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Olfactory identification deficit in relation to schizotypy

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Abstract

Past studies have shown that schizophrenic men tend to be impaired on the olfactory identification task. We examined individual differences in the olfactory function in relation to schizotypy. Healthy individuals who might carry latent liability for schizophrenia participated in olfactory identification and acuity tasks. Psychometrically ascertained schizotypic men showed deficits on the olfactory identification task but not on the olfactory acuity task. The olfactory identification function partly depended on the menstrual cycle in women. But further systematic research is needed to clarify the possible role of estrogen. © 1997 Elsevier Science B.V.

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1. Introduction

Past studies have reported that despite normal olfactory sensitivity, about 50% of men with schizophrenia show olfactory agnosia, whether neuroleptic-naive or chronically medicated (Kopala et al., 1992; Wu et al., 1993; Malaspina et al., 1994). The neural circuitry mediating olfactory identification overlaps with several regions that are implicated in the pathophysiology of schizophrenia, including the orbitofrontal cortex (Zatorre and Jones-Gotman, 1991). Lesions in the orbitofrontal cortex lead to deficits in olfactory identification, in the absence of deficits in olfactory sensitivity or acuity (Potter and Butters, 1980; Jones-Gotman and Zatorre, 1988). A significant

increase in cerebral blood flow is observed in the orbitofrontal cortex in healthy volunteers during an olfactory task (Koizuka et al., 1994). A recent PET study of never-medicated schizophrenia patients found that reduced left inferior frontal and left limbic regional metabolic rates (during a continuous performance task) were correlated with the error scores on the olfactory identification task conducted off the PET scanner (Wu et al., 1993). In addition, several neuropsychological studies report that olfactory identification errors are associated with frontal lobe deficits (Seidman et al., 1992; Malaspina et al., 1994; Brewer et al., 1996; Pantelis and Brewer, 1995). Temporal lobes may also play an important role in the olfactory identification task (Eskenazi et al., 1986), but some authors report that temporal lobe lesions affect olfactory acuity while leaving the olfactory recognition function intact (Rausch and Serafetinides, 1975).

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The orbitofrontal cortex also plays a crucial role in the control of social–emotional responses (e.g., Girgis, 1971; Goldman-Rakic, 1991) and, therefore, some of the negative symptoms, such as anhedonia and social/interpersonal deficits may reflect dysfunctions of the circuitry mediated by the orbitofrontal cortex. Schizophrenia patients show deficits in tasks that tap orbitofrontal function (e.g., Seidman et al., 1992). Negative symptoms in schizophrenic patients are correlated with an increase in olfactory identification errors (Brewer et al., 1996) and with an elevated olfactory threshold (Geddes et al., 1991).

Although olfactory deficits have been studied systematically in schizophrenia patients, olfactory identification function in individuals who might carry latent liability for schizophrenia has not been examined. Hypothetically ‘psychosis-prone’ or schizotypic individuals within general population may carry a latent liability for schizophrenia although they may never become clinically ill (Chapman and Chapman, 1985; Lenzenweger and Loranger, 1989a,b; Meehl, 1990). Psychometrically identified schizotypic subjects show subtle deficits in frontal lobe function, as assessed by the Wisconsin card sort test (e.g., Lenzenweger and Korfine, 1994; Park et al., 1995), sustained attention (e.g., Lenzenweger et al., 1991) and spatial working memory (Park et al., 1995). Thus, it is possible that a sub-group of schizotypic subjects might show subtle deficits in olfactory identification. Furthermore, those who have elevated scores on items that tap ‘withdrawn’ or negative syndrome (e.g., blunted affect, absence of close friends, social anxiety) on the psychometric scales of schizotypy, might show greater olfactory identification deficits.

One complicating factor might be sex (see Kopala et al., 1989; Kopala and Clark, 1990). Compared with 50% of men with schizophrenia, only about 10% women with schizophrenia show olfactory identification deficits (Kopala et al., 1992). Men with schizophrenia have equivalent or even superior olfactory *acuity* compared with women with schizophrenia or normal controls (Kopala et al., 1989), but schizophrenic men consistently make more errors than do schizophrenic women on the olfactory identification task

(Kopala et al., 1994, 1995). In women, the estradiol level is associated with their olfactory identification performance; lower estrogen level is correlated with increased errors on the olfactory identification task (Kopala et al., 1995). Therefore it is important to examine men and women separately and also to monitor the hormone levels. The menstrual cycle provides a convenient and non-invasive method for studying estrogen fluctuations in humans (Hampson and Kimura, 1992).

To summarize, we examined the olfactory identification function in relation to schizotypy in the undergraduate population for several reasons. Olfactory identification performance is mediated by the neural circuitry that is implicated in the pathophysiology of schizophrenia, including the orbitofrontal system. We examined the individual differences in olfactory identification function in relation to schizotypy, since schizotypic individuals might carry latent liability for schizophrenia. By testing young, healthy individuals we were also able to bypass any medication effects. We hypothesized that those who score high on the schizotypy scale will also make more olfactory identification errors. We also examined possible sex differences in olfactory identification, since there is evidence pointing towards the involvement of estrogen in olfactory identification performance (Kopala et al., 1995).

2. Methods

2.1. Subjects

Participants for the present study were recruited randomly from the psychology subject pool, which consists of undergraduate students enrolled in an introductory psychology course at Northwestern University. Students received partial course credits for participating in psychology experiments. Potential participants from the subject pool were asked to fill out a questionnaire to screen for familial history of mental illness, head injury, olfactory diseases, medication, oral contraceptives, smoking, history of drug use and allergies. The legal drinking age in Illinois is 21. All the participants were under 21 but, nevertheless, we asked

the participants to refrain from drinking any alcohol for 24 h before they came to the laboratory. All women were asked to fill out a short questionnaire about their menstrual cycles in order to exclude those with amenorrhea. No participants were amenorrheic. Forty-four male (mean age 19.1, $SD=1.1$) and 43 female (mean age=19.1, $SD=1.2$) undergraduate students participated.

2.2. Olfactory identification task

The University of Pennsylvania Smell Identification Test (UPSIT) was used to assess olfactory identification (see Doty, 1983; Doty et al., 1984). There are four booklets, each containing 10 cards. On each card, there is a micro-encapsulated patch which is activated by scratching. There is a list of four answers next to the patch. Subjects were asked to scratch the scented patch and choose one of the four alternatives.

2.3. Olfactory sensitivity task

Olfactory acuity was assessed by the method described by Kopala et al. (1992). Solutions containing different concentrations of *n*-butyl alcohol were prepared in test tubes which were 12 cm in height and 1.2 cm in base diameter. Each contained 6 ml of liquid. There were nine test tubes, each containing a different concentration of *n*-butyl alcohol, ranging from 1×10^{-5} M to 2 M. One test tube contained 100% distilled water. Subjects were presented with one test tube containing butanol and one containing distilled water. They were asked to smell each test tube and to indicate which smelled stronger. When the subject made a choice, the next weaker or stronger odorant was presented until the threshold was determined. The threshold was defined as four consecutive correct choices with chance performance for the next diluted concentration of butanol. A score of 5 was equivalent to a concentration of 8.1×10^{-3} M.

2.4. Schizotypal Personality Questionnaire (SPQ)

The SPQ is a 72-item true–false self-report measure of schizotypal personality that taps into the nine components of the DSM-III-R schizotypal

personality disorder (Raine, 1991). The sub-scales include perceptual aberration, ideas of reference, magical ideation, suspiciousness, constricted affect, no close friends, social anxiety, odd speech, and odd behavior. Factor analyses of the SPQ items indicate three major factors (e.g., Raine et al., 1994): positive, negative and disorganized features (Raine et al., 1994). This structure parallels the three-syndrome model of schizophrenia (Liddle, 1987; Raine et al., 1994). Raine (1991) found, in a large sample of undergraduates ($n=787$), that 55% of those scoring in the top 10% of SPQ met the clinical diagnosis of DSM-III-R schizotypal personality disorder. We designated those scoring in the top 10% of the SPQ as the ‘high schizotypes’. The other subjects served as the controls.

3. Results

Based on past studies on the role of sex hormones on olfactory function (e.g., Kopala et al., 1989, 1995), we analyzed women and men separately. SPQ scores are reported in Table 1.

3.1. Male subjects

3.1.1. Correlational analyses

We computed the correlations between olfactory identification errors, olfactory threshold scores and the SPQ scores. The total SPQ score was not significantly correlated with olfactory identification ($r=0.23$, $p>0.10$), or with olfactory threshold ($r=-0.018$). But when we examined the SPQ sub-scales, the olfactory identification score was correlated significantly with the negative factor ($r=0.36$, $p<0.03$). Neither the positive factor ($r=0.18$, $p>0.15$) nor the disorganized factor

Table 1
Mean scores on the schizotypal personality questionnaire

	Men	Women
Total SPQ	23.5 (SD=13.4)	19.9 (SD=14.6)
Positive factor	9.1 (SD=6.1)	8.7 (SD=6.1)
Negative factor	10.6 (SD=7.3)	8.2 (SD=8.1)
Disorganized factor	5.0 (SD=3.2)	5.1 (SD=3.9)

($r = -0.03, p > 0.50$) was significantly associated with olfactory identification.

3.1.2. Schizotypy as independent variable: 'high schizotypes' versus controls

Subjects were divided into two groups according to their SPQ scores. We designated those scoring in the top 10% of the SPQ as the 'high schizotypes'. Others served as the controls. According to this criterion, six male subjects were in the high schizotype group and 38 in the control group. High schizotypic men made 7.7 (SD=2.6) olfactory identification errors compared with 4.5 (SD=3.1) errors made by the control group. This difference was statistically significant ($F(1,42)=5.6, p < 0.03$) (see Fig. 1). There was no difference in olfactory sensitivity threshold between these two groups ($F(1,42)=0.52, p > 0.48$).

3.1.3. Olfactory identification as independent variable

Conversely, subjects were also identified as normosmic (i.e. intact olfactory function) or having a mild olfactory agnosia, using the criteria based on the standardization data (Doty, 1983). Normal olfactory identification performance for young men is defined as UPSIT score greater than 34 (i.e. six errors or less). By this criterion, 29% (10 out of 44) of the male undergraduate subjects had

olfactory identification deficits. This figure is higher than those reported in past studies. The 'agnosic' men scored higher on the SPQ than did the normosmic men ($F(1,42)=7.7, p < 0.009$). The total SPQ score for the agnosic men was 33.1 (SD=14.9) and that for the normosmic men was 20.7 (SD=11.7). Agnosic men had elevated SPQ positive syndrome scores (mean=13.3, SD=8.1) compared with the normosmic men (mean=7.9, SD=4.9); this difference was statistically significant ($F(1,42)=7.0, p < 0.02$). Agnosic men also had higher negative sub-scale scores (mean=16.6, SD=8.4) than had the normosmic men (mean=8.6, SD=6.0); this difference was also significant ($F(1,42)=10.7, p < 0.0025$). The disorganized factor score did not differentiate the two groups (see Fig. 2).

3.2. Female subjects

3.2.1. Correlational analyses

The total SPQ score, positive sub-scales, negative sub-scales and disorganized sub-scales were not significantly correlated with olfactory identification or with olfactory thresholds (the range for the non-significant correlations was $r = -0.065$ to $r = -0.214$).

Olfactory Identification Errors in Men

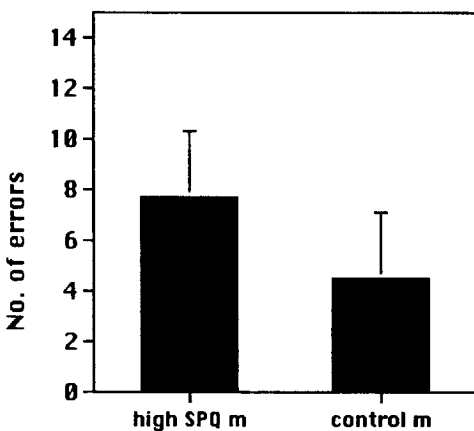


Fig. 1. Olfactory identification errors in men.

SPQ SCORES OF AGNOSIC VS. NORMOSMIC MEN

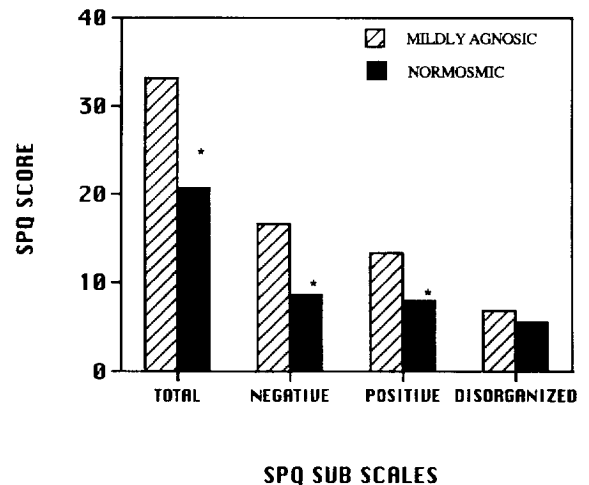


Fig. 2. SPQ scores of agnosic vs. normosmic men.

3.2.2. Schizotypy as independent variable: 'high schizotypes' versus controls

Subjects were divided into two groups according to their SPQ scores. We designated those scoring in the top 10% of the SPQ as the 'high schizotypes'. The other subjects served as the controls. According to this criterion, six women were in the high schizotype group and 37 in the control group. High schizotypes were not significantly different from the control group in their olfactory identification score ($F(1,41)=2.4$, $p>0.13$) (see Fig. 3). There was no difference in olfactory sensitivity threshold between the two groups ($F(1,41)=1.9$, $p>0.17$).

3.2.3. Olfactory identification as independent variable

According to Doty (1983), normal olfactory performance for young women is defined as UPSIT score greater than 35 (i.e. five errors or less). By this criterion, 25.6% (11 out of 43) of the female undergraduate subjects were mildly agnosic. This figure is higher than those reported in past studies. We divided women into agnosic and normosmic groups.

Contrary to our expectations, there was a trend for normosmic women to score higher on the SPQ than the agnosic women ($F(1,41)=3.8$, $p<0.06$). The normosmic women endorsed a mean of 22.3 items ($SD=15.5$) on the SPQ, compared with the score of 12.7 ($SD=8.5$) in agnosic women. This is the opposite of the pattern seen in males. The

difference was statistically significant when we examined the SPQ positive factor score ($F(1,41)=6.2$, $p<0.02$). Agnosic women had very low positive sub-scale scores (mean=5.0, $SD=3.1$) compared with the normosmic women (mean=10.0, $SD=6.4$). But negative and disorganized factors did not differentiate the two groups.

These results are contradictory to our global hypothesis linking olfactory identification function and schizotypy. However, we did expect women to perform differently from men, based on the past reports of the important role of the estrogen levels in olfactory identification performance (Kopala et al., 1994). We did not obtain serum estradiol levels, but we had participants' reports of their menstrual cycles.

3.2.4. Menstrual cycle analyses

By convention, the first day of menstruation was designated day 1. For our study participants, the mean cycle was 30 days. Three women who were not certain about the date of their last menstruation were excluded from the analyses reported below. There was no significant difference between the agnosic and normosmic women in the lengths of their menstrual cycles.

Of the 11 agnosic participants, six were menstruating at the time of testing when their estradiol level is expected to be low. Only two agnosics were tested on days when their estradiol levels are expected to be relatively high (day 17 and day 12). Of the 32 normosmic participants, eight were menstruating at the time of testing. Nine normosmics were tested on days 12–16, when ovulation is likely to occur.

We divided women into those who were tested in the first 10 days of the menstrual cycle and those in the last 20 days. The first 10 days include the days of menstruation, before the pre-ovulatory estradiol surge (see Becker et al., 1992). The mid-cycle plus the last third of the cycle include the days of the highest estradiol level. There was a significant difference between the two groups ($F(1,38)=5.3$, $p<0.03$). Those subjects who were tested during the first 10 days of the menstrual cycle made 6.1 ($SD=4.5$) errors on the UPSIT compared with 3.5 ($SD=2.6$) errors made by the women who were tested during the last 20 days of

Olfactory Identification Errors in Women

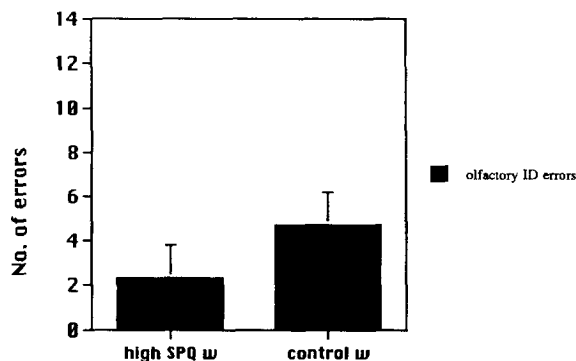


Fig. 3. Olfactory identification errors in women.

their menstrual cycle (see Fig. 4). We do not have direct evidence of the involvement of estrogen since the serum estradiol levels were not obtained, but we speculate that olfactory identification function may be affected by the menstrual cycle; further study is needed to verify the possible role of estrogen.

4. Discussion

Our findings are similar to the results from past studies of olfactory function in schizophrenia patients. Psychometrically ascertained schizotypic men showed olfactory identification deficits, implicating the possibility of impaired orbitofrontal system function in individuals who may carry liability for schizophrenia. In addition, high scores on the positive and the negative syndrome subscales of the SPQ were associated with olfactory identification errors in men. Association of negative symptoms and orbitofrontal function has been reported in schizophrenia patients (Brewer et al., 1996). We also replicated earlier findings that the olfactory identification function is independent of olfactory sensitivity/acuity.

Women did not confirm our hypothesis that psychometrically ascertained schizotypic participants would make more olfactory identification errors. The SPQ scores were not significantly associated with olfactory scores. When we grouped the

participants into normosmics and those with mild olfactory agnosia, we found that normosmic women tended to have higher SPQ positive syndrome scores than did the agnosic women. This surprising result was the opposite to that found in our male participants. We hypothesized that it could be partially accounted for by the role of estrogen in olfactory identification function. Kopala et al. (1994) reported that women with schizophrenia have lower peak serum estradiol levels than do control women, and that postmenopausal women with schizophrenia show deficits in the olfactory identification task. Although we do not have the serum estradiol data, we could infer indirectly the estrogen status of our participants from their menstrual cycle information. Most of the agnosic women in our sample happened to be tested on the days when their estradiol levels were expected to be low. This result points to the importance of monitoring estrogen levels in women when olfactory as well as other cognitive tasks are administered. In future studies, we will systematically investigate the possible role of estrogen in orbitofrontal function and schizotypal personality.

In this study, we found that schizotypic men, but not schizotypic women, tend to have mild olfactory agnosia, in the absence of illness and medication. These results implicate the possible role of the orbitofrontal system in schizotypy. However, the integrity of the olfactory identification function also depends on a network of cortical and subcortical structures, including the dorsomedial thalamus, the medial temporal regions and the basal ganglia. Schizophrenia patients with olfactory agnosia show lower right basal ganglia and thalamic metabolism than those with intact an olfactory identification function (Clark et al., 1991). Therefore, further examination of the functional neuroanatomy of the olfactory function in relation to schizotypy is needed in order to better understand the complex interplay between cortical functions and the behavioral features of schizophrenia and schizotypy.

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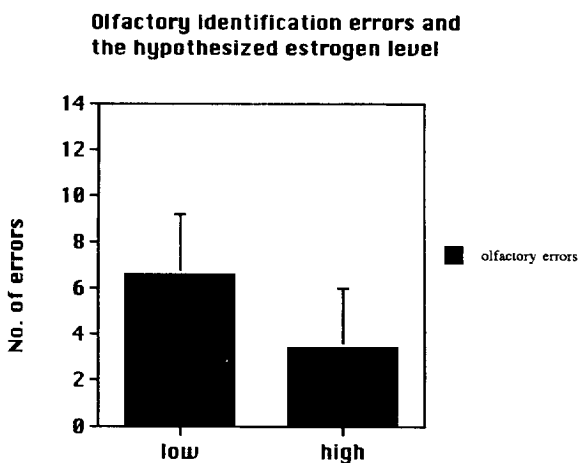


Fig. 4. Olfactory identification errors and the hypothesized estrogen level.

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