Psychiatry Research 220 (2014) 201–204

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Smell identification in individuals at clinical high risk for schizophrenia

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ARTICLE INFO

Article history:
Received 23 February 2014
Received in revised form
13 June 2014
Accepted 9 July 2014
Available online 17 July 2014

Keywords:
Olfaction
Odor
Ultra high risk
Prodrome
Prodromal
Schizophrenia
Negative symptoms

ABSTRACT

Smell identification deficits exist in schizophrenia, and may be associated with its negative symptoms. Less is known about smell identification and its clinical correlates in individuals at clinical high risk (CHR) for schizophrenia and related psychotic disorders. We examined smell identification, symptoms and IQ in 71 clinical high-risk (CHR) subjects and 36 healthy controls. Smell identification was assessed using both the 40-item University of Pennsylvania Smell Identification Test (UPSIT; Doty, R.L., Shaman, P., Kimmelman, C.P., Dann, M.S., 1984. University of Pennsylvania Smell Identification Test: a rapid quantitative olfactory function test for the clinic. Laryngoscope 94, 176–178) and its extracted 12-item Brief Smell Identification Test (Goudsmit, N., Coleman, E., Seckinger, R.A., Wolitzky, R., Stanford, A.D., Corcoran, C., Goetz, R.R., Malaspina, D., 2003. A brief smell identification test discriminates between deficit and non-deficit schizophrenia. Psychiatry Research 120, 155–164). Smell identification did not significantly differ between CHR subjects and controls. Among CHR subjects, smell identification did not predict schizophrenia ($N=19$; 27%) within 2 years, nor was it associated with negative or positive symptoms. This is the third prospective cohort study to examine smell identification in CHR subjects, and overall, findings are inconclusive, similar to what is found for other disorders in adolescents, such as autism spectrum, attention deficit and anxiety disorders. Smell identification deficit may not have clear utility as a marker of emergent schizophrenia and related psychotic disorders.

1. Introduction

Smell identification deficits (SID) are well documented in subjects with schizophrenia (reviewed by Moberg et al. (2014), in whom they are variably related to negative symptoms (Brewer et al., 1996; Malaspina and Coleman, 2003; Moberg et al., 2006; Ishizuka et al., 2010, but see Moberg et al. (2014) for null association of effect sizes with negative symptoms in meta-analysis). SID are also seen in children and adolescents with psychosis, particularly those with schizophrenia, in whom they are related to negative symptoms and IQ (Corcoran et al., 2005). Less is known about smell identification in youths at clinical high risk (CHR) for psychosis, ascertained on the basis of new or worsening subthreshold (i.e. attenuated) psychotic symptoms (McGlashan et al., 2003). To date, there have been two other prospective studies examining baseline smell identification in at-risk cohorts (Brewer et al., 2003; Woodberry et al., 2010). In the earlier study using the 40-item University of Pennsylvania Smell Identification Test (UPSIT; Doty et al., 1984), Brewer et al. found no difference in smell identification between healthy controls and CHR subjects, though SID did characterize those CHR subjects who later developed schizophrenia (though not psychosis more generally), when accounting for IQ (Brewer et al., 2003). However, questions arose as to the cross-cultural validity of the UPSIT in its entirety, such that later studies used the Brief Smell Identification Test (BSIT; Goudsmit et al., 2003), previously called the Cross-Cultural Smell Identification Test (Doty et al., 1996), which is composed of 12 items (among 40) in the UPSIT that are most familiar across cultures. In the second later prospective study of baseline smell identification in CHR subjects, using the BSIT (Doty et al., 1996; Goudsmit et al., 2003), SID were found in CHR subjects as compared with controls, but did not predict psychosis onset (Woodberry et al., 2010), findings opposite to that found by Brewer et al. (2003) in the earlier study using the UPSIT. Using Sniffin' Sticks (Hummel et al., 1997), we have previously shown equivalent smell identification in a subgroup of our current cohort, i.e. 20 healthy controls and 21 CHR patients, including three who progressed to schizophrenia, who otherwise differed in olfactory

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http://dx.doi.org/10.1016/j.psychres.2014.07.018
0165-1781/

event-related potentials and odor threshold (Kayser et al., 2013). Herein, we evaluated smell identification in an extended cohort of 71 CHR patients and 36 healthy controls, using both the total score from the UPSIT (Doty et al., 1984), and the sum of the 12 extracted items that constitute the BSIT (Doty et al., 1996; Goudsmit et al., 2003). Percentile scores were used to adjust for age and sex. First, we aimed to replicate the prior finding of relative deficit in smell identification in CHR subjects (Woodberry et al., 2010). Second, we evaluated the predictive value for schizophrenia and related psychotic disorders among CHR subjects of smell identification deficits, using both the UPSIT and its 12-item derived BSIT, given disparate findings in the other prior studies (Brewer et al., 2003; Woodberry et al., 2010). Finally, we examined the clinical correlates of smell identification in CHR subjects, specifically negative symptoms, an association variably observed in schizophrenia (Brewer et al., 1996, Malaspina and Coleman, 2003); Moberg et al., 2006; Corcoran et al., 2005; Ishizuka et al., 2010, but see Moberg et al. (2014) for null association in meta-analysis), and previously in a subgroup of our current cohort (Kayser et al., 2013), although not in other prior studies (Brewer et al., 2003).

2. Methods

2.1. Participants

Subjects at clinical high risk for psychosis (CHR; $n=71$) and healthy control (HC) participants ($n=36$) similar in demographics were participants in the Center of Prevention and Evaluation (COPE), a prodromal research program at New York State Psychiatric Institute at Columbia. Recruitment and ascertainment relied on clinician referrals, Craigslist, the program website, presentations in the community and the mailing of brochures. CHR subjects were help-seeking individuals ages 14–30 who met criteria for the attenuated positive symptom syndrome, as assessed with the Structured Interview for Prodromal Syndromes (SIPS; McGlashan et al., 2003). Exclusion criteria included any major medical or neurological disorder, IQ less than 70, significant risk of harm to self and others, an inability to speak English, and/or "prodromal" symptoms occurring solely in the context of substance intoxication or withdrawal, or which were better accounted for by another Axis I diagnosis, such as mood disorder. Additional exclusion criteria for healthy controls included any current Axis I disorder within the past 2 years, as assessed by structured diagnostic interview, and any personal or familial (first degree relative) history of psychosis. CHR subjects also had the Structured Clinical Interview for DSM-IV-TR Axis I disorders (SCID; First et al., 2002) to assess comorbidity. Use of antipsychotics and/or antidepressants was ascertained by self-report, as was any use of substances of abuse, including tobacco and marijuana. All CHR patients were offered treatment, which comprised individual psychotherapy and targeted pharmacotherapy (i.e. anxiolytics for anxiety, antidepressants for depressed mood).

Table 1
Sample characteristics.

Characteristic	Healthy controls ($n=36$)	CHR converters ($n=19$)	CHR nonconverters ($n=52$)
Demographics			
Male (%)	58	90	69
Caucasian (%)	47	32	52
Age in years, mean (S.D.)	21.7 (4.6)	19.4 (3.2)	19.3 (3.8)
Full scale IQ, mean (S.D.)	111.1 (12.3)	109.4 (15.1)	107.5 (17.6)
Clinical features			
Positive symptoms, mean (S.D.)*	1.0 (1.2)	14.5 (4.7)	12.2 (4.6)
Negative symptoms, mean (S.D.)*	1.1 (1.5)	15.1 (6.1)	12.4 (6.4)
GAF, mean (S.D.)*	83.9 (7.7)	42.5 (4.5)	46.2 (8.1)
Antipsychotic use (%)	0	11	14
Antidepressant use (%)	0	11	25
Marijuana use (%)	17	16	19
Smell identification			
UPSIT % score, mean (S.D.)	19.0 (20.9)	14.6 (16.4)	18.2 (18.6)
BSIT % score, mean (S.D.)	28.9 (29.1)	23.6 (33.4)	28.9 (29.3)

* ANOVA, overall model $F_{2,102}=116.5$ for positive symptoms, $F_{2,102}=63.6$ for negative symptoms, and $F_{2,102}=315.3$ for GAF, all p's <0.001; for all corresponding post-hoc Tukey tests: converters > controls ($p<0.001$), nonconverters > controls ($p<0.001$) and converters = nonconverters (n.s.)

2.2. Assessments

The Structured Interview for Prodromal Syndromes/ Scale of Prodromal Symptoms (SIPS/SOPS; McGlashan et al., 2003) was used to assess positive and negative symptoms, and administered prospectively every three months to determine transition to schizophrenia and related psychotic disorders among CHR subjects. Smell identification was assessed at baseline using the University of Pennsylvania Smell Identification Test (UPSIT; Doty et al., 1984), a standardized 40-item forced choice test of smell identification in which stimuli are embedded in "scratch and sniff" microcapsules fixed on strips at the bottom of each page. Subjects scratch and sniff each microcapsule and then pick one of four response alternatives that best describe the odor. Smell identification was identified as the total percentile score for both the UPSIT and its 12 extracted items that constitute the Cross Cultural Smell Identification Test (CC-SIT; Doty et al., 1996), also known as the Brief Smell Identification Test (BSIT) (Goudsmit et al., 2003). These 12 extracted items from the UPSIT include six food-related and six nonfood-related odorants familiar to persons not only from North American and European countries, but also from South American and Asian cultures (Doty et al., 1996), specifically: banana, chocolate, cinnamon, lemon, onion, pineapple, paint thinner, gasoline, rose, soap, smoke and turpentine. Full-scale IQ was measured using the 3rd edition of the Wechsler Adult Intelligence Scale (WAIS III; Wechsler, 1997).

2.3. Statistical analysis

ANOVA was used to test group differences among healthy controls and CHR subjects, stratified by transition to schizophrenia and related psychotic disorders within 2 years (i.e. "converters" and "nonconverters"), in terms of demographics, IQ, clinical variables (positive and negative symptoms, global function), and smell identification (percentile scores for both the UPSIT and the extracted BSIT). Post-hoc Tukey tests were used for pairwise comparisons. It was hypothesized that CHR converters would have worse smell identification than both CHR nonconverters and controls. Post-hoc analyses were conducted to test any group differences for individual items on the BSIT. χ^2 analyses were used to evaluate potential group differences in gender and ethnicity. Any demographic variables (i.e. age) that had a significant association with smell identification percentile scores or group were then included as covariates in partial correlational analyses of smell identification and clinical variables.

3. Results

There were 36 healthy controls and 71 CHR subjects, among whom 19 (27%) CHR subjects developed threshold psychosis (>90% with schizophrenia or schizoaffective diagnosis) over 2-year follow-up (i.e. "converters"). The cohort was in its late teens and early twenties, primarily male, and ethnically diverse (Table 1). IQ was similar across groups (Table 1). As expected, positive and negative symptoms, and impairment in global function were evident among CHR subjects; however, they were not significantly more severe among CHR converters (Table 1). Among CHR subjects, 18% endorsed current use of marijuana and none endorsed tobacco use. Eight percent of CHR subjects were taking antipsychotics and 14% antidepressants. Rates of comorbid diagnosis were 37% for depressive disorders and less than 10% each for anxiety disorders, autism spectrum, ADHD and eating disorders. While demographic characteristics were not significantly different among groups, healthy controls were about 2 years older on average than CHR subjects and had a numerically larger proportion of women (42% vs. 25%), hence, percentile scores specific to age and gender were used for assessment of smell identification.

Converters had lower percentile scores than both controls and nonconverters for both the UPSIT (14.6 vs. 19.0 in controls, 18.2 in