



## The neural basis of olfactory function and its relationship with anhedonia in individuals with schizotypy: An exploratory study

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### ABSTRACT

Previous studies have established a linkage between olfactory deficits and negative symptoms in schizophrenia. However, it is not known whether olfactory function is associated with hedonic traits in individuals with schizotypy. Seventeen individuals with schizotypy and 18 age- and sex-matched controls participated in this study. Hedonic traits were assessed with the Chapman Scales for Physical and Social Anhedonia (CSAS and CPAS). Olfactory function was assessed with the Sniffin' Stick Test (olfactory threshold, odour discrimination and odour identification). All participants undertook a structural imaging scan for grey matter volume measurements. Individuals with schizotypy had significantly higher CSAS and CPAS scores than healthy controls. They had normal olfactory function. Their odour identification ability was inversely correlated with physical and social anhedonia. The volume of the right parahippocampal gyrus was positively associated with odour identification ability, and negatively associated with physical and social anhedonia. Furthermore, mediation analysis suggested that odour identification ability influences anhedonia through its effect on the right parahippocampal gyrus. No such relationship was found in controls. These findings suggest that there is a relationship between odour identification and anhedonia in individuals with schizotypy, and the association may be mediated by parahippocampal gyrus volume.

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### 1. Introduction

Previous studies have established a link between olfactory deficits and negative symptoms in schizophrenia (Brewer et al., 1996; Malaspina et al., 2002; Malaspina and Coleman, 2003; Corcoran et al., 2005; Good et al., 2006; Moberg et al., 2006; Ishizuka et al., 2010; Strauss et al., 2010). In particular, Ishizuka et al. (2010) found that anhedonia was associated with odour identification deficits. However, it is not known whether olfactory function is associated with hedonic traits in individuals with schizotypy, and if so what the underlying mechanism is.

There is a significant overlap in the neural circuitry that subserves olfactory and emotional processing as well as the pathophysiology of schizophrenia, including the orbitofrontal cortex (OFC), the amygdala, the hippocampus and the parahippocampal gyrus (the entorhinal and perirhinal cortices) (Harrison, 1999; Shenton et al., 2001; Esiri and Crow, 2002; Gottfried and Zald, 2005; Schneider et al., 2007; Kamath et al., 2013). Therefore, it is interesting to investigate the role of the above-mentioned brain regions in the association between olfactory function and hedonic traits.

The purpose of the present study was to explore the correlations between olfactory function and hedonic traits in individuals with schizotypy. We also examined the role of olfactory-related brain regions involved in this association. We hypothesised that olfactory function would be negatively associated with anhedonia, and the grey matter volume in olfactory-related brain regions would mediate such an association.

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## 2. Methods

### 2.1. Participants

Participants were recruited from a sample of 1780 sophomore students in the Guangzhou Medical University, according to their scores on the Schizotypal Personality Questionnaire (SPQ) (Raine, 1991; Chen et al., 1997). According to Raine (1991), people scoring in the top 10% were identified as exhibiting schizotypal traits. In our sample, 223 individuals who scored higher than 36 were classified as individuals with schizotypy and 17 of them were randomly recruited to participate in this study. At the same time, 18 individuals who scored lower than 20 were recruited as healthy controls. The mean age of the schizotypy and control group was 20.94 years ( $SD=0.13$ ) and 20.89 years ( $SD=0.25$ ) respectively. There were no significant differences between the two groups in age and gender (see Table 1). All participants were right-handed and were free from ear–nose–throat problems. In addition, none reported any personal or family history of psychosis, depression, suicide, epilepsy or drug abuse. All participants gave informed consent to participate in the study, which was approved by the Ethics Committee of the Institute of Psychology, the Chinese Academy of Sciences. Informed consent was obtained from all the participants prior to testing.

### 2.2. Sniffin' sticks olfactory test

Olfactory function was assessed birhinally using the standardized "Sniffin' Sticks" test battery that included three tests, namely test for olfactory threshold (T), odour discrimination (D), and odour identification (I) (Hummel et al., 1997; Kobal et al., 2000) (see Supplementary Methods).

### 2.3. Hedonic traits

Self-reported hedonic traits was assessed with an adapted version of the Chapman Scales for Physical and Social Anhedonia (CPAS and CSAS) (Chapman et al., 1976; Chan et al., 2012). The CPAS consists of 61 True–False items, with higher scores indicating more severe physical anhedonia. The CSAS consists of 40 True–False items, with higher scores indicating less pleasure from social interactions. The Cronbach's alpha coefficients for the Chinese version of the CPAS and the CSAS were 0.85 and 0.86 respectively, indicating good internal consistency (Chan et al., 2012).

In addition, all the participants were administered the short form (e.g., information, arithmetic, similarities and digit span) of the Chinese version of the Wechsler Adult Intelligence Scale–Revised (WAIS-R) (Gong, 1992).

**Table 1**  
Participant characteristics, anhedonia, and olfactory test performance.

	Schizotypy (n=17)	Controls (n=18)	t/ $\chi^2$	p
Age (years)	20.94 ± 0.56	20.89 ± 1.08	−0.18	0.86
Gender (male/ female)	7/10	7/11	0.019	1
IQ	112.94 ± 10.85	119.00 ± 10.74	1.66	0.89
SPQ	42.59 ± 8.37	8.33 ± 5.52	−14.38	< 0.001
Anhedonia				
CPAS	15.41 ± 8.53	8.56 ± 6.00	−2.76	0.009
CSAS	11.18 ± 5.03	5.17 ± 4.74	−3.64	0.001
Olfactory test				
Identification	11.00 ± 1.66	10.89 ± 1.45	−0.21	0.83
Discrimination	12.53 ± 1.46	12.06 ± 1.80	−0.85	0.40
Threshold	11.97 ± 2.29	11.31 ± 2.80	−0.75	0.46

Note. SPQ: Schizotypal Personality Questionnaire; CPAS: Chapman Physical Anhedonia Scale; CSAS: Chapman Social Anhedonia Scale

### 2.4. MRI acquisition and pre-processing

Imaging data were collected on a 3T Siemens Verio scanner (Erlangen, Germany) at the Department of Radiology, Guangzhou First People's Hospital, using a 12-channel phased-array head coil. The T1-weighted images were acquired using a 3D magnetisation prepared gradient rapid acquisition gradient echo (MPRAGE) sequence, with the following parameters (TR, 2530 ms; TE, 2.34 ms; TI, 1100 ms; FOV, 256 mm; voxel size, 1 × 1 × 1 mm; flip angle = 7°, 192 contiguous slices of 1 mm thickness).

Data preprocessing was performed in VBM8 toolbox (available at <http://dbm.neuro.uni-jena.de/vbm/>) implemented through SPM8 software (available at <http://www.fil.ion.ucl.ac.uk/spm>). The MR images were first segmented for grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) using the new segmentation tools. Subsequently, these segmented grey matter images were spatially normalised to the customised template in standardized anatomical space using Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) (Ashburner, 2007). Finally, the images were smoothed with a Gaussian kernel (full width at half maximum = 8 mm) and normalised to MNI space. The sum of the volume of GM, WM and CSF for each participant was the total intracranial volume (TIV) (Ashburner and Friston, 2000).

The anatomical regions of interest (ROIs) implicated in olfactory and emotional processing were selected from the Automated Anatomic Labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002) as follows: the amygdala, the hippocampus, the parahippocampal gyrus, the left (Frontal\_Inf\_Orb\_L, Frontal\_Med\_Orb\_L, Frontal\_Sup\_Orb\_L) and the right (Frontal\_Inf\_Orb\_R, Frontal\_Med\_Orb\_R, Frontal\_Sup\_Orb\_R) orbitofrontal cortex (OFC). The averaged grey matter volume was then extracted from the unilateral ROIs for each individual using the Marsbar toolbox (<http://marsbar.sourceforge.net/>; Brett et al., 2002).

### 2.5. Data analysis

#### 2.5.1. Independent-samples T test and preliminary correlation

Statistical analyses were performed with SPSS (version 17.0) for windows (SPSS, Chicago, IL). Independent-samples T test was used to compare individuals with schizotypy and controls for continuous variables. Partial correlation within each group was used to correlate CPAS and CSAS with each of the olfactory test (identification, discrimination and threshold) score controlling for age and gender ( $p < 0.05$ ). Then, correlations between the volume of the predefined ROIs and the score of the olfactory test which had a significant association with CPAS or CSAS were calculated by partial correlation analysis controlling for age, gender and TIV ( $p < 0.05$ ). Finally, the same method was used to analyse the relationship between the volume of olfactory-related ROIs and anhedonia (CPAS and CSAS).

#### 2.5.2. Mediation analysis

Mediation analysis was conducted using SPSS PROCESS macro (Hayes, 2008) to examine the hypothesis that the volume of olfactory-related ROIs accounted for the link between olfactory function and anhedonia. In the hypothesised mediation model (see Fig. 4A), olfactory function (X) was the independent variable, the volume of olfactory-related ROIs (M) was the mediator, and anhedonia (Y) was the dependent variable. The direct effect of X on Y after controlling for mediator M was  $c'$  and the indirect effect of X on Y through M was  $ab$ . The bootstrapping method (with 5000 bootstrap samples) outlined by Shrout and Bolger (2002) was implemented. We selected the use of 90% confidence intervals (CIs) over 95% CIs to avoid type II errors, similar to Caes et al. (2011) and Reuther et al. (2010). Data from the group which

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