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REGULAR RESEARCH ARTICLE

Disrupted Olfactory Integration in Schizophrenia: Functional Connectivity Study

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Abstract

Background: Evidence for olfactory dysfunction in schizophrenia has been firmly established. However, in the typical understanding of schizophrenia, olfaction is not recognized to contribute to or interact with the illness. Despite the solid presence of olfactory dysfunction in schizophrenia, its relation to the rest of the illness remains largely unclear. Here, we aimed to examine functional connectivity of the olfactory bulb, olfactory tract, and piriform cortices and isolate the network that would account for the altered olfaction in schizophrenia.
Methods: We examined the functional connectivity of these specific olfactory regions in order to isolate other brain regions associated with olfactory processing in schizophrenia. Using the resting state functional MRI data from the Center for Biomedical Research Excellence in Brain Function and Mental Illness, we compared 84 patients of schizophrenia and 90 individuals without schizophrenia.
Results: The schizophrenia group showed disconnectivity between the anterior piriform cortex and the nucleus accumbens, between the posterior piriform cortex and the middle frontal gyrus, and between the olfactory tract and the visual cortices.
Conclusions: The current results suggest functional disconnectivity of olfactory regions in schizophrenia, which may account for olfactory dysfunction and disrupted integration with other sensory modalities in schizophrenia.

Keywords: olfaction, schizophrenia, functional connectivity, resting state fMRI, sensory integration

Introduction

There is established evidence supporting olfactory dysfunction in schizophrenia. Olfactory disturbances have been reported since the 1960s (Hoffer and Osmond, 1962; Hurwitz et al., 1988; Kopala et al., 1992; Wu et al., 1993; Brewer et al., 1996, 2003, 2007; Turetsky et al., 2009; Kästner et al., 2013). A previous and recent meta-analysis showed robust olfactory deficits in schizophrenia and also at-risk youths (Moberg et al., 1999, 2014). Although olfaction may not be the central pathology in the typical dopaminergic understanding of schizophrenia, it has been shown that olfactory dysfunction can be induced by NMDA antagonists (Javitt and Zukin, 1991) and that olfactory performance is associated with clinical measurements (Kästner et al., 2013).

In olfactory sensation, the olfactory nerve sends afferent projections from the olfactory epithelium to the forebrain structure, the olfactory bulb. Unlike other sensory pathways, the olfactory pathway bypasses the brain stem and directly enters to the olfactory bulb, further projecting to the lateral olfactory tract and the anterior and posterior piriform cortices. In humans, the posterior piriform cortex in the temporal lobe has been isolated to encode categorical perception of odors (Howard et al., 2009), while the anterior piriform cortex in the frontal lobe is sensitive to higher order attentional control (Zelano et al., 2005).

There is evidence suggesting that the pathology of olfactory dysfunction in schizophrenia may lie in the olfactory bulb. Olfactory bulb volume has been found to be smaller

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Significance Statement

Olfactory dysfunction has been repeatedly and consistently found in schizophrenia. However, it is unclear how olfactory dysfunction relates to other dysfunctions in schizophrenia and their pathophysiology. We examined functional connectivity of olfactory regions in schizophrenia using resting state fMRI data. Olfactory regions in schizophrenia showed less functional connectivity to other sensory regions and, multisensory integrative regions, and the prefrontal cortex compared with the healthy control group. Our results suggest that olfactory integration to other sensory modalities is disrupted in schizophrenia.

in schizophrenia (Turetsky et al., 2003). A postmortem study showed decreased synaptic efficacy in the olfactory bulb of schizophrenia patients (Egbujo et al., 2015). Smaller olfactory bulb volume has also been seen in first-degree relatives of schizophrenic patients (Kamath et al., 2011).

However, a limited number of neuroimaging studies of the olfactory system in schizophrenia have ever been conducted. A structural MRI study showed that association with olfactory sensation was found in the region that receives direct afferents from the olfactory bulb (Turetsky et al., 2003). Cortical volume of the anterior ventromedial temporal lobe is smaller in schizophrenia and shows association with olfactory threshold sensitivity. In a PET study, limbic and paralimbic regions showed lesser activation while experiencing unpleasant odors compared with the healthy cohorts. Patients of schizophrenia showed an impairment in detecting pleasant odors but not unpleasant ones (Crespo-Facorro, B et al., 2001). In another PET study, the left anterior cortex adjacent to the putamen, and the left inferior frontal gyrus showed association to dysfunction in olfactory sensation in schizophrenia (Plailly et al., 2006).

It remains largely unclear how and/or whether olfactory dysfunction relates and contributes to other dysfunctions in schizophrenia. To clarify the brain regions that are associated with olfactory dysfunction in schizophrenia, this study aimed to isolate olfactory connectivity disrupted in schizophrenia by examining resting state functional connectivity from the olfactory bulb, olfactory tract, anterior piriform cortex, and posterior piriform cortex.

Materials and Methods

Data Acquisition

The MRI images, the clinical data, and the demographic data from the Center for Biomedical Research Excellence in Brain Function and Mental Illness (Çetin et al., 2014) were obtained from Collaborative Informatics and Neuroimaging Suite (http://coins.mrn.org/). This data subset consisted of 183 individuals for whom both resting state and structural data were available. Among these individuals, 84 had a diagnosis of schizophrenia or schizoaffective disorder (hereafter SZ group, 36.85 ± 14.09 years old) based on the Structural Clinical Interview for DSM-IV for Axis I DSM-IV Disorders (First et al., 1998), and 90 were nonpsychiatric age-matched controls (control group, 37.5 ± 11.40 years old). Nine individuals who had a diagnosis of bipolar disorder were excluded from further analysis.

Resting state echo planner image (EPI) volumes had 32 slices of 4 mm 64 x 64 matrix with 4-mm thickness (voxel size = 3 x 3 x 4 mm), with repetition time (TR) of 2000 milliseconds and echo time (TE) of 29 milliseconds. A total of 150 volumes (5 minutes) were used in the analysis. High-resolution structural T1 volume was acquired as 176 sagittal slices of 256 mm x 256 mm with 1-mm thickness (voxel size = 1 x 1 x 1 mm, TR = 2530 milliseconds and TE = 3.25 milliseconds).

Data Processing

Data preprocessing and statistical analyses were conducted using FMRIB Software Library (FSL) as well as Analysis of Functional NeuroImages. The anatomical volume for each subject was skull stripped, segmented (gray matter, white matter, and CSF), and registered to the MNI 2-mm standard brain. The first 4 EPI volumes were removed. Transient signal spikes were removed by despiking interpolation. To correct head motion, the volumes were linearly registered to the then-first volume, through which 6 motion parameters and displacement distance between 2 consecutive volumes were estimated. Each of the resting state volumes was regressed by white matter and cerebrospinal fluid signal fluctuations as well as the 6 motion parameters. After smoothing with a 6-mm FWHM Gaussian kernel, the volumes were resampled, spatially transformed, and aligned to the MNI 2-mm standard brain space. Through this registration, 12 affine parameters were created between rs-fMRI volume and MNI152 2-mm space, so that a seed ROI can later be registered to each individual rs-fMRI space. To perform scrubbing where the volumes with excess motion are removed, as a displacement distance between 2 EPI volumes, the root mean square deviation was calculated from motion correction parameters, at an $r = 40$-mm spherical surface using FSL's *rmsdiff* tool (Power et al., 2012, 2015). Volumes whose displacement distance exceeded the threshold (0.3 mm) were removed (*scrubbed*) from further statistical analyses (Siegel et al., 2014).

The olfactory bulb, olfactory tract, anterior piriform cortex, and posterior piriform cortex were manually segmented in the MNI 2-mm space (Figure 1) following anatomical descriptions in the literature (Howard et al., 2009; Gottfried, 2010; Scherfler et al., 2013). For each ROI, voxel-wise connectivity analysis was conducted. The time course was spatially averaged within the ROI that was registered to the EPI space so that correlations can be tested between the ROI and each individual voxel across the brain. The Z-scores representing the correlations between the ROI and a voxel were used for group-level analysis after registration to the MNI 2-mm brain space.

The SZ and control groups were compared by *randomise* script in FSL. Z-statistic images were estimated where clusters were determined by the statistical threshold of $Z > 2.326$ with a family-wise error-corrected cluster significance threshold, assuming a Gaussian random field for the Z-statistics. The peak voxels within a cluster were calculated by using voxelwise family-wise error corrected *t* test images.

Results

Voxel-wise statistical analysis of functional connectivity from the olfactory tract, and anterior and posterior piriform cortices showed regions that have lesser connectivity in the SZ group, compared with the control group (Table 1; Figures 2–4). Specifically, the olfactory tract in the SZ group showed less

connectivity with the left occipital and parietal region, the anterior piriform cortex with the nucleus accumbens and prefrontal cortex, and the posterior piriform cortex with the left frontal cortex. There was no group difference found with the olfactory bulb. None of the 4 ROIs indicated any greater connectivity in the SZ group than the control group.

Discussion

To the best of our knowledge, this is the first study that examined functional connectivity from the olfactory regions in schizophrenia. The results indicate the presence of disrupted connectivity between the olfactory tract and visual cortices, between the anterior piriform cortex and the nucleus accumbens, and between the posterior piriform cortex and the middle frontal gyrus. The findings here are new but coherent with previous literature suggesting disrupted olfactory integration in schizophrenia.

The anterior piriform cortex (APC) showed disconnectivity to the nucleus accumbens (NAcc). While the NAcc and olfactory regions have been known to have similar projections (Heimer and Wilson, 1975; Brog et al., 1993), the association between the piriform cortex and NAcc has been shown as a part of a feeding-related circuitry for which odors play critical roles (Truong et al., 2002; Stratford, 2005). In schizophrenia, stronger functional connectivities of the NAcc have been found to be associated with hallucination (Rolland et al., 2015). In patients with auditory hallucination, NAcc functional connectivity to the superior temporal gyrus is increased, as well as to the cingulate gyrus and ventral tegmental area, suggesting the enhanced connectivity between the NAcc and auditory cortices that may underlie the auditory hallucinations. The NAcc has been implicated in audio visual integration of speech in schizophrenia (Szycik et al., 2009), suggesting that the NAcc is involved in multi-modal sensory integration. Our finding of decreased connectivity between the APC and NAcc may suggest that olfactory input to the NAcc is disrupted and may contribute to multi-sensory disintegration whose outcome includes auditory hallucinations.

The piriform regions in schizophrenia showed disrupted connectivities to the prefrontal regions. Disconnectivity in schizophrenia was found between the APC and right superior frontal gyrus extending to the orbitofrontal cortex (Figure 3) and between the posterior piriform cortex (PPC) and middle frontal gyrus (Figure 4). There has been known anatomical projections between prefrontal cortex and olfactory regions

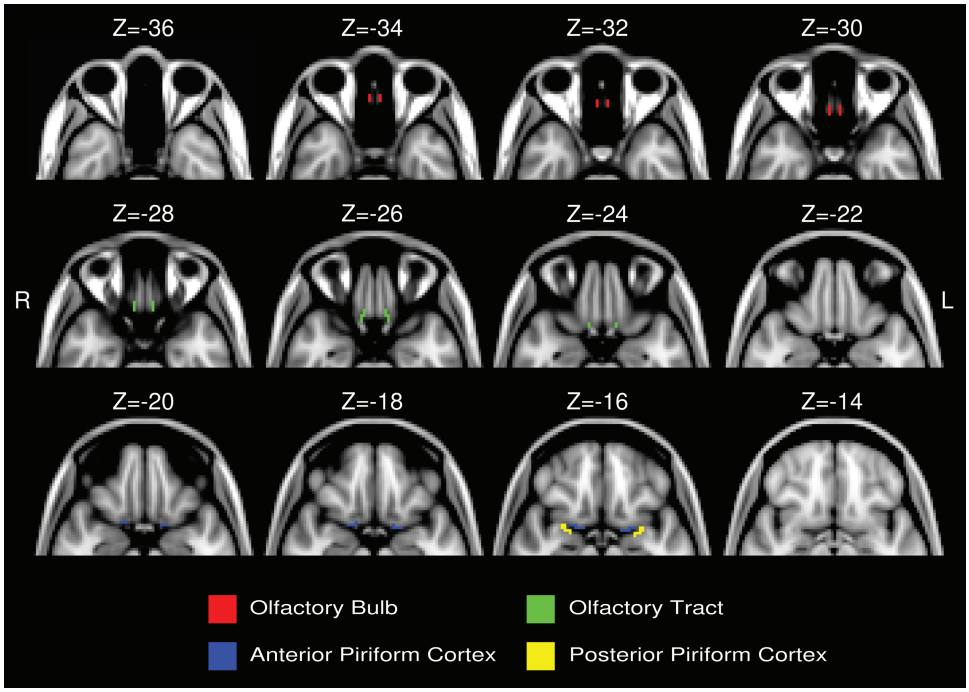

Figure 1. Four regions of interest (ROIs) specified in the MNI 152 2-mm brain space. Axial images shown included regions anterior to the brain stem (y ≧ -12).

Table 1. Regions of Lesser Connectivity in the SZ Group (Cluster Z > 2.326)

		Peak MNI Coordinates			
Seed	**Voxels**	**x**	**y**	**z**	**Region**
Olfactory tract					
	4458	-16	-66	54	Left lateral occipital cortex, precuneus cortex
Anterior piriform cortex					
	3358	16	18	-12	Right nucleus accumbens
		6	54	46	Right superior frontal gyrus
Posterior piriform cortex					
	3309	-24	20	42	Left middle frontal gyrus

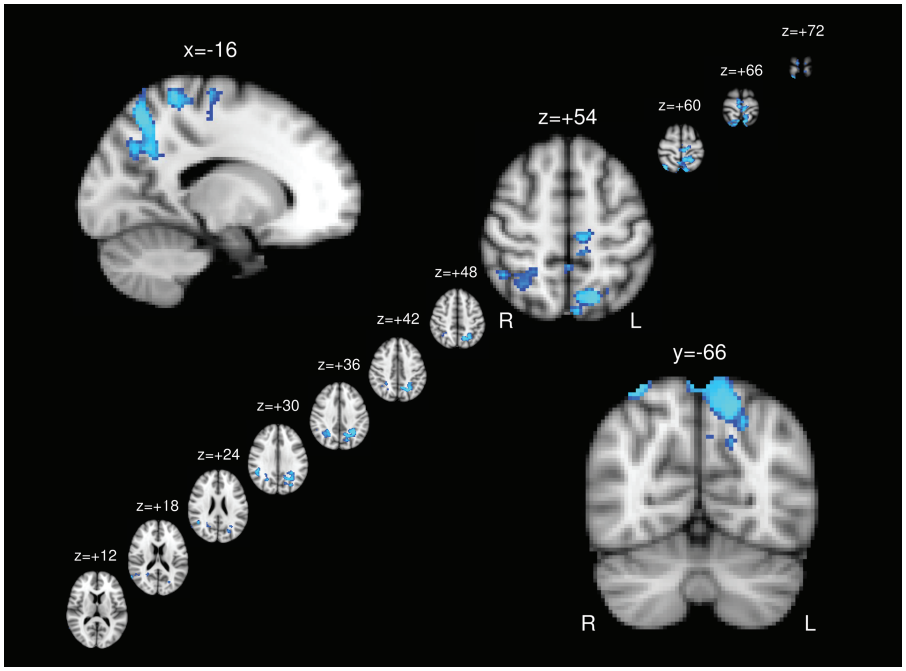

Figure 2. Olfactory tract connectivity. Regions that showed significantly lesser connectivity in the schizophrenia (SZ) group than the control group.

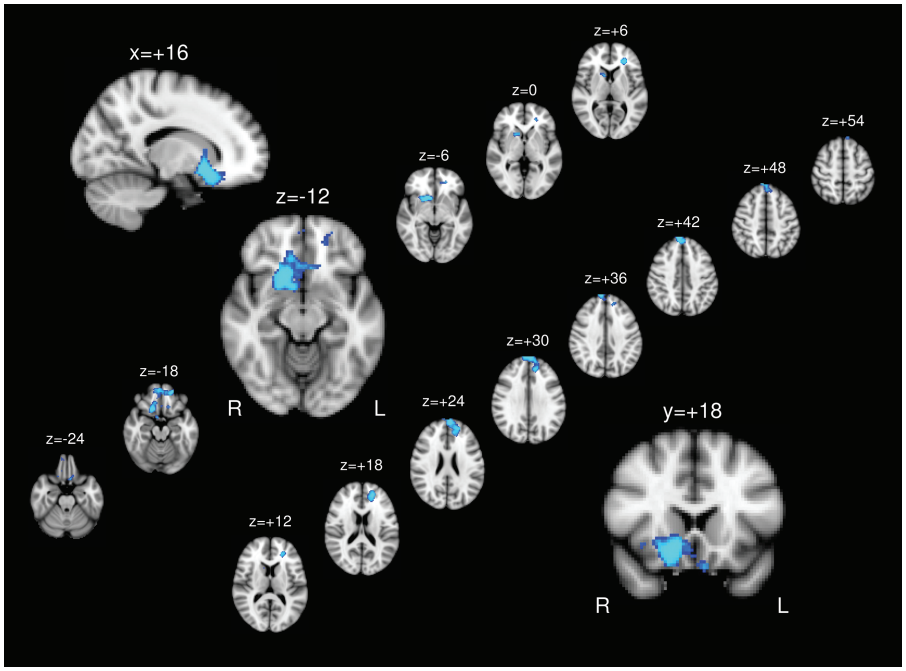

Figure 3. Anterior piriform connectivity. Regions that showed significantly lesser connectivity in the schizophrenia (SZ) group than the control group.

in rats and primates (Carmichael et al., 1994; Carmichael and Price, 1995). In human fMRI, the orbitofrontal cortex has been shown to be coding olfactory valence, independent from intensity (Anderson et al., 2003), suggesting that the connectivity between olfactory regions to orbitofrontal cortex accommodates odor valence. The piriform-prefrontal disconnectivity in schizophrenia in our results may account for the disrupted olfactory discrimination and identification in schizophrenia (Brewer et al, 1996; Moberg et al., 2014).

The PPC showed disconnectivity to the middle frontal gyrus. The PPC has been shown to furnish categorical perception (Howard et al., 2009). At the same time, the middle frontal gyrus has been implicated in detecting mixtures of odors (Boyle et al., 2009) compared with simplex odors, suggesting the associative role of categorical perception processed in the PPC. Indeed, tasks used in the previous studies employed complex odors where disruptions in performance were found in the schizophrenia group (Hoffer and Osmond, 1962; Hurwitz et al., 1988;

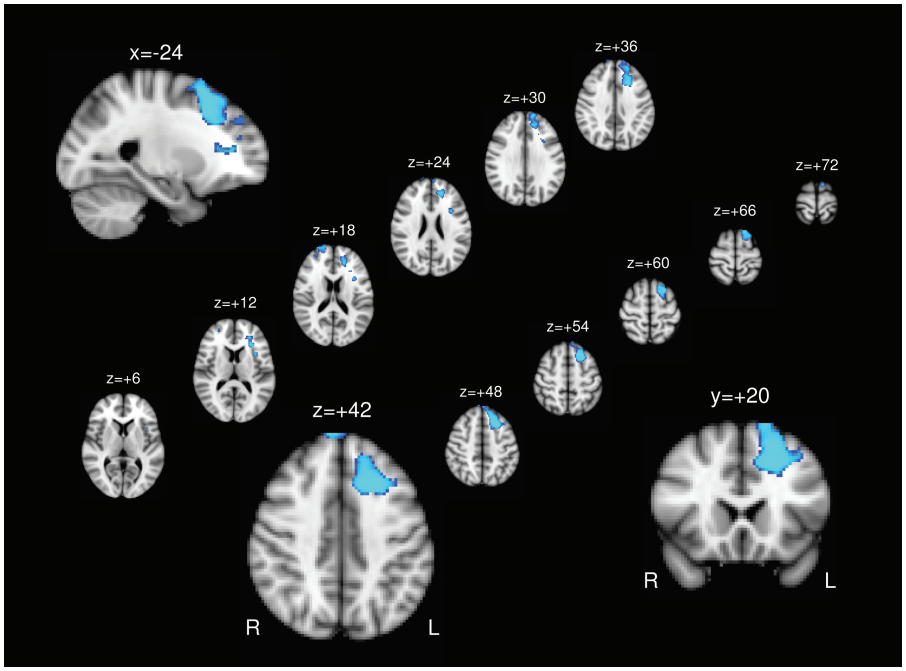

Figure 4. Posterior piriform connectivity. Regions that showed significantly lesser connectivity in the schizophrenia (SZ) group than the control group.

Kopala et al., 1992; Wu et al., 1993; Kästner et al., 2013). Although it remains unclear whether schizophrenia influences more selectively to sensing mixtures of odors, our finding suggests that the PPC-middle frontal gyrus disconnectivity in schizophrenia may account for the olfactory dysfunctions found in the literature.

Disconnectivity between the olfactory tract and visual cortices including the lateral occipital cortex and precuneus cortices suggests that olfactory information may not be synchronized with visual information in schizophrenia. This may be consistent with disrupted multisensory integration of olfactory input. At the same time, abnormalities in the occipital lobe have been consistently reported (Meador-Woodruff et al., 1997; Narr et al., 2005; Onitsuka et al., 2007). The current methods do not provide evidence to account for the relations between sensory integration and occipital disruptions.

While olfactory malfunction has been more widely known in Alzheimer's disease (Murphy et al., 1990; Devanand et al., 2015) and Parkinson's disease (Ross et al., 2008), olfactory malfunction is not usually considered to be one of the central symptoms in either disorder. Since it has been suggested that the pathology is in the central nervous system and not in the olfactory epithelium, we aimed to detect olfactory disruption in the olfactory bulb and its system (Minovi et al., 2015). The pathology, however, may originate further in the periphery. A reduced quantity of chondroitin sulfate proteoglycans is found in the olfactory epithelium tissues of patients of schizophrenia (Pantazopoulos et al., 2013), which may be accounted for by the pathology of olfactory dysfunction in schizophrenia. A reduction of protein synthesis in olfactory cells in schizophrenia has been reported (English et al., 2015). Olfactory neural epithelium has been recently suggested to indicate signatures of schizophrenia (Horiuchi et al., 2016). The design used in our study does not permit any judgment on whether the pathology in the epithelium affects the disconnectivity of the central olfactory regions found in this study. Although our study did not detect any disconnectivity in the olfactory bulb, our finding in the other olfactory regions may be the consequences of dysfunctions in the olfactory epithelium.

It has to be noted that the SZ groups are not treatment naïve. Therefore, our finding may be due to antipsychotic medications or other complications from the illness. Although olfactory dysfunctions have been reported in first relatives (Kamath et al., 2011), the current methodology does not distinguish schizophrenia pathology and consequences of medications.

This study suggests the presence of functional disconnectivity of olfactory regions in schizophrenia. The functional disconnectivity may account for olfactory dysfunction and disrupted integration with other sensory modalities in schizophrenia.

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Interest Statement

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