



# Olfactory and cognitive functions in Chinese individuals at clinical high risk for psychosis

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## ABSTRACT

The abnormal olfactory function has been regarded as a sign in psychosis. To confirm the theory that olfactory and cognitive functions are deficient in Chinese cohort with clinical high risk state of psychosis, 19 individuals at clinical high risk for psychosis (CHRs) and 37 healthy controls (HCs) were recruited. The CHRs scored significantly lower than the HCs in the olfactory identification test and all other cognitive tests. Our findings suggest that olfactory dysfunction may be an early change of psychosis.

## 1. Introduction

The olfactory system, which consists of the primary system (the olfactory epithelium and the olfactory bulb) and the secondary system (olfactory cortex), is one of the oldest human sensory systems for human. It is genetically and embryologically derived from the Central Nervous System (CNS), and also overlaps structurally with brain regions related to psychosis (Treloar et al., 2010). The olfactory bulb (OB) and hippocampus are the two most potential brain regions as they retain the capacity for lifelong neurogenesis (Lavoie et al., 2017). This coincides with the appearance of psychosis; most psychosis may occur at any age, but usually during early adulthood. In addition, this two brain regions are also belong to the limbic system, which is considered to be related to cognitive functions, such as memory and executive function. Although the importance of the hippocampus in psychosis has been well documented (Reif et al., 2007), the role of the olfactory system is still insufficiently studied. Based on the above and the consensus that cognitive dysfunction is a new core symptom of psychosis, we hypothesized that olfactory dysfunction probably occurs with the manifestation of psychotic symptoms and cognition impairments.

There are several studies that have reported the olfactory deficits in schizophrenia patients (SZs and those at clinical high risk for psychosis (CHRs) (Kotlicka-Antczak et al., 2017; Lin et al., 2015; Moberg et al., 2014; Takahashi et al., 2017). Some studies have outcome data and

have found CHRs with later psychosis onset tend to have worse olfactory functions, though the results are inconsistent (Brewer et al., 2003; Kotlicka-Antczak et al., 2017; Lin et al., 2015; Woodberry et al., 2010). However, olfactory function is highly correlated with culture (Kobayashi et al., 2006) and most of these studies were either focused on populations in the West or used tests that were developed for those in the West such as the UPSIT (University of Pennsylvania Smell Identification Test) (Doty et al., 1984) and the Sniffin's Sticks test (Hummel et al., 1997). The olfactory cortex is physically close to the auditory association, memory areas (hippocampus) and executive region (cingulate gyrus). Therefore in this study, we compared the olfactory identification function and cognitive functions (verbal memory and executive function) of CHRs and HCs by using the OSIT-J (Odor Stick Identification Test for Japanese) (Saito et al., 2006) in a Han Chinese population. We not only verified whether there is an olfactory identification deficit in Han Chinese CHRs, but also explored its relationship with cognition.

## 2. Methods

### 2.1. Participants

Nineteen CHRs and thirty-seven HCs were recruited at the Second Xiangya Hospital in Changsha, China. All participants were 13–30 years

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**Table 1**  
General characteristics and cognitive functions of the recruited subjects (mean  $\pm$  S.D.).

Variable	CHR ( <i>n</i> = 19)	HC ( <i>n</i> = 37)	adjusted <i>p</i> -value
Age [years]	20.47 $\pm$ 4.57	22.08 $\pm$ 3.35	0.140
Gender (male, female)	15 M, 4F	20 M, 17F	0.068
Education [years]**	11.26 $\pm$ 2.51	14.77 $\pm$ 2.79	< 0.001
HVLT-R total recall score**	21.21 $\pm$ 6.50	28.62 $\pm$ 3.52	< 0.001
HVLT-R delayed recall score**	8 $\pm$ 3.07	10.64 $\pm$ 1.55	0.002
TMT-A time**	42 $\pm$ 16.20	30.64 $\pm$ 8.48	0.009
TMT-B time**	138.06 $\pm$ 100.41	78.90 $\pm$ 28.91	0.005
SCWT-DOTS time**	25.74 $\pm$ 12.08	14.81 $\pm$ 4.11	< 0.001
SCWT-WORDS time**	27.06 $\pm$ 12.81	16.02 $\pm$ 3.18	< 0.001
SCWT-COLORS time**	44.02 $\pm$ 20.55	26.58 $\pm$ 6.48	0.003
OSIT-J score**	6.32 $\pm$ 2.52	8.16 $\pm$ 1.80	0.007

CHR, individuals at clinical high risk for psychosis; HC, health controls; ChiSq, Chi-square; M, male; F, female; HVLT-R, Hopkins Verbal Learning Test-Revised; TMT-A, Trail Making Test, Part A; TMT-B, Trail Making Test, Part B; SCWT-DOTS, Stroop Color Word Test, Dot Part; SCWT-WORDS, Stroop Color Word Test, Word Part; SCWT-COLORS, Stroop Color Word Test, Color-Word Part; OSIT-J, Odor Stick Identification Test for Japanese.

\*\* The difference between the groups is significant with a *p*-value less than 0.01.

old non-smoking drug-naive Han Chinese. Their demographic characteristics are detailed in Table 1. All HCs were screened for lifetime absence of mental disorders using the DSM-IV-TR criteria (APA, 2000) and were confirmed to have no family history of psychiatric disorder in their first-degree relatives. All CHR subjects were screened and identified by the Structured Interview for Prodromal Syndromes (SIPS) (McGlashan et al., 1997). Exclusion criteria for all subjects included: anosmia, nasal congestion, upper respiratory tract infections and serious organ disorders.

## 2.2. Olfactory evaluation

We applied the OSIT-J to evaluate the olfactory identification ability. The OSIT-J, which was developed by Saito et al. (2006), consists of 12 odors that are familiar to East Asians. After the subjects smelled 12 test odors one at a time, they had to choose from six options - the names of four different odors, one "unknown" odor and one "odor not detected". The total score is 12 and only a correct selection could count as one point.

## 2.3. Cognitive assessment

All subjects were assessed with the HVLT-R (Hopkins Verbal Learning Test-Revised) (Benedict et al., 1998), TMT (Trail Making Test) (Reitan and Wolfson, 1985) and SCWT (Stroop Color Word Test) (Stroop, 1935) to evaluate their verbal memory and executive function.

## 2.4. Statistical analyses

Statistical analyses were conducted using SPSS 20.0. Demographic characteristics were applied using the Chi-square test. The Student's *t*-test and Mann-Whitney U test were used to detect the statistical differences. Relationships between variables were evaluated with the Spearman's rank correlation test and the false discovery rate of multiple comparisons was controlled by the Benjamini & Hochberg method. The threshold of significance (*p*) was fixed at 0.05 for two-tailed test. The absolute value of the correlation coefficient ( $r_s$ ) between 0.3 and 0.7 indicated a moderate linear relationship.

## 3. Results

There were no significant differences in age ( $p = 0.140$ ) and gender ratio ( $p = 0.068$ ) between the CHR and HC group. The CHRs had significantly lower scores than the HCs in the OSIT-J (adjusted for age and gender) and all other cognitive tests including HVLT-R, TMA and SCWT (see Table 1).

Regarding the relationships between olfactory score and cognitive variables- we found that olfactory score has a moderate positive correlation with HVLT-R total recall score ( $r_s = 0.443$ ,  $p = 0.005$ ) and HVLT-R delayed recall score ( $r_s = 0.329$ ,  $p = 0.023$ ) and moderate negative correlations with TMT-B time ( $r_s = -0.379$ ,  $p = 0.01$ ) and all three SCWT sub-test times ( $r_s = -0.393$ ,  $p = 0.008$ ;  $r_s = -0.408$ ,  $p = 0.007$  &  $r_s = -0.478$ ,  $p < 0.001$  respectively). Other than that, there is no significant impacts of age ( $r_s = 0.034$ ,  $p = 0.801$ ) and education ( $r_s = 0.209$ ,  $p = 0.143$ ) on the olfactory score.

## 4. Discussion

To our knowledge, this is the first olfactory test in Han Chinese CHRs. Similar studies were all focused on Chinese with schizotypy rather than CHR (Zou et al., 2018, 2015). Even though we used a new smell identification tool, the olfactory function difference between CHRs and HCs was significant which is consistent with previous studies (Moberg et al., 2014). This result confirmed that the olfactory function was already impaired before the full onset of psychosis. But considering the inconsistent results from olfactory studies of FHRs (individuals at familial high risk for psychosis) (Moberg et al., 2014), we need more longitudinal studies to determine the exact time that olfactory impairment occurs. Moreover, the CHRs showed significantly worse verbal memory and executive functions compared to HCs. Except for the TMT-A time, all cognitive functions we measured were correlated with the olfactory identification ability. This reflects a global and interactive impairment of the limbic system (including hippocampus, OB, cingulate gyrus, etc.) during the progress of psychosis. However, there are several limitations of this study which include the small sample size, the nearly unbalanced gender ratio and the lack of outcome data for now. Hence, further studies with a larger sample size matched for gender and education are required to validate our findings.

In conclusion, this study is a preliminary exploration of olfactory function at clinical high risk state of psychosis and adds to the evidence that the olfactory system may be associated with the pathogenesis of psychosis.

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