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Olfactory identification deficits at identification as ultra-high risk for psychosis are associated with poor functional outcome

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ABSTRACT

Background: We have previously reported that olfactory identification (OI) deficits are a promising premorbid marker of transition from ultra-high risk (UHR) to schizophrenia, but not to psychotic illness more generally. Whether this remains the case at longer follow-up, and whether there is decline in OI ability are unclear.
Method: The University of Pennsylvania Smell Identification Test (UPSIT) was administered to 81 participants at baseline (identification of risk for psychosis) and 254 individuals at follow-up. Forty-nine participants underwent UPSIT assessment at both time points. UPSIT scores were investigated at an average of 7.08 years after identification of risk in relation to transition to psychosis, a diagnosis of schizophrenia, and psychosocial/functional outcome.
Results: UPSIT scores at baseline and follow-up did not differ between participants who transitioned to psychosis and those who did not. Similarly, there were no significant differences on UPSIT scores at baseline or follow-up between individuals with a diagnosis of schizophrenia and transitioned individuals without schizophrenia. Those with a poor functional outcome showed significantly lower baseline UPSIT scores than participants with good outcome. There was no significant association between functional outcome and follow-up UPSIT scores. There were no significant changes in UPSIT over time for any group.
Conclusions: These results suggest that impaired OI is not a good marker of the onset of psychosis and schizophrenia, but may differentiate UHR individuals who experience a poor functional outcome, regardless of transition status.

1. Introduction

Deficits in olfactory identification (OI) are a reliable finding in chronic schizophrenia and first-episode psychosis (Brewer et al., 1996a; Kopala et al., 1993; Rupp, 2010), with a recent meta-analysis demonstrating a medium to large effect size for these deficits (Moberg et al., 2013). They are also present in first-degree relatives (Kamath et al., 2014; Keshavan et al., 2009; Kopala et al., 1998; Moberg et al., 2013; Roalf et al., 2006) and people with schizotypal features, although to a lesser extent (Moberg et al., 2013), suggesting that they are a possible endophenotype for the disorder. This would imply that OI deficits are detectable in at-risk populations before the onset of frank psychotic illness. Indeed there is evidence that young people clinically at ultra-high risk (UHR) for psychosis also show impaired OI (Brewer et al., 2003; Kamath et al., 2014, 2012; Woodberry et al., 2010), with a pooled medium to large effect size (Moberg et al., 2013; Turetsky et al., 2012). Moreover, OI deficits may be a marker of transition from the UHR state to schizophrenia specifically (rather than "psychosis" more generally) (Brewer et al., 2003). It is worth noting, however, that Gill et al. (2014) failed to find a significant reduction in olfactory identification in the UHR sample, nor in relation to the onset of psychosis or schizophrenia.

One possible explanation for these findings is that OI deficits reflect neurodevelopmental compromise during adolescence (Brewer et al., 2006), since the development of OI ability closely parallels orbitofrontal cortex maturation through to adulthood (Doty et al., 1984). This suggests that OI deficits result from arrested prefrontal neural development, given that the lower-order pathways that mediate olfactory detection and sensitivity, despite some abnormalities (e.g. Kayser et al., 2013; Turetsky et al., 2008), allow sensory information to reach orbitofrontal regions (Brewer et al., 2006). This hypothesis is supported by the findings that OI deficits are associated with negative symptoms (Brewer et al., 1996a, 2001; Corcoran et al., 2005; Good et al., 2006;

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Ishizuka et al., 2010) and more specifically, the deficit syndrome of schizophrenia (Strauss et al., 2010).

This model would suggest that baseline OI deficits in at-risk samples would be likely to predict poor functional outcome at follow-up, and that progressive OI impairments (or perhaps failure to show normal developmental gains) would be associated with a later diagnosis of schizophrenia. While it has been reported that baseline OI deficits predict functional outcome four years later (Good et al., 2010) in people with a first episode of psychosis, it is unclear whether that is the case in at-risk samples. One reason this is not yet known is because follow-up times in at-risk research have generally been short and the degree of functional impairment has not been reported. The best available evidence (Barbato et al., 2012; Woodberry et al., 2013) suggests that OI deficits are stable over time in individuals meeting UHR criteria. However, because few of the at-risk participants in these studies developed psychosis, it is unclear whether the development of psychosis or schizophrenia specifically has any impact, or whether those with poor outcome show more decline.

In the current study, we investigated OI in a group of individuals identified as UHR at the Personal Assessment and Crisis Evaluation (PACE) Clinic in Australia between two and 15 years previously, some of whom had also completed the OI task at baseline. Based on our earlier findings (Brewer et al., 2003), we hypothesised that, at follow-up, OI deficits would be more apparent in those individuals with a diagnosis of schizophrenia relative to those who transitioned to psychosis more generally. Furthermore, we expected that baseline OI deficits would be associated with a diagnosis of schizophrenia and poorer functional outcome at follow-up. We expected that OI deficits would not show progressive decline regardless of outcome.

2. Method

2.1. Participants and procedure

Participants were 286 individuals (45.8% male) identified as UHR for psychosis between 2.39 and 14.87 years previously (mean = 7.08; SD = 3.58; median = 6.43). They were part of a larger study (N = 416) aimed at following up all participants consecutively admitted to the PACE Clinic for baseline assessment between 1993 and 2006. Details of the outcome of this cohort are described in Nelson et al. (2013). At follow-up assessment, 254 participants were assessed on the University of Pennsylvania Smell Identification Test (UPSIT; see Table 1). At baseline, 81 participants had been assessed on the UPSIT (Table 2). Findings for this group after clinical follow-up at 18 months post-baseline have been reported previously (Brewer et al., 2003), where we showed that OI deficits were evident in those that developed schizophrenia. An additional nine participants had transitioned to psychosis over the longer follow-up period. Forty nine participants had UPSIT assessment at baseline and follow-up (Table 3).

Detailed criteria for the identification of the UHR group are described by Yung et al. (2003) and are summarized as follows: 1) attenuated positive symptoms, 2) brief limited intermittent psychotic symptoms, and/or 3) trait vulnerability for psychotic illness (schizotypal personality disorder or a history of psychosis in a first-degree relative) and a deterioration in functioning or chronic low functioning. In addition to these inclusion criteria, participants were aged 15 to 30 years and had not experienced a previous psychotic episode (treated or untreated). Exclusion from the current analyses was based on the following criteria: documented organic brain impairment; history of head injury with loss of consciousness; current viral or other severe medical condition, upper respiratory tract disease, cold, sinus problem or hay fever; a history of nasal trauma; documented poor eyesight or hearing; and inadequate command of English. All participants were neuroleptic naive at baseline assessment.

To locate and recontact participants in this cohort, an extensive tracking system was employed [see (Nelson et al., 2013)]. Transition

Table 1
Characteristics of the subsample with UPSIT at follow-up.

Follow-up	UHR-NP (*n* = 186)	UHR-P (*n* = 68)	UHR-P-Other (*n* = 45)	UHR-P-SCZ (*n* = 23)	Good outcome (*n* = 191)	Poor outcome (*n* = 63)	UHR-NP vs UHR-P			UHR-P-Other vs UHR-P-SCZ			Good vs poor outcome		
							Estimate	df	*p*-Value	Estimate	df	*p*-Value	Estimate	df	*p*-Value
UPSIT, *M (SD)*	32.32 (3.96)	31.57 (4.57)	32.24 (4.15)	30.26 (5.15)	32.41 (3.99)	31.24 (4.5)	$F = 1.13$	1,251	0.3	$F = 2.49$	1,65	0.1	$F = 3.56$	1,251	0.06
Age (years), *M (SD)*	25.51 (4.88)	27.59 (5.34)	27.04 (5.10)	28.65 (5.75)	25.88 (5.09)	26.60 (5.05)	$t = -2.94$	252	0.004	$t = -1.18$	66	0.2	$t = -0.97$	252	0.3
Length of follow-up, *M (SD)*	6.84 (3.18)	8.85 (3.07)	8.82 (3.01)	8.89 (3.24)	7.18 (3.13)	7.95 (3.62)	$t = -4.50$	252	<0.001	$t = -0.09$	66	>0.9	$t = -1.50$	94.4	0.1
Female gender, *N (%)*	106 (57.0)	40 (58.8)	29 (47.8)	11 (64.4)	116 (60.7)	30 (47.6)	$\chi^2 = 0.01$	1	>0.9	$\chi^2 = 1.12$	1	0.3	$\chi^2 = 2.82$	1	0.07
Cigarette smoker, *N (%)*	82 (44.1)	34 (53.1)	26 (57.8)	8 (34.8)	87 (45.5)	29 (46.0)	$\chi^2 = 0.51$	1	0.5	$\chi^2 = 2.83$	1	0.1	$\chi^2 = 0.00$	1	>0.9
Ever a regular THC user, *N (%)*	56 (30.1)	22 (32.4)	15 (33.3)	7 (30.4)	56 (29.3)	22 (34.9)	$\chi^2 = 0.25$	1	0.6	$\chi^2 = 0.02$	1	0.9	$\chi^2 = 0.57$	1	0.5
Neuroleptic medication in past 2 years, *N (%)*	5 (2.7)	33 (48.5)	17 (37.7)	16 (69.6)	17 (8.90)	21 (33.3)	$\chi^2 = 79.99$	1	<0.001	$\chi^2 = 3.60$	1	0.03	$\chi^2 = 21.85$	1	<0.001
Current Full-Scale IQ, *M (SD)*	102.51 (14.31)	98.17 (15.31)	97.69 (17.01)	99.19 (11.15)	103.12 (14.21)	96.05 (14.90)	$t = 2.08$	249	0.04	$t = -0.37$	64	0.7	$t = 3.36$	249	0.001
BPRS psychotic subscale, *M (SD)*	5.70 (2.31)	8.81 (4.93)	7.09 (3.34)	12.17 (5.83)	5.60 (2.56)	9.37 (4.37)	$t = -4.99$	78.1	<0.001	$t = -3.87$	29.6	0.001	$t = -6.48$	76.6	<0.001
SANS total score, *M (SD)*	9.39 (11.58)	16.50 (16.60)	11.18 (11.66)	26.91 (19.89)	6.04 (6.77)	27.11 (16.01)	$t = -3.25$	92.2	0.002	$t = -3.50$	30.0	0.001	$t = -10.15$	69.5	<0.001

Abbreviations: UHR-P, transitioned to psychosis; UHR-NP, not transitioned to psychosis; UHR-P-SCZ, transitioned and has diagnosis of schizophrenia; UHR-P-Other, transitioned, but with no schizophrenia diagnosis; THC, tetrahydrocannabinol; BPRS, Brief Psychiatric Rating Scale; SANS, Scale of Assessment for Negative Symptoms.