Article

Stability of Olfactory Identification Deficits in Neuroleptic-Naive Patients With First-Episode Psychosis

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Objective: Olfactory identification deficits and their relationship to negative symptoms in patients with schizophrenia were examined in patients with recent-onset psychosis, the majority of whom were neuroleptic naive.

Method: Seventy-four inpatients with a first episode of psychosis (27 with schizophrenia or schizophreniform disorder, nine with schizoaffective disorder, 17 with affective psychoses, and 21 with other psychoses), 49 of whom had not received antipsychotic medication, were compared to 38 age- and gender-matched normal subjects. Olfactory identification ability was assessed with the University of Pennsylvania Smell Identification Test. Forty patients and 13 comparison subjects were reassessed at 6 months to examine whether olfactory deficits were specific to schizophrenia or schizophreniform disorder and were stable over time.

Results: At baseline, the patients had significant impairment in olfactory identification ability compared to the normal subjects. This difference persisted after controlling for gender, premorbid or current IQ, smoking history, cannabis use, or the effects of medication. Diagnostic subgroups did not differ in olfactory identification ability. The deficits remained stable at 6-month follow-up and were associated with negative symptoms at both time points. No relationship was found between olfactory identification ability and length of either untreated psychosis or illness prodrome.

Conclusions: Impairment in olfactory identification ability was apparent from the outset of psychotic illness and was not specific to schizophrenia or schizophreniform disorder. No change in the degree of this deficit was found after patients were stabilized and had responded to medication. The deficit could not be explained by peripheral factors that might contribute to olfactory identification ability, suggesting that it reflects central mechanisms.

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Studies in schizophrenia have consistently found deficits in the identification of various smells, usually among male rather than female patients (1–18), and in the presence of intact ability to detect odor (2, 6, 15, 19). The majority of these studies have examined patients with chronic illness who were taking neuroleptic medication, although the available evidence suggests that these deficits are not explained by medication (6–8, 13) or other confounds such as smoking (1, 3, 5, 9, 12). To our knowledge, no follow-up studies have been reported.

Reports on odor identification ability in affective disorders are contradictory and may reflect differences in treatment status of subjects, use of nonstandard odorants, or use of irritating odors, which trigger trigeminal nerve activation. Some studies have reported no differences in identification ability between comparison subjects and patients with depression (3, 8, 20), although Serby et al. (19) found poorer performance in a small group of nine patients with major depression than in a group of age-matched comparison subjects. Further, Solomon et al. (21) found decreased odor identification ability in elderly depressed patients. Thus, the limited evidence does not strongly support the presence of olfactory deficits in patients with depression. To our knowledge, no study has examined olfactory function in schizoaffective disorder, and only one study has reported on olfactory function in first-episode patients with schizophrenia or schizophreniform disorder (6). This study included some patients who had never taken neuroleptic medication, and the results suggested that smell identification deficits were apparent from the outset of the illness and perhaps reflected a trait marker. In a cross-sectional design assessing both younger and older patients with schizophrenia, Moberg et al. (13) found an association between olfactory identification deficits and illness duration and suggested that olfactory ability further deteriorated over time. However, to adequately assess the stability of olfactory deficits, prospective longitudinal studies from onset of the illness are required. Further, although high levels of cannabis use in young psychotic patients have been reported (22–24, unpublished 1999 study of Duke et al.), we are not aware of any studies that assessed the effect of cannabis on olfactory identification, despite the substance's reported neurotoxic effects on limbic structures (24).

The ability to identify odors has been attributed to prefrontal regions, particularly orbitofrontal cortex (5, 12,

14), and acuity has been linked to medial-temporal lobe structures (25–27). In our previous study of patients with chronic schizophrenia (12), measures of olfactory identification ability were used as a probe of orbitofrontal cortex function, while memory measures were used to assess medial temporal lobe function. Olfactory identification ability was impaired in the patients with schizophrenia and was associated with other executive function deficits, although no association was found with memory measures. There was also a relationship between negative symptoms and smell identification ability in these patients. Previous studies have found an association between negative symptoms and deficits of executive function in chronic schizophrenia (28–30), and one other recent study described an association between negative symptoms and olfactory identification (17). To our knowledge, no studies have examined the relationship of smell identification ability and negative symptoms in first-episode patients, and no studies have examined these relationships longitudinally.

In this longitudinal study, we examined the presence, severity, and specificity of olfactory identification deficits in a group of predominantly neuroleptic-naive patients with recent-onset psychosis. Consistent with the neurodevelopmental hypothesis of schizophrenia (31–33), which proposes that structural brain changes in early life predispose an individual to the development of schizophrenia, it was predicted that olfactory deficits would be apparent from the outset of illness, would be specific to patients with schizophrenia or schizophreniform disorder, and would remain stable over time. We also predicted that a relationship with negative symptoms would be apparent at both baseline and follow-up. Further, the effects of cannabis on olfactory identification were examined.

Method

Subjects

Baseline. The 112 study subjects included 74 first-episode psychosis patients and 38 age- and gender-matched comparison subjects. Table 1 shows the demographic and clinical characteristics of the two groups.

The 74 first-episode psychosis patients were consecutive admissions to the inpatient unit of the Early Psychosis Prevention and Intervention Program (Melbourne). Program admission criteria, described by McGorry et al. (34), were age at onset between 16 and 30 years and active psychosis, as reflected by the presence of at least one of the following: 1) delusions; 2) hallucinations; 3) disorder of thinking/speech, other than simple acceleration or retardation; and 4) disorganized, bizarre, or markedly inappropriate behavior. The 38 comparison subjects were recruited from a local technological college, by advertising in local bulletins, or from ancillary staff and their families.

All subjects were required to have English as their first language. Information about patients' recent medical conditions was available from the treating team on the ward. Any subject was excluded from the study if there was evidence of 1) significant neurological or medical history, including epilepsy, thyroid disease, or head injury with loss of consciousness; 2) past nasal trauma; 3) poor eyesight or hearing; 4) IQ of less than 70, estimated with the National Adult Reading Test, or 5) current viral illness, nasal congestion, or use of nasal spray medication. Comparison subjects were excluded if they had a personal or family history of psychiatric illness.

After a complete description of the study to subjects who met the inclusion criteria, written informed consent was obtained. The informed consent document included a clause with which participants could agree to being contacted for follow-up. The Behavioral Research and Ethics Committees for the North Western Health Care Network approved the study.

Follow-up. Forty patients and 13 comparison subjects consented to reassessment at 6–8 months. Follow-up patient and comparison groups did not differ in age and IQ estimated with the National Adult Reading Test (Table 2). Comparison subjects received $25 (Australian) to cover expenses during their participation in the follow-up neuropsychological assessment.

Measures

Demographic data and cannabis use. Clinical information, including age, age at onset of illness, period of untreated psychosis, years of education, history of smoking, history of illicit substance abuse, handedness (36), and medication dose (antipsychotics expressed in chlorpromazine equivalents) (37), was obtained from patient interview and chart review.

Full history of past and current cigarette and illicit substance use was assessed with an interview-style questionnaire. After questioning 15 regular users of cannabis, we developed a system for measuring the plant material containing tetrahydrocannabinol (THC) in which a unit was equivalent to one standard "joint" similar in size to a cigarette and consisting of a 50%–50% mix of cannabis leaf and/or stem and tobacco. If the subject used the more potent bud of the plant, this unit amount was increased by a factor of 5. This rate of increase was based on the opinions of the 15 regular users, who estimated the THC content to be 2%–4% in currently available leaf or stem and to be 15%–20% in currently available bud. If subjects reported using a water pipe or "bong" to smoke cannabis, we estimated that 13 uses of a bong represented use of an average equivalent of 1 g of cannabis or six standard joints.

Psychopathology ratings. DSM-III-R diagnoses were based on chart review and interview with the Royal Park Multidiagnostic Instrument for Psychosis (38) within 2 weeks of admission. The Royal Park Multidiagnostic Instrument for Psychosis is a comprehensive assessment procedure that uses serial interviews and multiple information sources to construct a psychopathological database for the patient's first psychotic episode. The assessment procedure uses 14 different systems of operational diagnosis, including DSM-III-R. This instrument has been described elsewhere (39), and its reliability and validity have been reported (40). The Manchester Scale (41), a 5-point scale, was used to assess symptoms of depression, anxiety, coherently expressed delusions, hallucinations, incoherence and irrelevance of speech, poverty of speech or mutism, flattened or incongruous affect, and psychomotor retardation. Patients' symptoms were assessed blind to the other assessments by a psychiatrist (D.V.) and/or a research assistant experienced in psychopathological assessment.

Intellectual functioning. Patients' estimated premorbid IQ was assessed with the National Adult Reading Test (35), adjusted for Australian normative data (42). Results of the National Adult Reading Test have been shown to be stable over time in patients with schizophrenia (43). The instrument provides a better estimate of the highest premorbid level of functioning than the Wechsler Adult Intelligence Scale—Revised (WAIS-R) (44), on which scores may decrease after the onset of illness in patients with schizophrenia (45). Current IQ was assessed by using a short form of the WAIS-R (46). The National Adult Reading Test and the

TABLE 1. Demographic and Clinical Characteristics of Patients With First-Episode Psychosis and Matched Normal Comparison Subjects at Baseline in a Study of Olfactory Identification Ability

	Patients (N=74)					Comparison Subjects (N=38)					Analysis		
Variable	Mean	SD	Range	N	%	Mean	SD	Range	N	%	Value	df	p
Age (years)	22.28	3.67	16–30			20.97	4.18	16–33			F=2.92	1, 110	n.s.
Gender											χ^2=0.14	1	n.s.
Male				55	74.3				27	71.1			
Female				19	25.7				11	28.9			
Handedness											χ^2=1.77	1	n.s.
Right handed				67	90.5				37	97.4			
Left handed				7	9.5				1	2.6			
Highest education level (years)	11.15	1.14	9–13			12.66	1.15	11–16			F=43.71	1, 110	<0.001
IQ estimated with the National Adult Reading Test[a]	98.84	10.93	78–125			109.22	9.38	88–126			F=23.43	1, 110	<0.001
Current WAIS-R full-scale IQ, (short form)[b]	89.39	11.83	70–123			114.41	9.64	81–131			F=32.60	1, 110	<0.001
Smoking and cannabis use history													
Current smoking				60	81.1				10	26.3	χ^2=30.19	1	<0.001
Duration of smoking (years)	6.10	5.34	0–19			1.79	3.09	0–13			F=20.50	1, 110	<0.001
Cigarettes smoked per day	17.53	14.58	0–75			9.83	6.91	1–20			F=4.83	1, 110	<0.05
Current cannabis use				60	81.1				20	52.6	χ^2=10.64	1	0.001
Duration of cannabis use (years)	3.90	3.65	0–14			2.74	1.58	0.5–7			F=0.08	1, 110	n.s.
Units of cannabis used per week[c]	9.51	16.90	0–100			3.34	6.73	0–30			F=0.40	1, 110	n.s.
University of Pennsylvania Smell Identification Test performance													
Total score[b]	28.45	5.23	13–27			33.56	3.00	29–39			F=11.68	1, 110	0.001
Normosmic				13	17.6				23	60.5	χ^2=17.87	1	<0.001
Medication													
No use of antipsychotic medication				49	66.2								
Dose of antipsychotic medication (mg/day chlorpromazine equivalents)	71.28	136.97	0–650										
Duration of current antipsychotic treatment (days)	1.30	2.60	1–10										
Psychopathology													
Diagnosis[d]													
Schizophrenia or schizophreniform disorder				27	36.5								
Affective psychosis				17	23.0								
Schizoaffective disorder				9	12.2								
Other[e]				21	28.4								
Length of prodrome (days)	532.83	537.79	31–1979										
Duration of untreated psychosis (days)	150.27	282.33	3–1461										

[a] Mean reported for patients represents estimated premorbid IQ.
[b] Covaried for IQ estimated with National Adult Reading Test (35).
[c] A unit is equivalent to the amount of cannabis in one standard cigarette-size "joint" consisting of a 50%–50% mix of cannabis and tobacco.
[d] Confirmed at 6-month follow-up by means of subject interviews with the Royal Park Multidiagnostic Instrument for Psychosis.
[e] Includes delusional disorder, brief reactive psychosis, substance-induced psychosis, and psychosis not otherwise specified.

WAIS-R were also used to determine estimated and current full-scale IQ for the comparison subjects.

Olfactory identification. The University of Pennsylvania Smell Identification Test (47) was administered by a single investigator (W.J.B.). The instrument is a standardized, multiple-choice test consisting of four booklets each containing 10 scratch-and-sniff items. The test typically takes 10–15 minutes to administer. The "suprathreshold" fragrances are micro-encapsulated and are embedded in plastic capsules coated onto labels. For each odorant, the subject was required to select the correct odor name from four possible choices, only one of which matched the odor. Ratio-level scores were graded for a range of correct responses between zero and 40, with standardized cutoff scores indicating abnormal responses. It should be noted that the standardized normative data for Australian samples differ by about 2 points less from those for North American samples (A. Mackay-Sim and R. Doty, personal communication, 1994).

Procedure

Baseline. Assessments were undertaken in the first week after admission. The patients were initially approached within the first 3 days of admission while they were neuroleptic free. Forty-nine patients (66.2%) were assessed during this neuroleptic-naive window, five (6.8%) were admitted to the program while taking medication commenced elsewhere, and 20 (27.0%) were assessed during the week after their admission, by which time they had begun taking medication (Table 1). Medications taken by patients at the time of the assessment included benzodiazepines. Small numbers of patients received anticholinergics (N=8), anxiolytics (N=9), lithium (N=6), anticonvulsants (N=1), or antidepressants (N=3).

Follow-up. Attempts were made to follow up all patients assessed at baseline either by keeping records of the last known address and phone number when the patient was first seen, by maintaining contact through related research projects, or by contacting those who remained engaged in treatment as outpatients in the Early Psychosis Prevention and Intervention Pro-

TABLE 2. Characteristics of Patients With First-Episode Psychosis and Matched Normal Comparison Subjects Followed Up 6 Months after Baseline Assessment in a Study of Olfactory Identification Ability

Variable	Patients (N=40)				Comparison Subjects (N=13)				Comparisons of Groups at Follow-Up		
	Baseline		Follow-Up		Baseline		Follow-Up				
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	χ^{2a}	*df*	*p*
Smoking and cannabis use history											
Current smoking	31	77.5	29	72.5	6	46.2	4	30.8	12.74	2	0.002
Current cannabis use	33	82.5	37	92.5	7	53.8	5	38.5	16.00	2	<0.001
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*F*	*df*	*p*
Duration of smoking (years)	8.77	4.79	8.30	4.72	3.00	1.83	3.13	1.65	4.20	1, 51	0.05
Cigarettes smoked per day	19.29	12.54	15.13	9.16	8.00	8.08	8.00	8.08	1.06	1, 51	n.s.
Duration of cannabis use (years)[b]	4.83	2.82	5.75	3.03	2.20	1.89	2.80	1.96	3.79	1, 51	n.s.
Units of cannabis used per week[c]	14.60	22.93	5.90	14.49	3.14	2.83	3.24	3.06	0.30	1, 51	n.s.
University of Pennsylvania Smell Identification Test total score	29.50	4.33	30.54	4.72	33.23	3.30	34.27	2.69	6.22	1, 51	0.02
IQ estimated with the National Adult Reading Test[d]	99.91	11.80	102.05	12.63	108.82	9.65	110.05	8.01	4.56	1, 51	0.04
Current WAIS-R full-scale IQ (short form)	92.00	13.29	94.16	13.83	107.77	7.55	110.16	7.69	15.56	1, 51	<0.001

[a] McNemar's nonparametric test for two related samples.
[b] Significant effect of time for comparison subjects (repeated measures ANOVA, F=36.00, df=1, 11, p=0.004).
[c] A unit is equivalent to the amount of cannabis in one standard cigarette-size "joint" consisting of a 50%–50% mix of cannabis and tobacco.
[d] Significant effect of time for patients (repeated measures ANOVA, F=–2.32, df=1, 38, p=0.05).

gram. Forty patients were successfully located and reassessed at their place of residence in the community at 6–8 months after their initial assessment. Of the remaining 34 patients, 15 (44.1%) could not be traced because they had no fixed address or had moved and no follow-up contact details were available, seven (20.6%) had left the state or the country, three (8.8%) had died or were seriously injured as a result of a suicide attempt, four (11.8%) had been readmitted as acute inpatients and were too unwell to provide consent or to be assessed, one (2.9%) had developed a nonpsychotic severe medical condition, and four (11.8%) either refused or, having consented, avoided follow-up assessment (up to five attempts at follow-up). Thirteen comparison subjects were followed up after a similar period. Reasons for the low follow-up rate for comparison subjects were economic (study cost restrictions).

Data Analysis

The Statistical Package for the Social Sciences (SPSS), version 8.0 (SPSS Inc., Cary, N.C.) was used for data analysis. Between-group comparisons of olfactory and cognitive ability at baseline were conducted by using one-way analysis of variance (ANOVA). Because IQ estimated with the National Adult Reading Test was not equivalent between these groups, this IQ score was included as a covariate in comparisons of olfactory and cognitive data. Chi-square analysis was performed for categorical variables. To analyze results at follow-up, repeated measures ANOVA was conducted by using a two-factor design that included a between-subjects factor (group) and a within-subject factor (e.g., University of Pennsylvania Smell Identification Test scores at both time points). Within-group effects and interaction effects were examined by using a repeated measures ANOVA or by using either Wilcoxon signed ranks test or McNemar's nonparametric test for two related samples. Post hoc analyses were conducted by using one-way ANOVA. Correlations used the Pearson product-moment correlation coefficient (r).

Results

Baseline

Subject characteristics. Table 1 presents the demographic, cognitive, and clinical characteristics of all subjects at baseline. Diagnoses for the first-episode patients were confirmed at 6 months postadmission by using the Royal Park Multidiagnostic Instrument for Psychosis and are reported in Table 1. The proportion of patients with schizophrenia or schizophreniform disorder in this study (36.5%) was low compared to the proportion of patients with these disorders in the general Early Psychosis Prevention and Intervention Program (55%) (30).

There was no significant difference between the patient and comparison groups in age and sex. However, the two groups differed in highest level of education and in IQ estimated with the National Adult Reading Test (Table 1), with the comparison group having slightly higher scores on each of these measures. In the analyses that follow, IQ estimated with the National Adult Reading Test was used as a covariate where appropriate (unless otherwise stated).

A significantly greater proportion of the patient group than of the comparison group smoked cigarettes. Among the smokers in the two groups, the patients smoked significantly more cigarettes per day and had smoked for a significantly longer period than the comparison subjects. In addition, significantly more patients than comparison subjects reported using cannabis. Of those using cannabis, patients and comparison subjects did not differ in the number of units of cannabis smoked per week or in how long they had used cannabis.

Smell identification. The results on the University of Pennsylvania Smell Identification Test for patient and comparison groups at baseline are shown in Table 1. The first-episode psychosis patients achieved a significantly lower mean score than did comparison subjects. No group-by-sex interaction was observed (F=0.80, df=1, 109, n.s.).

Effects of IQ. The patient group and the comparison group differed on current full-scale IQ derived from the WAIS-R and on IQ estimated with the National Adult

Reading Test, which represented premorbid IQ for the patients (Table 1). The discrepancy between IQ estimated with the National Adult Reading Test and current IQ was significantly more pronounced in the patient group (difference=–9.45) than in the comparison group (difference=5.19) ($F=46.20$, df=1, 102, $p<0.001$, for current IQ covaried for IQ estimated with the National Adult Reading Test). Although the difference between groups in IQ estimated with the National Adult Reading Test was significantly associated with poorer performance on the University of Pennsylvania Smell Identification Test ($F=7.70$, df=1, 80, $p<0.01$), the difference in smell identification ability between the groups remained significant even after controlling for difference in IQ ($F=12.46$, df=1, 80, $p=0.001$).

Effects of cigarette smoking and cannabis use. To examine the effects of cigarette smoking and cannabis use on performance on the University of Pennsylvania Smell Identification Test, the patient and comparison groups were divided into users and nonusers. Smoking had no significant effect on smell identification ability in either study group ($F=2.20$, df=1, 77, $p=0.14$), and no interaction of study group and smoking was found ($F=0.70$, df=1, 77, $p=0.41$). Similarly, there was no effect of cannabis use on smell identification ability in either study group ($F=0.13$, df=1, 79, $p=0.73$) and no interaction of study group and cannabis use ($F=0.18$, df=1, 79, $p=0.67$, with IQ estimated with the National Adult Reading Test as covariate).

University of Pennsylvania Smell Identification Test score and age when THC use began were significantly correlated in the patient group ($r=0.32$, $p<0.05$) but not in the comparison group ($r=–0.04$, n.s.), indicating that poorer smell identification ability was associated with earlier age of initiating THC use in patients with psychosis. No relationships were found in either group for smoking history measures.

Effects of diagnosis, symptoms, and medication. Within the patient group, there was no significant difference between diagnostic subgroups in performance on the University of Pennsylvania Smell Identification Test (mean=29.86, SD=4.26, for patients with schizophrenia or schizophreniform disorder; mean=30.75, SD=5.19, for patients with affective psychosis; mean=28.67, SD=2.88, for patients with schizoaffective disorder; and mean=27.38, SD=4.86, for patients with other psychoses) ($F=1.50$, df=3, 54, n.s.). To examine the effects of medication, the patient group was subdivided into those who were taking antipsychotics (N=25) and those who were assessed to be neuroleptic naive (N=49). There was no difference in smell identification scores between the two subgroups (mean=28.95, SD=5.26, for those receiving antipsychotics and mean=29.33, SD=4.30, for those who were neuroleptic naive ($F=0.09$, df=1, 72, n.s.). There were no differences in smell identification ability between patients who were receiving anxiolytics (N=9) or anticholinergics (N=8) and those who were not receiving those drugs.

Higher scores on the Manchester Scale negative symptom item of "flattened affect" was associated with poorer performance on the University of Pennsylvania Smell Identification Test ($r=–0.35$, $p<0.05$). No associations were found between score on the smell identification test and any medication or other clinical variables, including duration of untreated psychosis or length of the prodrome.

Follow-Up

There were no significant differences at baseline in age, sex, or smell identification ability between subjects who were followed up (both patients and comparison subjects) and those who were not followed up. Patients who received a follow-up assessment had a significantly higher mean current full-scale IQ at baseline (mean=92.00, SD=13.29) than the patients who were not followed up (mean=84.06, SD=11.27) ($F=7.39$, df=1, 72, $p=0.008$). This difference was not found for the comparison subjects.

The 40 patients assessed at follow-up differed diagnostically from those who were not followed up. Fewer patients with other psychoses (N=5) were followed up, compared to those with schizophrenia or schizophreniform disorder (N=16), affective disorders (N=12), and schizoaffective disorder (N=7) ($\chi^2=11.94$, df=3, $p<0.008$). There was no difference in the dose of antipsychotics or the use of anticholinergics at baseline between those who were followed up and those who were not.

As expected, the mean daily dose of antipsychotic medication (in chlorpromazine equivalents) at follow-up (mean=88.3 mg, SD=129.09) was higher than at baseline (mean=31.62, SD=73.16) (Wilcoxon $z=–2.6$, $p=0.009$, N=32). For patients who were assessed at follow-up, the mean Manchester Scale score for positive psychotic symptoms decreased significantly from baseline to follow-up, indicating that the patients' clinical state had improved (scores decreased from mean=2.16, SD=1.13, to mean=0.80, SD=0.90 for delusions, Wilcoxon $z=–4.08$, $p<0.001$, N=40; from mean=1.32, SD=1.28, to mean=0.62, SD=0.88 for hallucinations, Wilcoxon $z=–3.3$, $p=0.001$, N=40; and from mean=1.45, SD=1.09, to mean=1.03, SD=0.90 for incoherence of speech, Wilcoxon $z=–2.00$, $p<0.05$, N=40). No significant improvement in negative symptoms was found.

Data on substance use and cognitive measures for the 40 patients and 13 comparison subjects reassessed at follow-up are presented in Table 2. Differences between the patient and comparison groups in smell identification ability, IQ, and substance use at 6-month follow-up were similar to those at baseline. There was no significant change between baseline and follow-up in the proportion of patients or comparison subjects who smoked cigarettes or used cannabis. For the patient group, IQ estimated with the National Adult Reading Test showed a modest but significant increase at follow-up.

Although the difference in smell identification scores between groups was maintained between the two time points ($F=9.25$, df=1, 41, $p<0.01$), there was no significant change

in smell identification scores between assessments in either the patient group or the comparison group (effect of time: F=1.86, df=1, 41, n.s.; group-by-time interaction: F=0.01, df=1, 41, n.s.). No significant association was found between smell identification ability and medication dose at follow-up assessment. As at baseline, there were significant negative associations between the University of Pennsylvania Smell Identification Test score and the negative symptom items of flattened affect and poverty of speech (r=–0.39, p<0.05, and r=–0.34, p<0.05, respectively). Further, change in the University of Pennsylvania Smell Identification Test score between the two assessments was significantly associated with change in score for flattened affect (r=–0.43, p=0.03), indicating that improved performance on the smell identification test was associated with decreased severity of flattened affect. The association between change in the University of Pennsylvania Smell Identification Test score and change in poverty of speech did not reach significance (r=–0.36, p=0.07).

Discussion

This study examined olfactory identification ability, as measured by the University of Pennsylvania Smell Identification Test, in a group of patients assessed within the first week of presentation of their first episode of psychosis. Almost 70% of these patients were neuroleptic naive at the time of assessment. The patients had significantly impaired olfactory identification ability compared to a group of age- and gender-matched normal subjects. These results could not be explained by the influence of gender, premorbid or current IQ, smoking history, or cannabis use, or by the effects of medication. Follow-up assessment at 6 months indicated that the patients' olfactory identification ability remained impaired. Despite an improvement in positive symptoms (hallucinations and delusions), no parallel change occurred in performance on the University of Pennsylvania Smell Identification Test. However, poorer performance on this measure was significantly associated with the negative symptoms of psychosis at baseline and follow-up assessments. Further, change scores on this measure paralleled change scores for negative symptoms. These findings suggest a relationship between olfactory identification ability and persistent negative symptoms, which is consistent with the findings of our previous study of patients with chronic schizophrenia (12). Again, no relationship was found between olfactory identification ability and medication dose at follow-up. Poor smell identification ability was also apparent in diagnostic subgroups of these first-episode psychosis patients. Thus, olfactory identification ability was impaired from the outset of psychotic illness, and this deficit was not specific to schizophrenia or schizophreniform disorder, but was also seen in first-episode patients with affective and other forms of psychosis. The deficit in olfactory identification ability could not be explained by peripheral factors, such as nasal congestion, that impede smell identification ability. These results suggest that the deficit reflects central mechanisms.

To take into account differences in overall neurocognitive functioning between the patient and comparison groups, the relationship between olfactory identification ability and estimates of premorbid and current IQ was examined. Although current IQ was associated with smell identification ability, such relationships did not explain the olfactory deficits observed in first-episode psychosis patients. It should be noted that, relative to the comparison group, the patients had lower premorbid IQs, and the discrepancy between the patients' premorbid and current IQ was consistent with reports suggesting a decrease in IQ in schizophrenia after onset of illness (45, 48, 49). However, with illness stabilization, patients' scores on measures of both premorbid and current IQ increased significantly but with no corresponding improvement in olfactory identification ability. Other studies have also reported a relationship between University of Pennsylvania Smell Identification Test ability and IQ (5, 14, 16), but we are not aware of any study that has controlled for the effects of change in IQ from premorbid levels. Our results support the idea that olfactory identification deficits are not a consequence of any global change in intellectual functioning occurring in patients after the onset of psychosis. Rather, these deficits indicate a more specific disability. However, it is possible that the National Adult Reading Test underestimates premorbid intellectual functioning in psychosis because verbal ability may be affected in this disorder (5, 14) and that use of this instrument would underestimate the degree of decline in intellectual functioning after illness onset. Therefore, an accurate assessment of the decline in IQ could explain more of the patients' deficits in olfactory identification ability as measured by the University of Pennsylvania Smell Identification Test. To address this issue, longitudinal studies of high-risk individuals who subsequently develop psychosis would be useful, as suggested by our initial pilot data (50).

To our knowledge, this study is the first to report longitudinal olfactory deficits in neuroleptic-naive patients suffering from psychosis. The finding of persistent olfactory deficits soon after illness onset, taken together with the lack of any relationship between olfactory deficits and length of untreated illness or length of the prodrome, suggests that impaired olfactory identification ability may be a trait marker for psychosis. Few studies have identified trait markers of the illness, although studies of subjects at high risk for psychosis have identified impairments in attention before illness onset (e.g., references 51–54). However, these studies are inconclusive, and their findings suggest that the specificity of such attentional deficits for schizophrenia is poor, as qualitatively similar performance impairments are found in other neuropsychiatric disorders, including depression (55). The results of our study also indicate that olfactory identification deficits are

apparent in patients with affective psychoses. To our knowledge, no previous studies have reported on olfactory ability in a first-episode affective psychosis cohort. It is of interest that structural imaging data from a subgroup of patients from the present cohort identified similar structural abnormalities in the hippocampus in schizophrenia or schizophreniform disorder and in affective psychoses (56, 57). However, because not all patients could be followed up, further studies with larger numbers of subjects are necessary to adequately address the issue of progression of olfactory deficit, particularly in patients with affective psychosis, in whom we found a nonsignificant 2-point improvement in smell ability at follow-up. The need for further study of change in olfactory identification ability over time also applies to comparison subjects, of whom only a small number were successfully followed up in our study.

The findings of olfactory identification deficits in neuroleptic-naive patients are consistent with previous reports of deficits in schizophrenia (6–8, 13). The studies by Moberg et al. (13) and Wu et al. (7) each included a small subgroup of patients who were never treated with medications. Moberg et al. found no difference in olfactory ability in medicated compared with unmedicated patients. Although Moberg et al. found an association between olfactory ability and length of illness, our results suggest no progression over a 6-month period. Given that the study by Moberg et al. was cross-sectional rather than longitudinal, one explanation for the different results is that greater olfactory deficit is associated with poorer outcome. This explanation is supported by our findings of a relationship between negative symptoms and olfactory identification deficits and by earlier findings of greater impairment of olfactory ability in patients with chronic schizophrenia (12).

In the study by Kopala et al. (6), smell identification deficits were found in only 31% of never-medicated patients with schizophrenia or schizophreniform disorder who were recruited during their first hospital admission. This finding contrasts with our finding that 82.4% of the study cohort performed in the abnormal (microsmic or anosmic) olfactory range (after accounting for Australian norms). This difference was not explained by diagnostic differences, as 71.4% of the subgroup with schizophrenia or schizophreniform disorder in our study performed in the abnormal range. However, the patients in the study by Kopala et al. were older. Further, differences in levels of negative symptoms may be important, although data on specific symptoms were not provided in their study. Differences in cigarette smoking between the studies (81.3% of the patients in our study smoked cigarettes compared to only 43% of the patients in the study by Kopala et al.) would not explain the findings, as smoking in our study was associated with better smell ability. Kopala et al. excluded patients who used cannabis. Although we did not find any relationship between the extent of cannabis use and smell ability, it is possible that neurotoxic effects of THC on pathways mediating olfactory ability (22) may account for the greater degree of deficit found in our study's cohort. We did find that earlier age of beginning THC use was associated with greater deficits on the University of Pennsylvania Smell Identification Test only in the patient group. Thus, for patients with psychosis, earlier age of starting cannabis use was related to greater deficits in olfactory identification ability. As this relationship was not found in the normal comparison group, one possibility is that an interaction between cannabis use and psychosis may explain the higher proportion of patients with olfactory identification deficits in our study. The older patients in the study by Kopala et al. may have been less likely to use illicit substances (unpublished 1999 paper of Duke et al.) such as cannabis, making this interaction less apparent. Recent studies of cannabis users suggest that heavy use of this substance may adversely affect function in the orbitofrontal cortex (58). Similarly, olfactory identification ability is thought to be mediated by the orbitofrontal cortex. Therefore, it is possible that compromise of the orbitofrontal cortex in schizophrenia is compounded by the use of cannabis. Future studies that examine prefrontal cortical functioning in psychosis, particularly in younger patients, should consider the likely interaction between cannabis and the neuropsychological deficits apparent in this illness.

In summary, the study results support the presence of olfactory identification deficits at illness onset that remain stable over the initial course of psychosis. These deficits were not specific to schizophrenia and were found in patients with affective and other psychoses. Further work should examine larger numbers of subjects to confirm this lack of specificity and should assess patients over a longer follow-up period. Studies should also examine high-risk individuals before the onset of psychosis.

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