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


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Article info

Article history:
Received 3 May 2015
Received in revised form 31 August 2015
Accepted 2 September 2015
Available online 8 September 2015

Keywords:
Olfaction
Anhedonia
Schizotypy
Imaging

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.
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. Sniffing sticks olfactory test

Olfactory function was assessed bilaterally using the standardized “Sniffing Sticks” test battery that included three tests, namely test for olfactory threshold (T), odor discrimination (D), and odor 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

<table>
<thead>
<tr>
<th></th>
<th>Schizotopy (n = 17)</th>
<th>Controls (n = 18)</th>
<th>t/z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>20.94 ± 0.56</td>
<td>20.89 ± 1.08</td>
<td>-0.18</td>
<td>0.86</td>
</tr>
<tr>
<td>Gender (male/ female)</td>
<td>7/10</td>
<td>7/11</td>
<td>0.019</td>
<td>1</td>
</tr>
<tr>
<td>IQ</td>
<td>112.94 ± 10.85</td>
<td>119.00 ± 10.74</td>
<td>1.66</td>
<td>0.89</td>
</tr>
<tr>
<td>SPQ</td>
<td>42.59 ± 8.37</td>
<td>8.33 ± 5.52</td>
<td>-14.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anhedonia</td>
<td>15.41 ± 5.83</td>
<td>8.56 ± 6.00</td>
<td>-2.76</td>
<td>0.009</td>
</tr>
<tr>
<td>CSAS</td>
<td>11.18 ± 5.03</td>
<td>5.17 ± 4.74</td>
<td>-3.64</td>
<td>0.001</td>
</tr>
<tr>
<td>Olfactory test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Identification</td>
<td>11.00 ± 1.66</td>
<td>10.89 ± 1.45</td>
<td>-0.21</td>
<td>0.83</td>
</tr>
<tr>
<td>Discrimination</td>
<td>12.53 ± 1.46</td>
<td>12.06 ± 1.80</td>
<td>-0.85</td>
<td>0.40</td>
</tr>
<tr>
<td>Threshold</td>
<td>11.97 ± 2.29</td>
<td>11.31 ± 2.80</td>
<td>-0.72</td>
<td>0.46</td>
</tr>
</tbody>
</table>

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 (Tour�io-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
demonstrated a significant relationship between olfactory function and anhedonia, (the schizotypy group) were used in this analysis.

3. Results

3.1. Participant characteristics, anhedonia, and olfactory test performance

Individuals with schizotypy and controls did not differ in demographic characteristics, IQ, olfactory test performance (see Table 1) and the predefined ROI grey matter volume (see Table S1). However, individuals with schizotypy had significantly higher CPAS \((t_{33} = -2.76, p = 0.009, d = 0.93, 95\% CI [-11.91, -1.81])\) and CSAS scores \((t_{33} = -3.64, p = 0.001, d = 1.22, 95\% CI [-9.37, -2.65])\) than healthy controls.

Furthermore, odour identification ability was inversely correlated with physical \((r = -0.61, p = 0.017)\) and social anhedonia \((r = -0.52, p = 0.049)\) after controlling for age and gender in the schizotypy group (see Fig. 1). Such correlations were not significant for the other olfactory tests (i.e. discrimination and threshold). In addition, no such relationship was observed in controls.

3.2. Correlations between grey matter volume, olfactory function and anhedonia

The results showed that participants with higher odour identification score had larger grey matter volume at the right parahippocampal gyrus in individuals with schizotypy after controlling for age, gender and TIV \((r = 0.55, p = 0.043)\) (see Fig. 2). This association was not observed with the other predefined ROIs. Furthermore, anhedonia were negatively correlated with grey matter volume of the right parahippocampal gyrus in individuals with schizotypy after controlling for age, gender and TIV (CPAS: \(r = -0.61, p = 0.019\); CSAS: \(r = -0.60, p = 0.022\)) (see Fig. 3). This was not observed in healthy controls.

3.3. Mediation analyses

The preliminary results showed that odour identification ability and anhedonia were significantly related to grey matter volume of the right parahippocampal gyrus in the schizotypy group. In addition, grey matter volume of the right parahippocampal gyrus appeared to mediate the relationship between odour identification and anhedonia (CPAS: \(ab = -1.10, 90\% CI [-4.09, -0.08]\); CSAS: \(ab = -0.55, 90\% CI [-2.03, -0.01]\)). The direct effect of odour identification on anhedonia was not significant (CPAS: \(c' = -0.99, 90\% CI [-3.26, 1.28]\); CSAS: \(c' = -0.85, 90\% CI [-2.18, 0.48]\)) (see Fig. 4B).

4. Discussion

The present study aimed to explore the correlation between olfactory function and anhedonia, and the role of olfactory-related brain regions in this relationship in individuals with schizotypy. To the best of our knowledge, this is the first study examining a brain-based mediating factor of the association between olfactory function and anhedonia. Individuals with schizotypy had significantly higher CSAS and CPAS scores than the healthy controls and had normal olfactory function. In people with schizotypy, odour identification ability was inversely correlated with both physical and social anhedonia. The grey matter 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 influenced anhedonia through its effect on the right parahippocampal gyrus.

Most of the extant literature on anhedonia has mainly focused on the effect of decreased reward and impaired memory for reward (Dodell-Feder et al., 2014). Since there is a significant overlap in the brain regions that subserve olfaction and emotional processing as well as the pathophysiology of schizophrenia (Schneider et al., 2007; Kamath et al., 2013), olfactory measures may have a unique advantage in investigating anhedonia in schizophrenia spectrum disorders. Our findings that individuals with schizotypy exhibited significant levels of social and physical anhedonia are consistent with previous studies (Yan et al., 2011; Chan et al., 2012; Wang et al., 2014). In addition, the lack of difference in odour identification ability in individuals with schizotypy relative to healthy controls is also consistent with previous studies (e.g. Kamath and Bedwell, 2008, see also Moberg et al., 2014). Furthermore, we demonstrated a previously investigated link between olfactory function and anhedonia in individuals with schizotypy. In the present study, odour identification ability was correlated with anhedonia in individuals with schizotypy. In the present study, odour identification ability was correlated with anhedonia in individuals with schizotypy, similar to previous studies in patients with psychosis (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) and clinically high-risk individuals (Kayser et al., 2013).

The strength of the relationship between odour identification ability and physical and social anhedonia appeared to be mediated by parahippocampal gyrus grey matter volume. Segura et al. (2013) reported a significant positive correlation between odour identification ability and parahippocampal grey matter volume. In addition, the right parahippocampal gyrus has also been found to be activated when processing happy emotions in previous studies (Ramnani and Miall, 2003; Domes et al., 2010; Rahko et al., 2010; Huang et al., 2013). In individuals with schizophrenia, many studies have reported smaller parahippocampal gyri (Becker et al., 1990; Deborah Dauphinais et al., 1990; Jernigan et al., 1991; Shenton et al., 1992; Kawasaki et al., 1993; Prasad et al., 2004). Specifically, individuals with schizophrenia responded with decreased parahippocampal gyrus activation to affective pictures and human faces (Gur et al., 2002; Taylor et al., 2002; Takahashi et al., 2004) and reward prediction (Juckel et al., 2006). Such deficits in patients with schizophrenia may help explain the relationship between olfaction and anhedonia.

Several limitations were inherent in the present study. First, the sample size of psychometrically-defined schizotypy was small. A larger sample size, including prodromal cases and clinically diagnosed patients with schizophrenia, is desirable in future research. In addition, with a larger sample size in future studies, it is also important to address the impact of gender. Nonetheless, we were able to replicate the results of previous studies on anhedonia and odour in individuals with schizotypy. Second, the MRI results showed there may be lateralization in olfactory identification and hedonic processing. However, olfactory tasks were presented bilaterally in our study. A more direct approach would have been to present odours unilaterally in future studies. Third, the findings were restricted to pre-defined regions of interest; hence, whole brain analysis was not used and the effects of other brain regions could also have contributed to the results.

Notwithstanding these limitations, the present study suggests that there is an association between odour identification ability and anhedonia in individuals with schizotypy, and the strength of this association appears to be mediated by parahippocampal gyrus grey matter volume. Anhedonia has been identified as a core component of negative schizotypy and schizophrenia (Meehl, 1962). Social anhedonia has been reported as a predictor for the development of schizophrenia-spectrum pathology in longitudinal studies (Kwapil, 1998; Gooding et al., 2005). Olfaction may play a unique role in identifying people with anhedonia.

Author contributions

LQZ designed the study, collected and analysed the data, and wrote the first draft of the paper. FLG, WHL, HSS administered the tests and screening tools. YW analysed and interpreted the data.
XHW and XQJ administered scanning and corresponding examination of the imaging data. EFCC commented significantly to the drafts of the paper. RCKC generated the idea and supervised the study, and wrote the first draft of the paper.

Competing financial interests
The authors declare no competing financial interests.

Declaration of conflicts
The authors declare no conflicts in authorship and publication for this paper.

Acknowledgements
This study was supported by grants from the National Science Fund China (81088001, 81571317, and 91132701), the Strategic Priority Research Programme (B) of the Chinese Academy of Science (XDB02030002), and the Beijing Training Project for the Leading Talents in S & T (Z1511000003150200). These funding agents had no role in the study design; collection, analysis, and interpretation of the data; writing of the manuscript; or decision to submit the paper for publication.

Appendix A. Supplementary material
Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pscychresns.2015.09.011.

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