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Deficits in the identification of pleasant odors predict the transition of an at-risk mental state to psychosis

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ABSTRACT

Objective: Existing knowledge of the relationship between olfactory identification (OI) ability and clinical risk of psychosis is inconsistent. To address this inconsistency, the aim of the present study was to identify the relationship between OI ability, with regard to the hedonic attributes of odors, and the risk of transition to psychosis in individuals with an ARMS.
Methods: A group of 81 individuals meeting the ARMS criteria according to the Comprehensive Assessment of At Risk Mental State were at baseline administered with the University of Pennsylvania Smell Identification Test. The hedonic attributes of odorants were normatively established. Participants were followed up for transition to psychosis for a mean period of 36.1 months (SD:27.5 months).
Results: The presence of deficits in the identification of pleasant odors was found to be a risk factor for conversion from an ARMS to schizophrenia. The hazard ratio for each point in deficit scores in the Cox regression model was 1.455 (95% CI: 1.211–1.747), $p < 0.0001$.
Significant deficits in the identification of pleasant odors were associated with a risk for conversion at both early and late time points from baseline.
Conclusions: The findings imply that the impaired identification of pleasant odorants may be a risk factor for the transition of an ARMS into a psychotic disorder, and highlights the need for further research of OI in "at-risk" cohorts, taking into account the hedonic attributes of odors.

1. Introduction

The olfactory system shares common origins with the central nervous system, and its development is strongly genetically determined (Treloar et al., 2010). Hence, the system has become a subject of interest in studies on the pathogenesis of schizophrenia, which itself is considered a neurodevelopmental disorder with genetic determinants (Murray, 1994). The presence of olfactory impairment in schizophrenia has been widely documented, with an effect size estimated as medium to large (Moberg et al., 1999, 2014; Turetsky et al., 2009). This impairment manifests itself as a wide variety of abnormalities, including impairments in odor detection threshold (Isseroff et al., 1987; Rupp et al., 2005a; Serby et al., 1990), odor identification (Brewer et al., 2001; Hurwitz et al., 1988; Houlihan et al., 1994; Kamath et al., 2014; Kästner et al., 2013; Kopala et al., 1993) and odor discrimination abilities (Rupp et al., 2005a), as well as odor memory (Campbell and Gregson, 1972; Wu et al., 1993). There is also a growing body of evidence suggesting that the hedonic judgment of smells is also impaired in schizophrenia, with various patterns of misassignment being attributed to the hedonic valence of odors (Crespo-Facorro et al., 2001; Doop and Park, 2006; Hudry et al., 2002; Kamath et al., 2011a, 2011b, 2013b; Moberg et al., 2003; Plailly et al., 2006; Rupp et al., 2005b). Neuroanatomical, cellular and even intracellular mechanisms have been recognized to play a role in olfactory deficits in schizophrenia (Borgmann-Winter et al., 2016; Egbujo et al., 2015; for a review see Turetsky et al., 2009).

Some studies report the presence of olfactory identification deficits (OIDs) in non-affected first-degree relatives of patients with schizophrenia, including monozygotic twins discordant for the illness (Kamath et al., 2014; Kopala et al., 1998, 2001; Roalf et al., 2006; Turetsky et al., 2008). Results from both the clinical and biological domains suggest that OIDs may be a potential vulnerability marker of schizophrenia (Moberg et al., 2014; Turetsky et al., 2008).

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In the case of schizophrenia, clinical signs of abnormal functioning are present long before the development of the frank psychosis (Jones et al., 1994). It can therefore be assumed that other manifestations of neurodevelopmental pathology should be present in early phases of the disease, including prodromal ones. Over the years, the concept of the prodrome (Mayer-Gross, 1932) has evolved into that of the ultra-high risk-UHR or at-risk mental state-ARMS (Yung and McGorry, 1996). While the predictive value of ARMS is relatively low when defined based solely on clinical symptoms, with the conversion rate reaching approximately 36% within a three-year follow-up period (Fusar-Poli et al., 2012), the validity of the ARMS concept could be improved with the inclusion of complementary tools addressing, inter alia, neurobiological features (Fusar-Poli et al., 2013; Modinos and McGuire, 2015). One encouraging tool, potentially allowing the evaluation of further risk of transition from ARMS to psychosis, could be the assessment of smell identification ability. Although only few studies regarding olfactory impairment have been performed in clinical high risk for psychosis (CHR) cohorts, some indicate that olfactory deficits are in fact, more common in "at-risk" individuals than healthy controls (Kamath et al., 2014; Woodberry et al., 2010). The results, however, are conflicting, and the findings regarding OID and the future transition of ARMS to psychosis are inconsistent (Brewer et al., 2003; Gill et al., 2014; Lin et al., 2015).

Only one study has attempted to determine the effect of odor hedonic valence on olfactory identification (OI) in CHR individuals; in this case, the hedonic valence of an odor was found to have a significant effect on identification accuracy (Kamath et al., 2013b). No follow-up for transition of CHR state to psychosis was performed in this study. Hence, it is accepted within the field that further studies of olfactory dysfunctions are required in CHR individuals (Moberg et al., 2014; Turetsky et al., 2012). No study has yet investigated the associations between the identification of odors from different hedonic categories and the transition to psychotic disorders.

The objective of the present study was to identify the relationship between general smell identification ability as well as OI performance, according to the hedonic attributes of the odors, and the risk of conversion to psychosis in a cohort of ARMS individuals.

2. Methods

2.1. Settings and subjects

Eighty-one individuals aged 15–32 years meeting the criteria of an ARMS were included in the study. All were recruited from the 105 participants of the Programme of Recognition and Therapy (PORT), which is a programme affiliated with the Medical University of Łódź, Poland, intended for young people at risk of developing a psychotic disorder. The PORT programme is described in detail elsewhere (Kotlicka-Antczak et al., 2015).

The following exclusion criteria were used: 1) the presence of a known organic disease of the central nervous system, 2) evidence of intellectual disability, 3) a diagnosis of psychotic disorder or 4) current infectious or allergic rhinitis, 5) current sinusitis, 6) current upper respiratory tract disease, 7) report of nasal trauma or anatomical anomalies within nasal cavities, 8) severe general medical condition.

2.2. Baseline clinical assessment

ARMS was identified with the use of the Comprehensive Assessment of At Risk Mental State-CAARMS (Yung et al., 2005), Polish Version (Jaracz et al., 2012). According to CAARMS outlines, subjects were classified to one of the three following ARMS subgroups: 1) attenuated psychotic symptoms-APS (psychotic symptoms that do not reach the level of psychosis in terms of either their intensity or frequency in the previous year), 2) brief limited psychotic symptoms-BLIPS (a recent episode of brief psychotic symptoms that resolved spontaneously within one week) or 3) vulnerability or genetic risk type-VUL (having a first-degree relative with a psychotic disorder, or symptoms of schizotypal personality disorder). Additionally, the criterion of a functional decline within the past 12 months had to be met in all cases. If the person met the criteria for more than one ARMS subtype, they were classified as presenting double features: for example, APS plus VUL.

The CAARMS composite score was calculated by weighting the intensity of four positive symptoms domains by their frequency (Lim et al., 2015).

The level of psychosocial functioning was evaluated with the Social and Occupational Assessment Scale (SOFAS), as an essential part of CAARMS (Yung et al., 2005).

Comorbid disorders, including substance misuse, were diagnosed using the Structured Clinical Interview for DSM-IV-Axis I Disorders-SCID I (First et al., 1997).

Demographic data was obtained with the use of a semi-structured interview.

Since the study was a part of a larger one addressing a range of risk factors of conversion to psychosis, all participants underwent an analysis of their past medical history, together with a physical and psychological examination. The results were used as a basis for potential exclusion from the study. Cigarette smoking status, expressed as pack-years, was established through a clinical interview.

The study was carried out in accordance with the latest version of the Declaration of Helsinki. The study protocol was accepted by the Medical University of Łódź Ethics Committee. Written informed consent was obtained from all participants. If subject was a minor, further consent was also obtained from a parent.

2.3. Assessment of odor identification

OI assessment was performed at baseline, by an assessor blinded to the baseline CAARMS status, using the University of Pennsylvania Smell Identification Test-UPSIT (Doty et al., 1984), consisting of 40 "scratch & sniff" strips with particular odorants. The subject scratched the provided strips with an attached pencil and chose the name of each odor from four alternatives provided, with a correct selection being scored as one point. The test was self-administered under the supervision of a trained researcher, with odorants being sniffed birhinally. Study participants were instructed to refrain from smoking or applying any kind of fragrance on the day of testing. A previously-created Polish version of the test was used (Doty, 2015; Podskarbi-Fayette et al., 2005). The hedonic attributes of odorants were normatively established according to the UPSIT outlines. Sixteen odors from the 40 included in the test were classified as pleasant, 15 as neutral and nine as unpleasant (Doty et al., 1984).

2.4. Treatment

The study participants did not receive standardized treatment. According to PORT rules, the main therapeutic interventions were psychological. Treatment with antipsychotics was implemented only in response to clinical indications, according to the International Clinical Practice Guidelines for Early Psychosis (International Early Psychosis Association Writing Group, 2005). Alternatively, antipsychotic treatment administered before entering the study could be continued if the participants expressed their willingness. In clinically justified situations, comorbid disorders were pharmacologically treated.

2.5. Outcome measures

The study participants were followed-up every three months (or more often, if required) with clinical symptoms being evaluated with CAARMS. All follow-up CAARMS evaluations were performed by a clinician blind to olfactory status. A CAARMS-based psychosis threshold defined as a score of six (maximum) on the CAARMS Positive Symptoms subscales (a score greater to or equal to five was required only for the Perceptual Abnormalities subscale), with the symptoms at a frequency

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