Smell Function in Schizophrenia During Acute Psychosis and Correlation with Clinical Symptomatology and Length of Hospitalization

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ABSTRACT **Background:** While several studies have noted smell impairment in schizophrenia, it is unclear whether this impairment extends to acute psychosis and whether it is associated with more severe illness as expressed in extended hospitalization.

Objectives: To evaluate the olfactory function of patients in an acute psychotic state and correlate it with clinical symptomatology and length of hospitalization.

Methods: Olfactory function was assessed in 20 patients with schizophrenia in their first week of hospital admission for acute psychosis compared with matched controls. Olfaction was evaluated via three stages: threshold, discrimination, and identification of different odors utilizing the Sniffin' Sticks test battery.

Results: Schizophrenia patients scored significantly lower on total smell score, discrimination, and identification abilities. A significant association was observed between hospitalization duration and total smell score and smell discrimination. No significant associations between smell and clinical symptomatology were observed.

Conclusions: Study observations confirm impaired sense of smell in schizophrenia patients and suggest that smell impairment may be a potential marker of more serious illness as expressed in longer hospital stay.

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KEY WORDS: olfactory system, schizophrenia, smell deficit

Cognition includes a wide range of mental processes such as memory, attention, language, and odor perception. Olfactory processing is mediated by several brain regions; however, psychophysical, imaging, and computational studies have indicated that the orbitofrontal cortical region functions as the likely locus of odor percept formation in mammals [1]. It is believed that cognitive factors are strongly related to olfactory perceptions with the source of this activation and correlation lying in the orbitofrontal cortex [2]. Orbitofrontal activation greatly predicts olfactory perception [3]. Objective measures of smell, such as the Sniffin' Sticks kit [4] have shown smell deficits in several medical conditions including Parkinson's disease [5].

Smell deficits are also observed in psychiatric illnesses involving the orbitofrontal cortex, including obsessive-compulsive disorder, mood disorders, and psychosis [6]. In a meta-analysis, a similar medium-to-large olfactory deficit has been observed in at-risk for psychosis youth population and patients with schizophrenia [6]. Hyposmia exists in patients as well as their unaffected relatives [7]. Olfactory deficit can already be detected during the first episode of psychosis [8] and, in patients with schizophrenia, substantial olfactory deficits across all domains were observed, with no differential deficits in odor identification, detection threshold sensitivity and discrimination [9]. These findings suggest that olfactory impairments may be useful markers of high-risk for schizophrenia status.

Some researchers hypothesized that a correlation may exist between severity of the psychosis and the olfactory deficits. A correlation of negative symptoms (such as blunted affect, apathy, and anhedonia) with olfactory performance has been observed [10]. It has even shown that Positive and Negative Syndrome Scale (PANSS) scores were negatively associated with olfactory identification and showed that patients with schizophrenia had a low self-awareness of their olfactory deficits [11]. Olfactory identification deficits in schizophrenia were also correlated with duration of illness [12].

Since smell may function as an important marker of illness severity, we investigated a range of olfactory functions in a group of patients with schizophrenia during their first week of hospitalization for acute psychosis. In this manner we evaluated patients in their acute state and obtained a sense of their olfactory function when they are in a severe state of the illness.

In addition, for the first time, to the best of our knowledge, we correlated this olfactory function with length of hospitalization. Thus, we explored a potential illness severity predictor (olfactory function) with the assumption that patients with more severe acute psychotic illness take longer to respond to treatment before they are discharged. In addition, we performed a correlation test between smell scores and clinical symptomatology.

METHODS

STUDY POPULATION

The study population consisted of Diagnostic and Statistical Manual of Mental disorders (DSM-5) diagnosed schizophrenia in-patients at the Beer Yaakov Mental Health Center, a large state referral institution. Patients were between the ages of 18–70 years. Two board certified psychiatrists verified patient diagnoses. Patients with any significant medical or neurological illness were excluded from the study. Controls were matched for age and sex, as well as for smoking habits. Controls were randomly selected as willing voluntary participants from the community; however, without matching during screening for education level, socioeconomic status, parental education, or knowledge of biological relative with schizophrenia. Prior to study entry, all participants provided written informed consent after receiving a full explanation regarding the nature of the study and potential risks and benefits of study participation. All patients were deemed appropriate to provide informed consent by their treating psychiatrists. No patients with legal guardians (apotropos) were included as study participants. The study was approved by the Beer Yaakov Mental Health Center Institutional Review Board.

STUDY DESIGN

All patients with schizophrenia were examined within the first week of hospitalization, with the intention of testing their smell abilities in an acute state of psychosis following the initial period of admission. Only patients admitted for the purposes of management of acute psychosis exacerbation were recruited for study participation. All patients recruited were cooperative and attentive. Patients were assessed for substance abuse on admission by means of a careful history (and chart review by NS and RM) and targeted urine sampling if deemed indicated. No patients with active substance abuse were recruited for study participation. Patients were rated for clinical symptomatology at the time of testing of smell by means of the PANSS [13] and the Clinical Global Impression scale (CGI) [14]. Patients were then followed to determine the number of days each patient was hospitalized for the current hospitalization.

OLFACTORY ASSESSMENT

Olfactory functions were evaluated utilizing the Sniffin' Sticks kit (AESKO diagnostics, Germany), which is based on a pen-like odor dispensing device [15]. This method includes both non-verbal requirements (i.e., odor threshold and discrimination) and a more complicated evaluation that includes verbal requirements (odor identification). The three smell functions were examined in three independent stages:

- **Threshold detection:** The threshold detection is the minimum concentration of a sensory stimulus needed to give rise to a sensation [16]. At this stage, we assessed the threshold of the patients by using n-butanol as a single odorant. Using a triple-forced-choice paradigm, threshold detection was determined by employing a staircase method. Three sticks were presented to each patient in a randomized order, two of them contained solvent and the third contained the odorant at a certain dilution. The task was to identify the stick with the odorant. Presentation of the triplets continued at increasing doses of n-butanol until the patient had correctly discerned the odorant, and a successive trial was followed by a reversal of the staircase.
- **Discrimination:** At this stage, the ability of the patient to discriminate between two different odorants was assessed. The patient was presented with triplets of pens; two of which contained the same odorant and one that contained a different one. The task was to determine the stick with the different smell. The task was based on the measure of the individual's ability to differentiate the perception of the quality of one odorant when compared to another one. Accurate performance requires intact acuity but not identification of the odorant [17].
- **Identification:** At this stage the ability of the patient to identify different odorants was assessed. When a pen was presented, the patient had to identify the smell out of four options.

The maximum score in each stage was 16 points; hence, the maximum total score (TDI) is 48 points. Any score above 30 is considered normal sense of smell (normosmia); any score between 15 to 30 is considered decreased sense of smell (hyposmia), and any score below 15 is considered loss of smell (anosmia).

RESULTS

STUDY SAMPLE

Twenty patients with schizophrenia and 18 age- and sex-matched controls agreed to participate in the study. Sex segregation was equal between groups: 50% males and females in each group. Age did not differ between groups ($P = 0.77$) (schizophrenia: mean = 37.4 ± 14.8, range 19–68; control: mean = 36.1 ± 13.2, range 18–61). The percentage of smokers did not differ between groups (control 50%, patients 55%). Mean length of treatment was 192.65 months (range 0–480 months) and mean dose of antipsychotic medication in chlorpromazine equivalents was 633.3 mg (range 0–2500 mg). At study recruitment, 6 patients were receiving first-generation antipsychotic medication, 3 patients were receiving second-generation antipsychotic medication, and 2 patients were receiving a combination of the two

Table 1. Patient symptomatology ratings

	Patients (n)	Minimum	Maximum	Mean ± SD
CGI	19	4	6	5 ± 0.667
PANSS-positive	19	14	38	23.63 ± 6.95
PANSS-negative	19	8	25	15.95 ± 4.34
PANSS-general	19	19	46	37.21 ± 17.24
PANSS-total	19	25	98	60.53 ± 17.24

CGI = clinical global impression, PANSS = positive and negative symptom scale, SD = standard deviation

Table 2. Schizophrenia patients and control group smell ratings

	Group	n	Mean	SD	SE, mean
Threshold	**Control**	18	7.8667	2.17432	0.51249
	Schizophrenia	18	7.6356	3.02283	0.71249
Discrimination	**Control**	18	13.5556	1.54243	0.36355
	Schizophrenia	20	10.65	2.70039	0.60383
Identification	**Control**	18	13.7222	1.31978	0.31108
	Schizophrenia	20	12.5	1.84961	0.41359
Global Olfactory Score	**Control**	18	35.1944	3.24735	0.76541
	Schizophrenia	18	29.0244	5.7818	1.36278

SD = standard deviation, SE = standard error

medication subtypes. Nine patients were receiving no medication, including two patients in the midst of their first episode of psychosis.

CLINICAL ASSESSMENT

Data on patient symptoms (PANSS) and CGI are presented in Table 1. One patient with schizophrenia had missing psychiatric scales data.

SMELL ASSESSMENT

The smell test data from patients and controls are presented in Table 2. Analysis of the data indicated that all four variables showed normal distribution. Accordingly, the data were analyzed using parametric tests. Grouped *t*-tests of the smell data indicated significant differences between the groups in the parameters of discrimination, identification, and TDI, but not threshold [Figure 1]. Controls showed higher discrimination ($t = 4.01$, df = 36, $P < 0.001$), higher identification ($t = 2.32$, df = 36, $P = 0.026$), and higher TDI scores ($t = 3.94$, df = 34, $P < 0.001$). No difference in threshold was seen ($t = 0.26$, df = 34, $P = 0.79$). Associations between smell measures were calculated using Pearson correlations. A significant positive association was observed between discrimination and identification (r = 0.36, $P = 0.028$). No significant associations were indicated between the number of hospitalization days from admission at time of testing and smell measures.

SEX DIFFERENCES

ANOVA models with main factors of group (control, schizophrenia) and sex (M, F) were performed on the smell test measures. Tendency to significant main effects of sex were observed on identification (M 13.3; F 12.9) ($P = 0.058$). No significant group by smoking interactions were observed (all *P*-values > 0.53).

INFLUENCE OF SMOKING

ANOVA models with main factors of group (control, schizophrenia) and smoking (no, yes) were performed on the smell test measures. No significant main effect of smoking (all *P*-values > 0.09) or group by smoking interactions were observed (all *P*-values > 5.8).

INFLUENCE OF AGE

A tendency to significant negative association between age and discrimination was seen (r = -0.029, $P = 0.077$). This effect was more pronounced among patients (r = -0.39, $P = 0.09$) compared to controls ($P = -0.19$, $P = 0.44$).

ASSOCIATIONS BETWEEN SMELL AND CLINICAL MEASURES

No significant associations were observed between PANSS and CGI and smell measures. However, a tendency to significant association was observed between PANSS-negative sub-score and discrimination (r = -0.42, $P = 0.076$).

ASSOCIATIONS BETWEEN SMELL AND LENGTH OF HOSPITALIZATION

A significant association was observed with the total period of hospitalization and smell measures of discrimination: r = 0.51, $P = 0.02$; TDI: r = 0.60, $P = 0.008$. When two severely ill patients with long hospitalization periods (99 and 109 days) were excluded, the significant association was lost (r = -0.03, r = -0.025). Additional analyses were performed to test for possible associations between symptom level (PANSS) and days of hospitalization and smell. For this purpose, patients were categorized as *low* or *high* on each of the PANSS scales and hospitalization days according to median split. The association between the categorized scale and smell parameters were then calculated using grouped *t*-tests. No significant associations were observed.

DISCUSSION

Study results confirm previous reports of diminished smell ability in patients with schizophrenia. In addition, observations suggest in a preliminary and very cautious fashion that this smell impairment is associated with longer hospitalization. In contrast to other studies that have examined smell function in patients with schizophrenia irrespective of the stage of illness, we analyzed this sensory ability in patients within the first week of admission to the hospital and thus with acute illness (but not necessarily first onset of psychosis). Statistical analysis did not indicate any significance to the specific day of testing within the first week of admission suggesting that in an acute state of psychosis within the first week of admission, patients are similar in smell function.

Since several studies have noted smell impairment in patients with schizophrenia, we hypothesized that the patient's smell scores in the acute state might be able to predict the disease severity as reflected in length of hospitalization. This hypothesis was strengthened by our findings.

The identification test has been found to be very reliable and sensitive to even subtle olfactory deficits in several diseases including Alzheimer's disease, Parkinson's disease, schizophrenia, and depression [17,18]. The location of the olfactory receptor neurons in the nasal epithelium allow noninvasive access to these neurons in living patients. Thus, a unique opportunity exists to directly assess neuronal integrity in patients [19].

The identification test is highly sensitive to conditions involving the central nervous system (CNS) since it requires verbal involvement in addition to the initial recognition. In a previous study by our group, which investigated smell and SLE [20], we hypothesized that the discrimination task (the ability of the patients to discriminate between two different odorants) would be the most sensitive since it is the simplest. It does not require verbal abilities or any involvement of the CNS, but the most primitive ability of distinguishing between the perceptions of the quality of one odor compared to another. Accurate performance requires intact acuity but not naming [17]. Our study further confirms this consideration. The discrimination task is a highly predicting diagnostic tool, which can accurately distinguish between the healthy and the ill under various conditions.

Results from this study do not show any significant difference in the threshold scores between patients and controls; thus, indicating that patients understood the test and did have some intact olfactory function, at least in this domain. The threshold detection ability is important and the lack of it seriously compromises quality of life and independence. Impaired smell ability was not related to the high prevalence of smoking in patients with schizophrenia since similar previous studies also noted that smoking habits did not affect smell scores [12,15,21].

Another further finding that corresponds with existing literature was the tendency to a correlation between older age and lower smell scores [12]. In our sample, older age tended to correlate only with lower discrimination score, perhaps with a larger sample size this would have been significant and would have been noted in the other smell variables as well. Smell deficits observed in schizophrenia appear in the early stages of the disease and correlate with its clinical course [22]. Several studies have shown that smell abilities decrease with duration of the illness until the very late stages of life [23]. It has been noted that elderly patients with schizophrenia have more olfactory deficits relative to age-matched comparison participants, and that the magnitude of the deficit is greater than that seen in younger schizophrenic patients [12].

Interestingly, while our study results did not find any correlation between smell scores and CGI or total PANSS scores, a tendency to a significant association was observed between PANSS-negative sub-scores and smell discrimination scores (P = 0.076). Precedent for correlation between lower smell scores and negative symptoms of the illness has already been established [23].

Limitations of the study include the relatively small sample size, the lack of a comparison follow-up smell testing once the patient stabilized out of the acute psychotic state, and the lack of any structural or functional neuroimaging correlates. In addition, there was a wide age range of patients in the study. While it may be suggested that this may have affected study observations given the normal deterioration of smell function with age, we believe that we circumvented this potential confound by age-matching participants with schizophrenia with non-schizophrenia controls. While it is true that cigarette use is best reported in terms of *pack years*, we found reliability of long-term report to be poor in our patients and reported cigarette use as yes/no.

In many countries, patients with schizophrenia are admitted for reasons other than acute symptom exacerbation. However, in Israel, within the context of a large government psychiatric institution, patients are predominantly admitted for symptom exacerbation only. Since the study investigated patients in their acute stage of illness following a new hospitalization and initial screening, we would have excluded any patients who would have been admitted for reasons other than acute psychosis exacerbation, including housing reasons and substance dependence. No patients met these alternative admission criteria during the screening process.

Future studies should explore the influence of medication subtypes and dosages on olfactory performance. Since patients were presenting with an acute phase of illness, it is conceivable that attention deficits could have been a likely confound. However, all patients were cooperative, and those who were considered agitated or inattentive as demonstrated by clinical examination were not recruited for study participation. Further studies of such nature may want to consider more formal attention testing prior to patient recruitment.

CONCLUSIONS

Impaired sense of smell exists in some patients with schizophrenia and may be a potential marker of more serious illness as expressed in longer hospital stays.

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A career is wonderful, but you can't curl up with it on a cold night.
Marilyn Monroe (1926–1962), American actress, model, and singer

Capsule

Instructing tumor cell turncoats

Cancer cells down-regulate antigen presentation to evade recognition by the immune system. **Zimmermannova** and colleagues reprogrammed cancer cells into tumor-derived antigen presenting cells (tumor-APCs). Mouse or primary human cancer cells transduced with a set of transcription factors acquired a stable dendritic cell phenotype, could present endogenous tumor antigens to stimulate the effector function of CD8+ T cells, and showed decreased tumorigenicity. In mouse models, intratumoral injection of tumor-APCs decreased tumor growth, increased the survival of tumor-bearing mice, and enhanced responses to immune checkpoint inhibitors. This study highlights that future immunotherapies aimed at reprogramming cancer cells in situ could combine reversing malignancy with mobilizing the cellular antigen-presenting machinery to enhance the activity of CD8+ T cells toward tumors.

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