficits in odor identification but normal detection threshold sensitivity. Poorer odor identification scores were associated with longer duration of illness, increased negative and disorganized symptoms, and the deficit syndrome, as well as impairments in verbal and nonverbal memory. Better odor detection thresholds were specifically associated with first-rank or productive symptoms. Larger left temporal lobe volumes with MRI were associated with better odor identification in controls but not in patients. Given the relevance of the neural substrate, and the evidence of performance deficits, psychophysical probes of the integrity of the olfactory system hold special promise for illuminating aspects of the neurobiology underlying schizophrenia.

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Introduction

There is considerable evidence that schizophrenia is a neurodevelopmental disorder that primarily affects frontal, temporal, and limbic brain systems. Recent reviews and meta-analyses of neurocognition in schizophrenia have shown a wide range of deficits with some areas, primarily learning, memory, and attention being most impaired (Alman, Hijman, deHaan, & Kahn, 1999; Heinrichs, 2004; Heinrichs & Zakzanis, 1998). Correspondingly, neuroanatomic and physiologic imaging studies have also noted abnormalities in a number of brain regions, with functions mediated by the temporal and frontal lobe areas appearing to be most affected. Efforts to precisely characterize the nature of these deficits and their clinical correlates have employed a variety of methods and an array of neurobehavioral probes, including physiologic assessments of memory, executive function and vigilance (Gur & Pearlson, 1993). A potentially more direct probe of frontal and temporal limbic system function is olfaction. Olfactory processing is mediated by a set of limbic neuroanatomical structures that have been implicated in the pathophysiology of schizophrenia, both in terms of its anatomy, neurochemistry, and neurodevelopmental time course. The olfactory system is unique among the sensory modalities, in that it does not utilize the thalamus as a central relay station (Kratskin, 1995; Price, 1987). Primary olfactory neurons arising in the nasal epithelium project unmyelinated afferent fibers through the cribriform plate into the brain cavity, where they terminate on mitral and tufted cells whose dendrites are clustered in glomeruli in the ipsilateral olfactory bulb (OB). Axons from these second order OB neurons form the olfactory tracts, which project directly to the ipsilateral pyriform and entorhinal cortices, the ventral striatum and the ventromedial hypothalamus, with essentially no crossover to the contralateral hemisphere (Eslinger, Damasio, & Van Hoesen, 1982; Greer, 1991). Olfactory information passes, in turn, from these primary recipient zones to the amygdala, hippocampus, thalamus and orbitofrontal cortex (Potter & Nauta, 1979; Tanabe, Yarita, Iino, Ooshima, & Takagi, 1975). While these secondary projections remain predominantly ipsilateral, a small percentage of fibers cross over to the contralateral hemisphere via the anterior commissure. With only two synapses between olfactory receptors and secondary cortical and subcortical targets (Eslinger et al., 1982; Kratskin, 1995), the olfactory system provides the most direct environmental access to several structures that have been implicated in schizophrenia.

Deficits in olfactory function in schizophrenia have been well described, with impairments in odor identification, detection threshold sensitivity, discrimination and memory being reported (Martzke, Kopala, & Good, 1997; Moberg et al., 1999; Moberg &Turetsky, 2003). These deficits are seen early in the course of the disorder (Brewer et al., 2003; Kopala, Clark, & Hurwitz, 1992), but appear to be correlated with duration of illness (Hudry, Saoud, D'Amato, Dalery, & Royet, 2002; Moberg et al., 1997). These reports suggest that olfactory brain regions are affected by both pathological neurodegenerative and genetically-mediated neurodevelopmental processes. The majority of studies have indicated that neuroleptic use, smoking, cognitive deficits and illness severity are unrelated to the observed olfactory abnormalities (Martzke et al., 1997; Moberg et al., 1999; Moberg et al., 1997). Lastly, relationships have been reported between measures of odor identification and clinical ratings of negative symptoms (Brewer, Edwards, Anderson, Robinson, & Pantelis, 1996; Brewer et al., 2001; Malaspina & Coleman, 2003), depression (Stedman & Clair, 1998), social deficits and poor hygiene (Brewer et al., 1996), and the deficit syndrome (Goudsmit et al., 2004; Malaspina et al., 2002; Seckinger et al., 2004). Given the relevance of the neural substrate, and the evidence of performance deficits, psychophysical probes of the integrity of the olfactory system hold special promise for illuminating aspects of the neurobiology underlying schizophrenia.

Furthermore, the relationship between olfactory deficits and neuropsychological disturbances in patients with schizophrenia remains unclear. While some studies have reported relationships between tests of odor identification and neuropsychological measures of frontal (Brewer et al., 1996; Goudsmit et al., 2004; Purdon, 1998; Saoud, Hueber, Mandran, Dalery, & d'Amato, 1998; Stedman & Clair, 1998) and temporal (Good, Martzke, Milliken, Honer, & Kopala, 2002) lobe functions, other investigations have generally not supported a link between cognitive abilities and olfactory impairment in patients with schizophrenia (Kopala, Good, Martzke, & Hurwitz, 1995; Martzke et al., 1997; Moberg et al., 1999; Moberg et al., 1997; Seidman et al., 1997; Seidman et al., 1992). It should be noted, however, that neuropsychological tests generally are not "pure" measures of specific brain regions and are better at capturing integrated brain functions. As such, the relationship between these neuropsychological measures and olfactory indices might not be expected to be strong.

Recent data indicate structural volume decrements in the olfactory bulb in schizophrenia patients (Turetsky et al., 2000) and first-degree family members (Turetsky, Moberg, Arnold, Doty, & Gur, 2003). Additionally, volumetric deficits in patients with schizophrenia are observed in the anterior ventro-medial brain regions including the entorhinal and perirhinal cortices (Turetsky, Moberg, Roalf, Arnold, & Gur, 2003). More recently, Rupp and colleagues (Rupp et al., 2005) showed an association between unirhinal odor discrimination deficits in schizophrenia and morphological abnormalities in the temporal lobe. Despite these advances in our understanding of the nature of the olfactory deficit in schizophrenia, there has not yet been an examination of how birhinal olfactory psychophysical measures relate to whole brain and lobar structural MRI indices.

Despite considerable progress in our understanding of how olfactory measures relate to the phenomenology and neurobiology of schizophrenia, there has not been a study examining all of these factors in a unitary sample of patients and controls. The present study had three primary goals. First, we sought to probe the association between psychophysical olfactory measures and clinical symptomatology, including duration of illness, and negative and positive symptom clusters. Second, to explore whether olfactory test scores of schizophrenia patients or controls correlate with neuropsychological measures of frontal and temporal lobe function. Third, to investigate whether morphometric abnormalities in frontal and temporal lobe volumes are related with olfactory test measures in either patients or controls.

Methods

Participants

Twenty-one patients (13 men and 8 women) who met DSM-IV criteria for schizophrenia and 20 healthy controls (10 men and 10 women) were recruited from the Schizophrenia Research Center (SRC) at the University of Pennsylvania Medical Center, Philadelphia. All subjects were right-handed, as assessed by a structured lateral dominance questionnaire (Raczkowski, Kalat, & Nebes, 1974). Exclusion criteria included: (1) history of psychiatric disorder (other than schizophrenia for patients); (2) electroconvulsive therapy; (3) neurologic disorder (including tardive dyskinesia); (4) head trauma with loss of consciousness; (5) alcohol and other substance abuse (according to DSM-IV criteria; assessed by history from patient and family, review of records, and toxicology screening); (6) medical conditions that may alter cerebral functioning (assessed by examination and routine laboratory tests), including cardiac, endocrine, renal, and pulmonary disease, as well as

hypertension (blood pressure >140/90 mm Hg); (7) age less than 18 or greater than 45 years; (8) upper respiratory infection; or (9) other conditions known to affect olfactory functioning (e.g., common cold, blocked nasal passages). Subjects were not excluded based on smoking history. Healthy control subjects were recruited by newspaper advertisement and underwent medical, neurologic and psychiatric (SCID-NP) evaluation (Shtasel et al., 1991; Spitzer, Williams, & Gibbon, 1987). Controls were excluded for any history of Axis I psychiatric illness, Axis II diagnosis of schizotypal, schizoid or paranoid personality disorder, or any medical condition or occurrence, including substance abuse, that could compromise brain function. After description of the study, written informed consent was obtained for all subjects prior to participation.

Patients also underwent comprehensive medical, neurologic, and psychiatric examination by research psychiatrists from the SRC. This evaluation included a clinical examination and the Structured Clinical Interview for DSM-IV (Spitzer, Williams, & Gibbon, 1986). Four were evaluated as inpatients; 17 as outpatients. Other clinical characteristics of the patient group included age at onset (mean ± SD: 22.6 ± 7.3), duration of illness (5.9 ± 4.7 years), and number of previous hospitalizations (median, six). Eleven patients were neuroleptic-naive at the time of testing. The other 10 were on a regimen of neuroleptics. Of those patients on medication, the mean dose was 323.3 ± 213.6 mgs/day chlorpromazine equivalents (median dose = 250).

Patients and controls did not differ in age ($F[1,39] = 3.2$, $p = .08$), sex ($\chi^2 = .58$, df = 1, $p = .44$), or ethnic background ($\chi^2 = 2.11$, df = 1, $p = .14$). As expected, patients had lower educational attainment than controls ($F[1,39] = 6.6$, $p = .014$). Because schizophrenia adversely affects educational attainment, maternal and paternal education provides the most appropriate estimate of pre-illness educational expectation (Resnick, 1992). Mean parental (maternal and paternal) education did not differ between patients and controls ($F[1,39] = .18$, $p = .66$). Patients and controls did not differ with regard to smoking history ($\chi^2 = 1.10$, df = 2, $p = .57$). Demographic and clinical information for the study sample is presented in Table 1.

Materials

Psychophysical Olfactory Assessment

Odor identification. Odor identification performance was assessed using the University of Pennsylvania Smell Identification Test (UPSIT) (Doty, Frye, & Agrawal, 1989; Doty, Shaman, & Dann, 1984). The UPSIT is a standardized, four-alternative, forced-choice test of olfactory identification comprised of four booklets containing ten odorants apiece, one odorant per page. The stimuli are embedded in "scratch and sniff" microcapsules fixed and positioned on strips at the bottom of each page. A multiple-choice question with four response alternatives for each item is located above each odorant strip. The specific stimuli, basis for their selection, as well as the reliability and sensitivity of this test, have been described in detail elsewhere (Doty et al., 1989a; Doty et al., 1984b). The UPSIT was administered individually by a trained technician, who released the microencapsulated stimuli, placed them under each patient's nostrils, and recorded the answer following the patient's response.

Following administration of the UPSIT, subjects were given the Picture Identification Test (PIT) (Vollmecke & Doty, 1985). The PIT is identical to the UPSIT in item composition and response characteristics, except that line drawings instead of odors are presented. This test was designed to screen for individuals with cognitive deficits that may confound

Table 1
Sample characteristics for healthy comparison (HC), and patients with schizophrenia (SZ). Mean (±standard deviation)

Variable	HC (N = 20)	SZ (N = 21)
Age (years)	28.6 (8.3)	24.6 (5.4)
Sex (male/female)	10/10	13/8
Ethnic Group (Caucasian/African-American)	14/6	10/11
Smoking (never/previous/current)	17/1/2	15/2/4
Handedness (right/left/amb)	20/0/0	21/0/0
Education (years)	14.5 (1.9)	12.9 (2.0)**
Parental Education (years)	14.1 (3.0)	14.5 (2.6)
Duration of Illness (years)		5.9 (4.7)
SANS (total)		53.0 (21.0)
SAPS (total)		46.6 (26.0)
Olfactory measures		
UPSIT	37.5 (1.7)	34.7 (4.6)*
PEA (log vol/vol)	–5.1 (1.5)	–5.3 (1.5)

Note: Duration of illness = difference in years between date of diagnosis and psychophysical assessment; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; UPSIT = University of Pennsylvania Smell Identification Test; PEA = Phenyl Ethyl Alcohol Odor Detection Threshold Sensitivity Test.

*p = .026.

**p = .014.

the UPSIT score. The two groups did not differ significantly on this task (F[1,39] = .17, p = .68), and no patient or control score on the PIT fell below the cut-off of 38.

Odor detection threshold sensitivity. All subjects received a single staircase, forced-choice odor detection threshold test to estimate basal detection sensitivity to phenyl ethyl alcohol (PEA: Gold Label Grade; Aldrich Chemical Co., Milwaukee, WI), a compound with low trigeminal stimulation properties (Doty et al., 1978; Doty et al., 1984a). In this procedure, the staircase was begun at the −6.50 log concentration step of a half-log step (vol/vol) dilution series extending from −10.00 log concentration to −2.00 log concentration. Initially, presentations were moved upward in full-log steps until correct detection occurred on five sets of consecutive trials at a given concentration level. If during this initial phase, an incorrect response was given on any trial, the staircase was moved upward a full-log step. Once the criterion of five consecutive correct responses was made on five trials at a given concentration step, the staircase was reversed and subsequently moved up or down in half-log decrements, depending upon the subjects' performance on two pairs of trials (i.e., each pair consisting of a choice between diluent and odorant) at each concentration step. The geometric mean of the last four staircase reversal points of a total of seven served as the estimate of threshold sensitivity (Doty, Gregor, & Monroe, 1986).

Clinical Assessment Scales. Clinical rating scales were completed on entry to the SRC. In addition to the SCID, the following instruments were administered to characterize a patient's clinical status: Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1980); the Scales for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984a),

and Positive Symptoms (SAPS) (Andreasen, 1984b). A factor analytic approach, to derive the fewest separable symptom dimensions from these ratings (Gur et al., 1994), yielded four symptom scales: (1) Negative Symptoms, (2) Disorganization, (3) Schneiderian Delusions and Hallucinations and, (4) Suspicion-Hostility. These dimensions have been shown previously to have adequate reliabilities and are statistically independent of one another (intercorrelations ranging from −0.16 to 0.15, $p > .05$). Details of this procedure, item composition of the scales, and their item-scale correlations have been presented elsewhere (Gur et al., 1994). Patients were also subtyped into deficit and nondeficit categories following established criteria (Carpenter, Heinrichs, & Wagman, 1988). Eight patients were categorized as having the deficit syndrome, and 13 as having the nondeficit syndrome.

Neuropsychological Assessment. Patients and controls underwent a brief neuropsychological screening to further characterize their cognitive functions. Given our interest in frontal and temporal lobe function, a subset of tests was selected to examine the relationship between olfaction and performance on these measures. Putative tests of frontal lobe function included the Wisconsin Card Sorting Test (number of categories, perseverative errors, perseverative responses) (Heaton, 1981), and the Stroop Color-Word Test (word, color, color-word conditions) (Golden, 1978). Measures of temporal lobe function included Logical Memory and Visual Reproduction subtests from the Wechsler Memory Scale (immediate and delayed recall) (Wechsler, 1945), and the sum of trials 1–5 on the California Verbal Learning Test (CVLT) (Delis, Kramer, Kaplan, & Ober, 1987).

MRI Measurement. MRIs were acquired on a GE Signa 1.5 Tesla scanner (Milwaukee, WI). Transaxial images were obtained in planes parallel to the orbitomeatal line. Each slice was 5mm thick with no interslice gaps. A multiecho acquisition sequence was used, TR = 3000, TE = 30 and 80 msec. This protocol allowed measurement of the two independent properties of proton density and T2-weighted value. Prior to regional measurement, images were realigned in three dimensions and resliced into transaxial images parallel to the anterior commissure – posterior commissure axis, to standardize for differences in head tilt during image acquisition. The borders of the frontal and temporal lobes were then drawn on these resliced images, using operationally standardized boundary criteria (Cowell et al., 1994). A segmentation program with established reliability and validity (Kohn et al., 1991) was applied to each lobar region, to separate brain parenchyma from surrounding cerebrospinal fluid within the operator-defined region of interest. Volume calculation was performed for brain, ventricular (central), and sulcal (peripheral) CSF in milliliters (ml) for each hemisphere. Regional brain parenchymal and CSF volumes were then computed separately for temporal and frontal lobes in each hemisphere, by summing across slices. The resolution of these scans precluded a more detailed anatomic analysis of these images (e.g., orbitofrontal cortex, entorhinal regions, etc.). In addition, in order to maximize power, we examined only those brain regions thought to be intimately involved in olfactory processing.

Because age and gender have been shown to affect MRI indices (Cowell et al., 1994; Gur et al., 1991), and significant differences exist between patients and controls in total cranial volume (Gur et al., 1994), regional MRI indices were adjusted for age, gender, age by gender interaction, and total cranial volume using linear regression (Cowell et al., 1994). Thus, the corrected lobar volume measures submitted for these analyses were not influenced by effects of gender or differences in overall cranial volume.

Results

Odor Identification

Analysis of variance (ANOVA) with diagnosis and sex as grouping factors was used to examine differences in UPSIT scores. Overall, patients demonstrated a deficit in odor identification performance relative to controls (F[1,37] = 5.34, p = .026). No interaction between diagnosis and sex was observed (F[1,37] = 1.14, p = .29), nor was a main effect seen for sex (F[1,37] = .96, p = .33). In patients, duration of illness was significantly correlated with UPSIT performance (r = –.80, p < .001), with longer illness being associated with poorer odor identification abilities. A number of studies have reported a greater incidence of negative symptoms over the course of illness, perhaps confounding the duration of illness effect. Partial correlations between UPSIT scores and duration of illness, holding negative and positive symptoms constant, did not eliminate the observed relationship.

Within the schizophrenia group, no differences in UPSIT score were observed between medicated and unmedicated patients (F[1,19] = .15, p = .70) or between patients with or without smoking history (F[2,38] = .86, p = .42).

Odor Detection Threshold Sensitivity

Odor detection threshold sensitivity was not significantly different between patients and controls (F[1,37] = .08, p = .76), nor were there effects of sex (F[1,37] = .90, p = .34), or a diagnosis by sex interaction (F[1,37] = 1.44, p = .24). Unlike UPSIT performance, odor detection thresholds were not significantly related to duration of illness (r = .13, p = .56).

Similar to the findings for the UPSIT, within the schizophrenia group no differences in PEA threshold were observed between medicated and unmedicated patients (F[1,19] = 1.17, p = .29) or between patients with or without smoking history (F[2,38] = 1.33, p = .27).

Clinical Scales

The relationship between UPSIT performance and symptom factor scores is shown in the upper panel of Figure 1. UPSIT performance was inversely related to scores on both the Negative Symptom (r = –.60, p = .004) and Disorganization (r = –.57, p = .007) Factors; that is, low UPSIT scores were associated with higher severity ratings of negative symptomatology and thought disorder, respectively. Consistent with these findings, patients classified as having the deficit syndrome using Carpenter, et al.'s criteria had poorer UPSIT scores relative to non-deficit patients (F[1,19] = 6.9, p = .016). No significant correlations were observed between the UPSIT and scores on the Schneiderian Hallucinations and Delusions (r = –.27, p = .22) or Suspicion-Hostility (r = –.09, p = .66) Factors.

In contrast to the relationships seen on the UPSIT, PEA sensitivity was inversely related to scores on the Schneiderian Hallucinations and Delusions Factor (r = –.54, p = .01); that is, increased odor detection threshold sensitivity was associated with higher scores on hallucinatory and delusional phenomena (lower panel, Figure 1). No other significant correlations were seen between PEA scores and the other symptom factors (p's>.50). In contrast to the poorer scores on the UPSIT observed in the deficit subgroup, patients classified as having the deficit syndrome did not differ from non-deficit patients with regard to PEA thresholds (F[1,19] = .06, p = .81).

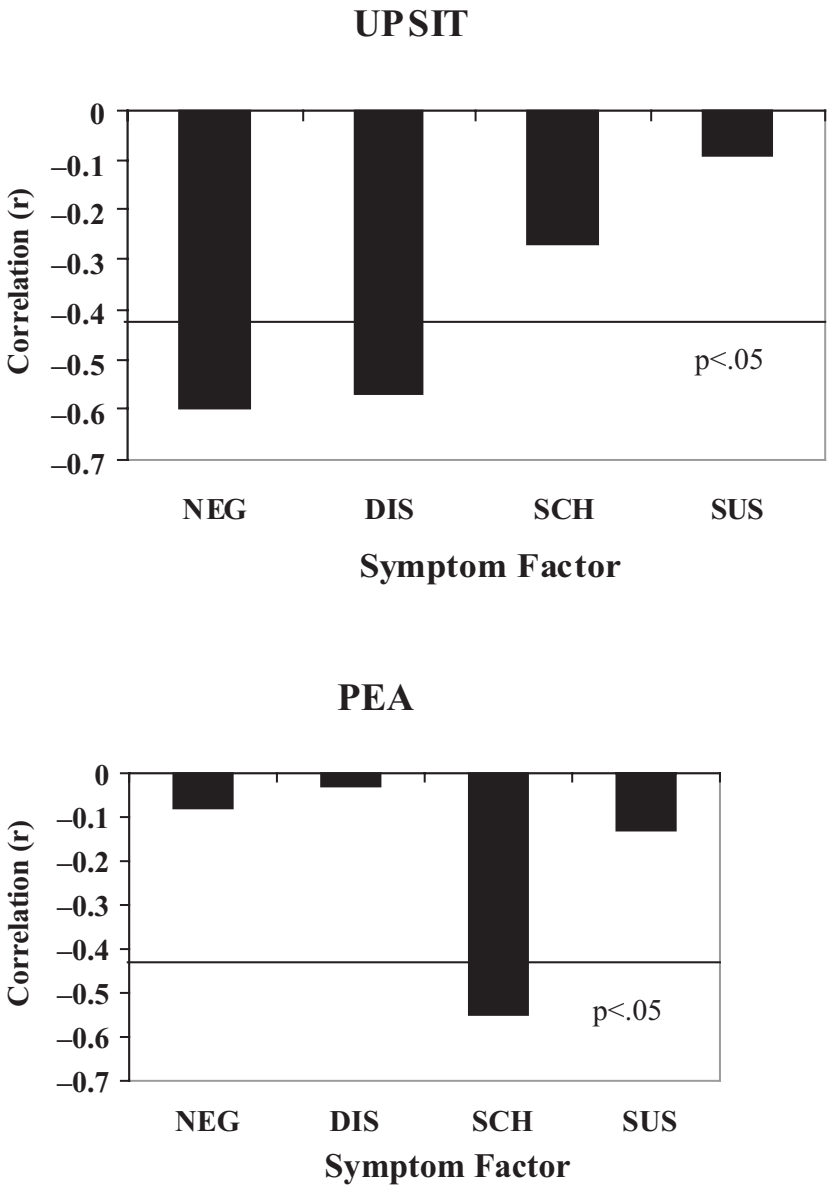

Figure 1. Relationship of odor identification (UPSIT: upper panel) and odor detection threshold sensitivity (PEA: lower panel) performance to symptom factor scores in patients with schizophrenia.

Note: NEG = Negative Symptom factor; DIS = Disorganization factor; SCH = Schneiderian Delusions and Hallucinations factor; SUS = Suspicion-Hostility factor.

Neuropsychological Measures

As can be seen in the upper and lower panels of Figure 2, no significant relationships were seen between measures of olfactory function and neuropsychological indices of frontal or temporal lobe abilities in the control group. In patients, however, significant relationships

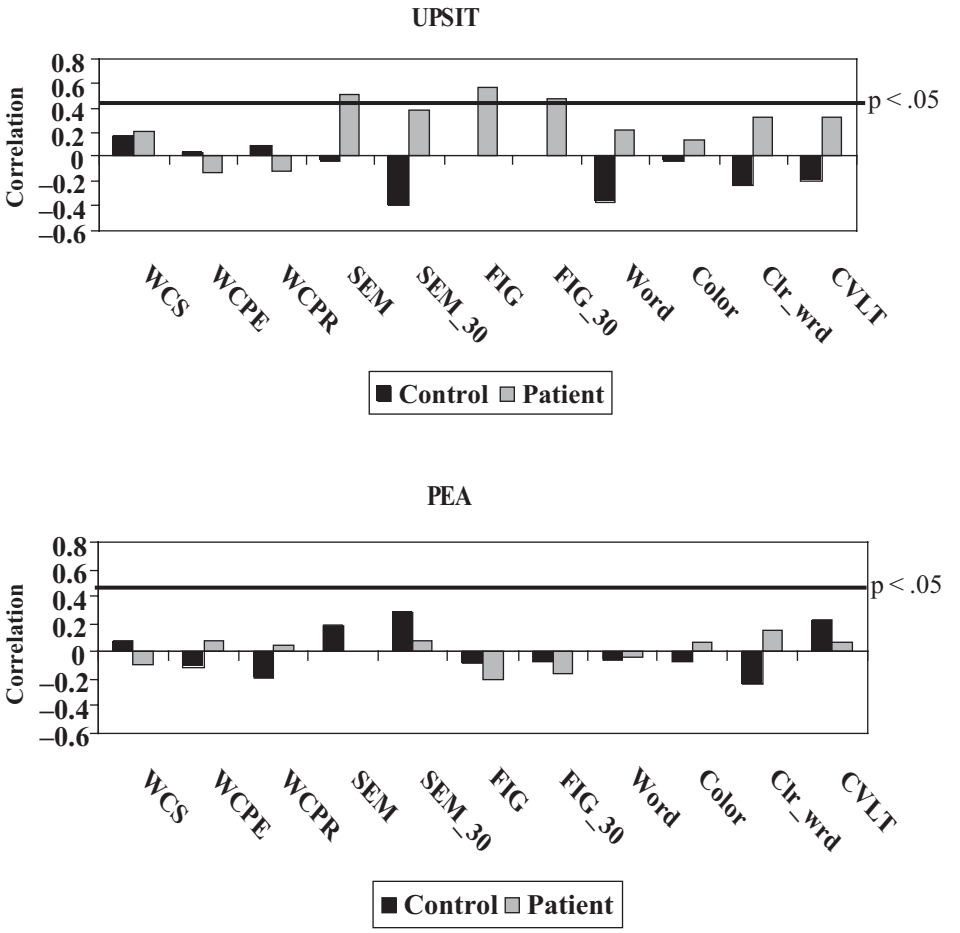

Figure 2. Relationship of odor identification (UPSIT: upper panel) and odor detection threshold sensitivity (PEA: lower panel) performance to tests of neuropsychological functioning.

Note: WCS = Categories attained, Wisconsin Card Sorting Test (WCST); WCPE = Perseverative errors, WCST; WCPR = Perseverative responses, WCST; SEM = Immediate recall, Logical Memory-Wechsler Memory Scale (WMS); SEM_30 = Delayed recall, Logical Memory-WMS; FIG = Immediate recall, Visual Reproduction-WMS; FIG_30 = Delayed recall, Visual Reproduction-WMS; Word = Word reading trial, Stroop Color-Word Test (Stroop); Color = Color reading trial, Stroop; Clr_wrd = Color-word reading trial, Stroop; CVLT = Total words recalled, trials 1–5, California Verbal Learning Test.

were observed between the UPSIT and immediate verbal and figural memory as well as delayed recall of figural information. In contrast, PEA scores were not significantly correlated with any measure of neuropsychological function in the patient group.

Volumetric MRI Measures

In healthy controls, UPSIT performance was significantly related to left temporal lobe volume ($r = .63$, $p = .004$), with larger volumes being associated with better odor identification performance. Despite a trend toward a relationship with frontal lobe volumes, no other significant correlations were observed in other whole/regional brain or CSF/sulcal

volumes. In contrast to controls, no significant correlations between UPSIT scores and whole/regional brain volumes or CSF were observed in patients.

To further examine the association between degree of brain asymmetry and olfactory identification, whole brain and regional asymmetry measures (left hemisphere minus right hemisphere ÷ left hemisphere plus right hemisphere) were computed for each subject from adjusted lobar volumes. Consistent with the previous finding, in controls, better UPSIT scores were associated with relative increases in left temporal lobe volume ($r = .67$, $p = .002$).

Surprisingly, PEA thresholds were related to both right- ($r = .64$, $p = .003$) and left- ($r = .52$, $p = .023$) frontal lobe volumes. This relationship suggests that greater frontal lobe volume is associated with increased odor detection thresholds (i.e., poorer sensitivity) in healthy controls, an association that seems somewhat counter-intuitive. Similar to observations in UPSIT performance, no significant correlations between PEA scores and whole/regional brain or CSF/sulcal volumes were observed in patients.

Discussion

To our knowledge, this study is the first to examine birhinal olfactory performance in relation to clinical, neuropsychological, and volumetric MRI measures in a single sample of schizophrenia patients and healthy controls. This investigation provides new and extended evidence that schizophrenia patients show odor identification deficits that are related to specific clinical, neurocognitive, and anatomic features of the disorder. The observed psychophysical impairments could not be explained by differences in smoking history, medication status, or cognitive abnormalities. Additionally, the use of an analog nonverbal identification test (i.e., PIT) in these subjects ensured that the deficit in UPSIT performance could not be explained by poorer cognitive skills or unfamiliarity with the test items. In contrast to expectations, odor detection threshold sensitivity to PEA did not differ between patients and controls. While some authors have argued for the presence of an "olfactory agnosia" based on similar findings (Kopala & Clark, 1990; Kopala et al., 1992), the establishment of a differential or selective deficit in olfactory abilities in patients with schizophrenia requires demonstration of a specific dysfunction against the expected background of more diffuse impairments in function (Chapman & Chapman, 1978, 2001). Based on these criteria, the observed differences between odor identification and detection threshold sensitivity in the current study may simply reflect differences between these measures in difficulty, variance, or reliability. Future studies using standardized residualized scores or titration of accuracy by manipulation of test conditions to match for task difficulty will be required to explore this speculation.

Consistent with prior findings by our group and others (Hudry et al., 2002; Moberg et al., 1997), a strong relationship between duration of illness and odor identification was observed, suggesting that the UPSIT may be a sensitive marker to possible slow neurodegenerative or other progressive changes in this disorder. This relationship remained even after accounting for sex and severity of negative- or positive-symptoms, indicating that the effect was not simply a worsening of general clinical status or increasing incidence of negative symptoms over the course of illness. No relationship was seen between duration of illness and odor detection threshold sensitivity, suggesting that this association is specific to odor identification abilities. The link between odor identification abilities and duration of illness is consistent with recent studies suggesting that the clinical course of schizophrenia is most consonant with a progressive developmental disorder (de Haan & Bakker, 2004). Indeed, a number of studies examining pupillary response (Granholm, Morris,

Asarnow, Chock, & Jeste, 2000), structural MRI indices (DeLisi, 1999; Lieberman et al., 2001; Molina et al., 2002), and neuropsychological function (Bilder, Lipschutz-Broch, Geisler, Mayerhoff, & Lieberman, 1992; Harvey, 2001) have reported that some decline does occur, at least in a subset of patients.

Clinical Scales

The relationship between UPSIT scores and severity of negative symptomatology is consonant with findings by Brewer and colleagues (Brewer et al., 1996), where poorer UPSIT performance was noted to be associated with higher levels of negative symptoms and poorer physical hygiene in a sample of men with schizophrenia. The relationship with the clinical symptoms that make up the disorganization factor (i.e., formal thought disorder, conceptual disorganization) has not been described previously, however, and when taken together with the finding of a relationship with negative symptoms, suggests that greater odor identification deficits would be expected in patients who have been classified as suffering from the deficit syndrome. Consistent with this hypothesis, patients classified as having a predominantly deficit syndrome were most impaired in odor identification abilities. Indeed, 50% of patients in the deficit subgroup exhibited clinically significant odor identification impairment as opposed to only 8% in the nondeficit subgroup ($\chi^2 = 4.88$, df = 1, $p = .027$). Carpenter and colleagues (Carpenter et al., 1988) have defined the deficit syndrome of schizophrenia as a theoretically homogenous subgroup of patients. This syndrome is characterized by poor premorbid adjustment, a deteriorating course of illness, severe negative symptoms, as well as prominent deficits in cognitive function and thought disorder (Buchanan, Kirkpatrick, Heinrichs, & Carpenter, 1990; Fenton & McGlashan, 1994; Kirkpatrick et al., 1996a; Kirkpatrick, Buchanan, Ross, & Carpenter, 2001; Kirkpatrick, Ram, & Bromet, 1996; Pogue-Geile & Harrow, 1985). The finding of a relationship between the UPSIT and this cluster of symptoms may point to an underlying anatomical substrate for impairment in odor identification skills and the deficit syndrome. It is notable that this relationship was unique to odor identification as PEA thresholds did not correlate with these symptoms nor differ between deficit and non-deficit patients. There are extensive interconnections of temporal lobe limbic and olfactory regions, which are thought to be crucial in the modulation of both affective and motor responses (Fuster, 1989). Because these areas act as modulators, dysfunction in the olfactory system may result in the emotional under-responsiveness seen in patients with the deficit syndrome.

The relationship between increased olfactory sensitivity and hallucinatory and delusional phenomena is also noteworthy. While the patients did not differ from controls with regard to odor detection threshold sensitivity, patients who evidenced more productive psychiatric symptomatology tended to show decreased (i.e., more sensitive) PEA detection thresholds. We hypothesize that the increased sensitivity may reflect increased vigilance to external and internal stimuli seen in patients with more predominant Schneiderian symptoms. Very few published studies have examined olfactory thresholds in patients with schizophrenia, and the results have been somewhat inconsistent with some studies reporting deficits in threshold and some not. Results of a recent meta-analysis by our group (Moberg et al., 1999) revealed that the effect sizes for deficits in odor detection threshold sensitivity were quite large, mirroring those seen on tests of odor identification, memory and discrimination. While olfactory threshold tests have relatively lower reliabilities than the UPSIT and might account for some of the variability in findings (Doty, McKeown, Lee, & Shaman, 1995), some of the inconsistency seen in the literature conceivably reflects differences in the degree of positive symptomatology in different patient

samples. Further examination of clinical status, severity, and type of symptoms warrants greater attention in the study of odor detection threshold sensitivity skills in these patients.

Neuropsychological Indices

In general, tests of odor identification and detection threshold sensitivity were not related to neuropsychological function in healthy controls. These findings are consistent with results of a principal components analysis in healthy controls and Parkinson's disease patients (Doty, Riklan, Deems, Reynolds, & Stellar, 1989), where olfactory tasks were observed to load on a single "olfactory factor" separate from other measures of neurocognitive function. The current data, however, indicated a significant relationship in patients between UPSIT performance and tasks thought to tap temporal lobe verbal and nonverbal memory functions. Olfactory deficits have been observed in epilepsy patients who have undergone temporal lobectomy and relationships between memory and olfactory measures have been described in this population (Carroll, Richardson, & Thompson, 1993; Eskenazi, Cain, Novelly, & Mattson, 1986). There are substantial reasons to believe that important olfactory information processing takes place in areas within the inferior frontal and temporal lobes bilaterally. It is important to note, however, that despite this correlation the impairments in memory did not obscure the significant olfactory deficit seen in patients on the UPSIT. The extant literature has generally supported the relative independence of odor identification deficits and cognitive dysfunction in these patients, though significant relationships between the UPSIT with neuropsychological measures have been reported (Brewer et al., 1996; Good et al., 2002; Goudsmit et al., 2004; Purdon, 1998; Saoud et al., 1998; Stedman & Clair, 1998). The current data highlight the importance of continuing to explore the relationship between neuropsychological functions and olfactory disturbances. For example, in animals and humans, failures on Go-NoGo tasks have been strongly related to orbitomedial frontal lobe dysfunction and have also been linked to olfactory system impairment (Malloy Bihrle, Duffy & Cimino, 1993; Malloy, Webster & Russell, 1985; Rosenkilde, 1979). Tasks that more specifically target brain regions important in olfactory processing may help identify other neuropsychological processes that may modulate or influence this chemosensory impairment.

MRI Indices

The relationship between left temporal lobe volume and UPSIT performance in controls suggests a left temporal lobe substrate for odor identification in healthy men and women. Some early studies have suggested a left nostril (and thus conceivably largely left hemisphere) advantage in identifying odors following callosotomy (Eskenazi, Cain, Lipsitt, & Novelly, 1988; Gazzaniga, Risse, Springer, Clark, & Wilson, 1975; Risse, LeDoux, Springer, Wilson, & Gazzaniga, 1978); however, more recent investigations with patients who have undergone temporal lobe excision have highlighted the importance of both temporal lobes in olfactory processing (Carroll et al., 1993; West & Doty, 1995). It is likely that the act of identifying an odor draws on functions of both temporal lobe regions, but a greater emphasis on label retrieval and the search of semantic stores reflects the stronger relationship with left-sided temporal volumes. In the present study, the lack of a parallel correlation in the patient group suggests that olfactory processing normally occurring in left temporal regions may be disrupted in schizophrenia. Physiologic (Gur et al., 1994; McCarley, Faux, Shenton, Nestor, & Adams, 1991; Stevens, 1988) and structural abnormalities in temporal lobe limbic sites (Bogerts, Meertz, & Schonfeldt-Bausch, 1985;

Stevens, 1982) have been previously described in schizophrenia, and this finding lends further support to the hypothesis of greater left temporal lobe dysfunction in this disease. Consistent with this hypothesis, a recent study examining unirhinal UPSIT performance in a sample of male schizophrenia patients reported a greater tendency toward poorer left nostril dysfunction relative to right nostril scores which was felt to reflect greater left hemisphere dysfunction in these subjects (Good, Martzke, Honer, & Kopala, 1998).

A more recent study of unirhinal olfactory function and MRI indices, however, did not observe any relationship between odor identification skills and hippocampus–amygdala complex volumes in either schizophrenia patients or healthy controls (Rupp et al., 2005). Potential reasons for this discrepancy in findings likely lie in the fact that olfactory functions in the Rupp et al., study were assessed unirhinally, relatively isolating the contribution of each hemisphere. In addition, an alternate odor identification test (Hummel, Sekinger, Wolf, Pauli, & Kobal, 1997) that consisted of a smaller number of odors than the UPSIT was used, perhaps restricting variability in the subject groups. Further studies of possible differences between unirhinal and birhinal presentation of olfactory stimuli are clearly needed.

What is clear from the findings of the current study is that clinically significant olfactory dysfunction is not seen in every patient with schizophrenia, with approximately 24% of the patient sample being classified as microsmic as defined by normative age and gender cutoffs on the UPSIT (i.e., <34 for men or <35 for women). As such, the presence of olfactory deficits may reflect subtype differences in the basic underlying anatomical and physiological substrate. The differential relationships in olfactory test scores seen in the symptom clusters and in deficit/nondeficit patients indicate that patients who suffer from chemosensory deficits may differ from those patients with normal olfactory abilities in fundamental ways.

A number of caveats must be added to the current findings. First, olfactory performance was tested birhinally, that is, via both nostrils. Several authors have argued that a "summation effect" occurs when presenting olfactory stimuli birhinally (Bromley & Doty, 1995; Cain, 1977), indicating that presentation unirhinally (each nostril tested separately) may be a better method to examine laterality. The primary olfactory projections course mainly ipsilaterally, providing a unique opportunity to isolate, to a large degree, olfactory performance to each hemisphere. Second, given the relatively small sample size due to our intent to probe olfactory, clinical, neuropsychological, and structural MRI indices in a single group of patients and controls, we did not correct for multiple comparisons in the correlational analyses. As such, replication of these findings will be important to validate the reported relationships. Third, the MRI measures obtained in the current study were based on whole brain volumes. Future studies utilizing more refined segmentation algorithms to permit discrimination of grey from white matter, and high resolution MRI scans to permit unambiguous quantitation of focal cortical and subcortical regions of interest, will be important in further elucidating the relationships of MRI indices with olfaction.

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