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The Olfactory System in Schizophrenia: an rsfMRI Study of the Piriform Cortex

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THE OLFACTORY SYSTEM IN SCHIZOPHRENIA: AN RSFMRI STUDY OF THE PIRIFORM CORTEX

By
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I dedicate this research to my parents who never fail to inspire me. Mom and dad, thanks for doing all of my science fair projects in middle school. Here's what I've been working on lately.

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ABSTRACT
SARA KIPARIZOSKA: The Olfactory System in Schizophrenia: an rsfMRI Study of the Piriform Cotex
(under the direction of Dr. Tossi Ikuta)

This thesis is a study of rsfMRI imaging in order to examine coactivation patters of the piriform cortex between healthy subjects and people with schizophrenia. As part of the olfactory system, the piriform cortex is an integral part of the smell sensation. Our studies showed that coactivation among the piriform cortex and other sensory brain regions differ in people with schizophrenia compared to healthy subjects. People with schizophrenia exhibit patterns of less coactivation among their sensory brain regions compared to control subjects, specifically the intracalcarine cortex, the right planum temporale, and the left occipital lobe. The purpose of this study is to gain a better understanding of schizophrenia functionality. Further studies of these results could be used to create novel therapies or identify new markers for schizophrenia.

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Introduction

Patients with schizophrenia often have an altered sense of smell sensation when compared to healthy subjects (Minor, Park, & Wright, 2004). Past studies have shown cognitive differences in the olfactory system function among schizophrenia patients and healthy patients. Patients with schizophrenia can be characterized as having an impaired sense of odor identification, recognition, and discrimination. They also have a deficit in the reliable change in odor sensitivity (Atanasova et al., 2008). In schizophrenia, cognitive olfaction impairment is considered a potential marker of the disease. The use of an odor identification test is suggested for discrimination among different psychiatric disorders and schizophrenia when other symptoms overlap (Nguyen, Shenton, & Levitt, 2010).

Literary Research of Schizophrenia

Schizophrenia Introduction

Schizophrenia is a psychological disorder characterized by delusions and altered perceptions of the world. The symptoms of schizophrenia are more identified than the causes. Patients diagnosed with schizophrenia may experience varying symptoms such as hallucinations, delusions, withdrawal, apathy, lack of facial expression, depression, mania, and paranoia (The Negative Symptoms of Schizophrenia, 2006). There are several specific types of schizophrenia with their own set of special symptoms. However, generally, all patients with the disorder suffer through a very emotionally straining life.

Schizophrenia has a genetic contribution. People with the disorder are likely to have a relative with schizophrenia as well. According to the National Institute of Mental Health in 2015, schizophrenia occurred in about 1% of the general population and about 10% of the population with first-degree relatives who also had schizophrenia (Piotrowski & Tischauser, 2015). In 2003, a specific gene named dysbindin was identified as the marker for schizophrenia. Dysbindin is said to interrupt the normal synapse processing of neurons. Current researchers continue to investigate this disorder and try to encourage patients to start either preventative or early treatment if they suspect to be at risk for carrying the gene.

Typically, schizophrenia onset occurs after adolescence. Treatment for schizophrenia symptoms has advanced and we now have effective medications and psychotherapies to manage the disorder. However, regardless of therapy and medication, all patients and their loved ones struggle to manage an effective lifestyle. Many schizophrenia patients struggle with public acceptance since much of the media portrayal of schizophrenia is nothing more than a scene in a horror film (Piotrowski & Tischauser, 2015).

Schizophrenia Symptoms

Schizophrenia occurs in all ethnic groups and cultures around the world and affects both males and females. Typically, schizophrenia symptoms occur between adolescence and early adulthood. Statistics show that schizophrenia occurs in more males than females, but females show a later onset. It is especially difficult to identify

schizophrenia onset in young adults due to their ever changing behavior due to puberty (Schizophrenia, 2016).

Specifically, the symptoms of schizophrenia are organized into three different categories: positive, negative, and cognitive. All of these symptoms affect people differently and have therefore made schizophrenia one of the most complex psychological disorders to study. For some, these symptoms preside over a large period of time, for others, they come and go in a pattern or randomly.

The positive symptoms are defined as positive not because something good is happening, but rather, because, something psychotic is occurring (The Negative Symptoms of Schizophrenia, 2006). In particular, positive symptoms include hallucinations, delusions, thought disorders, and movement disorders. Hallucinations can occur in any of the five senses, including smell. Voice hallucinations are the most common and many people with schizophrenia hear voices that no one else detects. People with schizophrenia may experience delusions that seem bizarre to others. Many schizophrenia patients falsely believe that others are controlling their behavior or able to read their thoughts. While experiencing delusions, many people with schizophrenia experience paranoia and become secluded. Thought disorders occur when schizophrenia patients have dysfunctional ways of thinking. For example, people with schizophrenia have experienced symptoms where their speech is hard to understand or when they abruptly stop talking in a middle of a thought. For movement disorders, a person with schizophrenia might experience symptoms that appear as irregular body movement. In rare and some untreated cases, a person with schizophrenia may experience catatonia

where they are not able to undergo any body movement for an abnormal period of time (Schizophrenia, 2016).

The negative symptoms of schizophrenia are called negative because of the absence of their presence. Common negative symptoms include inexpressive faces, monotone, few gestures, and lack of empathy. Positive symptoms may seem to be more obvious and are treated more effectively. However, it is the negative symptoms that alter the everyday social life of people with schizophrenia. (The Negative Symptoms of Schizophrenia, 2006).

The cognitive symptoms of schizophrenia are caused by the negative symptoms. The distinction between these two categories is blurred and many are caused or affected by the other. Studies have associated cognitive symptoms such as thinking deficiencies to be caused by the negative symptoms (The Negative Symptoms of Schizophrenia, 2006).

Together, the combination of positive, negative, and cognitive symptoms leads to an increase in social discrimination and a lower quality of life for patients with schizophrenia. Thankfully, advances in symptom treatment for schizophrenia patients have increased the quality of life in many people.

Treatment for People with Schizophrenia

It is important to treat schizophrenia as soon as the first episode is experienced. The most efficient treatment of schizophrenia occurs with a strong patient and physician alliance. Most commonly, a psychiatrist leads the treatment of a schizophrenia patient. It is important that the psychiatrist and the patients have a strong alliance with each other as well as the patient's other physicians. Treatment of schizophrenia is lifelong and

continues even when symptoms have subdued. Medication is the most common form of schizophrenia treatment followed by psychotherapy.

Antipsychotic medications are the most common medication used to treat schizophrenia symptoms. However, many of these medications also have side effects which ultimately affect the person in many different ways. Often, additional medication has to be administered in order to cancel out the effect of the antipsychotic such as antianxiety medication or antidepressants. Since there are so many different medication treatments and possible side effects, many schizophrenia patients are reluctant to take their prescribed treatments.

Another area of treatment for schizophrenia patients is psychotherapy. Common methods of psychotherapy include individual therapy, social skills training, family therapy, and vocational rehabilitation or supported employment. Treatment for schizophrenia is not just for the patient but also for their support system. It is important to establish and educate a strong support system for the person in order to increase the quality of life of the patient.

Most people with schizophrenia must manage their symptoms on a daily basis. If on a proper and structured treatment, patients can manage their disorder and be a part of the community. In the United States, there are many resources and programs available for schizophrenia patients that help them with finding jobs, housing, and support groups (American Psychiatric Association, 2013).

Quality of Life for People with Schizophrenia

Literarily speaking, the word "schizophrenia" can be translated to mean "split mind." However, people with schizophrenia do not have two personalities or two minds, but rather, they experience the world in two different ways. People with schizophrenia seem to have a split mind because most of what they are experiencing in their mind is not what is actually going on around them (Piotrowski & Tischauser, 2015). This split mind phenomena causes an extreme internal frustration among people with schizophrenia that may lead to the development of other psychological disorders.

The public's understanding of the positive and negative symptoms of people with schizophrenia has an additional effect on the quality of life of schizophrenia patients. When experiencing these symptoms in public, lots of people with schizophrenia have also experienced discrimination due to lack of public knowledge about schizophrenia. Recent studies on self-stigma, quality of life, somatic complaints, and depression among schizophrenia patients have influenced the importance of providing adequate education of schizophrenia symptoms to the public (Lin, Chang, Wu, & Wang 2016).

A recent pilot study confirmed their hypothesis that patients with schizophrenia have a change in their quality of life after onset. The study reported that people with schizophrenia had the highest self-stigma at 54 to 86 months after their onset and the lowest quality of life and highest somatic complaints and depression at 89 to 100 months after diagnosis. The study suggests that early detection and management might be the key to help improve patient quality of life and minimize depression (Lin et al., 2016).

Schizophrenia and the Olfactory System

Several studies have examined the connection among olfaction and psychiatric disorders, including schizophrenia.

From previous studies, there are two particular papers which thoroughly examine the connection among olfaction and patients of schizophrenia. One of the studies has examined how administering a smell test could be used as a possible detection test for schizophrenia (Minor et al., 2004). Another study examined the neuroanatomy and psychophysiology of olfactory dysfunction in schizophrenia (Nguyen et al., 2010).

The results of empirical tests of odor detection and perception describe the impairments in olfaction of patients with schizophrenia. Olfactory neuroanatomy studies also describe the impairments of olfaction in patients with schizophrenia. There are patients with schizophrenia that have neuroanatomic changes in the orbitofrontal, temporo-limbic, and olfactory cortex brain regions. Also, the psychometric studies show impairment in many aspects of olfaction such as odor sensitivity, odor detection, odor identification, odor acuity, odor discrimination, and odor memory in patients with schizophrenia (Nguyen et al., 2010).

Overall, these two particular studies along with other papers on olfaction, schizophrenia, and olfaction associated with other psychological diseases were the inspiration for this thesis research.

The Olfactory System

In humans, smell perception initiates in the nasal olfactory epithelium and is processed in different specialized brain areas. Volatile substances are initially sensed by humans by the olfactory receptors in the nasal epithelium. The specialized olfactory receptors of the nasal olfactory epithelium synapse by primary axons to the olfactory bulb. The olfactory bulb processes smell senses on a peripheral level and then relays the information for detailed processing to different brain areas. The information from the olfactory bulb to the different brain areas is transmitted by specialized olfactory axons. The different brain areas associated with olfactory sensation processing include the amygdala, the piriform cortex, the entorhinal cortex, and the frontal cortex (Atanasova et al., 2008).

The study of olfactory perception in schizophrenia is especially important since smell sensation represents the most direct form of human sensory perception. Lacking a formally defined thalamic relay, smell sensation provides one of the most direct links among the external environment and the central nervous system (Nguyen et al., 2010). Studying the different disturbances of the specialized areas associated with olfactory processing can be useful in identifying the source of olfactory impairment in schizophrenics.

The Piriform Hypothesis

Each specialized brain area associated with olfactory processing represents a different form of odor processing. The orbitofrontal cortex has been found to play a role in odor identification, discrimination, odor memory, and judgment of hedonic values of

odors (Zald & Pardo, 1997). The amygdala has been associated with discrimination of odor intensity (Anderson et al., 2003). A particular interest in this study, the piriform cortex is also associated with discrimination of the intensity of odors (Gottfried & Wu, 2009). The piriform cortex is considered a valuable structure of study because it serves as the main hub for olfactory processing.

The piriform cortex has major connections with associated structures of the olfactory system. Physically, the piriform cortex in humans is located at the junction of the temporal and frontal lobes and is composed of three distinct cell layers (Vaughan & Jackson, 2014). Structurally, the piriform cortex has connectivity to the olfactory bulb, the anterior olfactory nucleus as well as some higher order processing centers. The anatomy of the lateral olfactory tract includes afferent projection from the olfactory bulb to the anterior olfactory nucleus, to the olfactory tubercle, to the anterior piriform cortex, the posterior piriform cortex, the amygdala, and the entorhinal cortex. The information in this system is not transferred serially but rather, it is transferred in numerous parallel ways through interconnected regions (Gottfried, 2010).

The piriform cortex and its many neural connections have multiple neurotransmitter pathways. Odor processing affects behavioral, memory, and emotional states due to the vast variety of neural and hormonal associations with the piriform cortex (Wilson & Rennaker, 2010). The neurotransmitters acetylcholine (Ach) and norepinephrine (NE) have varying effects on the piriform cortex. Ach depolarizes pyramidal cells and interneurons and therefore suppresses the action potential of pyramidal cells. Norepinephrine has similar effects as acetylcholine. Both neurotransmitter pathways enhance synaptic modification and long-term potentiation.

This suppression could lead to the encoding of new olfactory information (Linster & Hasselmo, 2001).

Figure 1 summarizes some of the brain activity among the piriform cortex and other areas. The known neurotransmitter pathways are labeled and the bidirectional arrows represent a higher order of processing (Wilson & Rennaker, 2010).

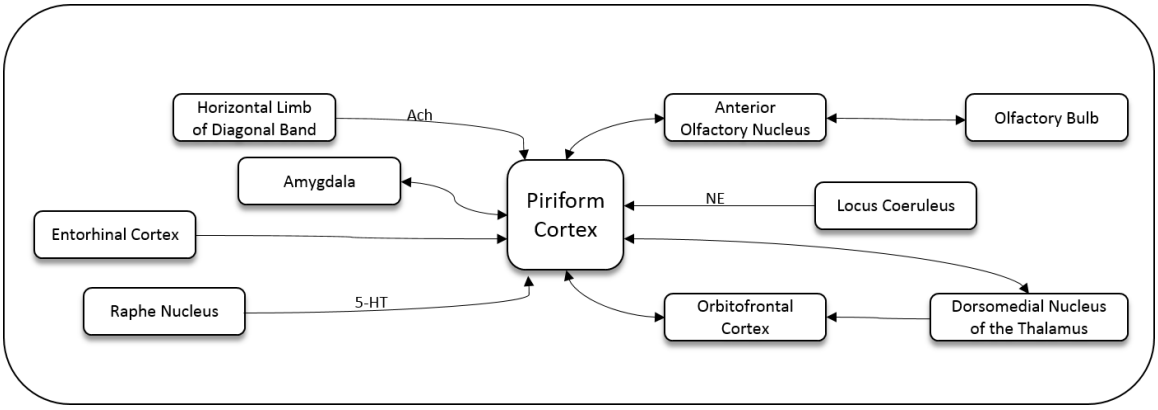

Figure 1: Piriform Cortex Connections
Connections among the piriform cortex and other brain areas associated with the olfactory system. The neurotransmitter abbreviations are: ACh = acetylcholine; NE = norepinephrine; 5-HT = serotonin.

Because of its complex activity, the piriform cortex in the human brain of schizophrenic patients is the main focus of this study. The wide range of connections associated with the piriform cortex and different parts of the olfactory system can be studied to understand the olfactory processing of schizophrenic patients.

In this study, we examined the functional connectivity of the olfactory system components in schizophrenia patients using MRI images. We hypothesized that patients with schizophrenia would have a lesser functional connectivity to/from the piriform cortex compared to control patients.

Methods

Data Acquisition

For this study, the MRI images, the clinical data, and the demographic data were obtained from studies by the Center for Biomedical Research Excellence (COBRE), (http://fcon_1000.projects.nitrc.org/indi/retro/cobre.html).This data subset consisted of 145 individuals for whom resting state and structural data were both available. Among these individuals, 71 had a diagnosis of schizophrenia (hereafter SZ group, 38.14±13.99 years old), and 74 had no diagnosis of schizophrenia (control group, 35.82±11.57 years old).

Resting state echo planner image volumes had 32 slices of 4mm 64x64 matrix with 4mm thickness (voxel size = 3x3x4mm), with repetition time (TR) of 2000ms and echo time (TE) of 29ms. Total of 150 volumes (5 minutes) were used in the analysis. High resolution structural T1 volume was acquired as 176 sagittal slices of 256mm x 256mm with 1mm thickness (voxel size = 1x1x1mm, TR=2530ms and TE=3.25ms).

Data Processing

Script libraries (fcon) from the 1000 Functional Connectomes Project (http://fcon_1000.projects.nitrc.org/) were used for preprocessing and analysis of the Region of the Interest (ROI). Resting state images were first motion corrected and spatially smoothed to 6mm full width and at half-maximum the Gaussian kernel. The structural T1 images were individually registered to the MNI152 2mm brain. Through registration, 12 affine parameters were created between the rs-fMRI volume and MNI152 2mm space so that a seed ROI could be registered to each individual rs-fMRI space. The rs-fMRI time series were band-pass filtered (between 0.005 Hz and 0.1 Hz). Each resting

state volumes were regressed by white matter and cerebrospinal fluid signal fluctuations as well as the six motion parameters.

The bilateral piriform ROI was created as 3mm radius sphere centered at MNI: ±20, +8, -22 (Figure 2). For this ROI, the voxel-wise connectivity analysis was conducted by the singlesubjectRSFC fcon script. The time course in this script is spatially averaged within the ROI so that correlations can be observed. Correlations were observed from the ROI to each individual voxel across the brain. The Z-scores representing the correlations between the ROI and each individual voxel were used for analysis.

The SZ and control groups were compared by *randomise* script in FSL. Z-statistic images were estimated where clusters were determined by $Z > 3.09$ with a family-wise error-corrected cluster significance threshold, assuming a Gaussian random field for the Z-statistics.

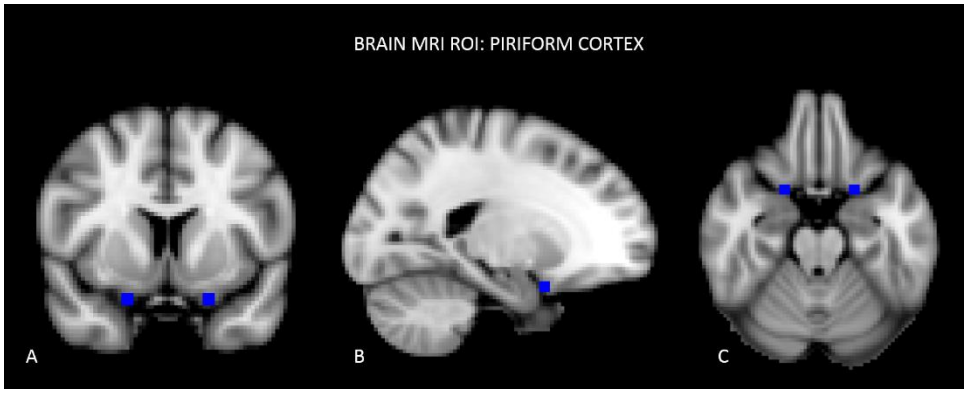

Figure 2: Brain MRI ROI Piriform Cortex
The labeled section on each image represents the region of interest (ROI) for this study. The piriform cortex is represented as the ROI. Each bilateral piriform ROI was created as 3mm radius sphere centered at MNI: ±20, +8, -22 (Figure 2).

Results

The bilateral intracalcarine cortices, right planum temporale, and left occipital pole showed greater connectivity from the bilateral piriform ROI (Table 1, Figure 3). Voxel-wise statistical analysis of functional connectivity from the piriform cortices revealed lesser connectivity in the occipital and temporal lobes in the SZ group, compared to the control group. Compared to the control group of non-patients to the SZ group, there were no regions that showed greater functional connectivity in the SZ group. Table 1 shows the voxel analysis of functionality among four peak regions functionally connected to the piriform cortex ROI. These particular regions were chosen because they had a peak voxel p value of less than .05. Everything with a peak voxel p value of greater than .05 was not measured. The higher the voxel, the stronger the significance of functional connectivity between individual brains within regions of the brain.

Table 1: Voxel-Wise Statistical Analysis Results

Region	MNI Coordinates (x,y,z)	Voxels	Peak Voxel P
Right intracalcarine cortex	16, -64, 8	1209	0.008
Left intracalcarine cortex	-12, -66, 12	591	0.021
Right planum temporale	56, -22, 12	342	0.043
Left occipital lobe	-26, -96, 8	293	0.048

The right intracalcarine cortex shows the highest voxels. The left intracalcarine cortex has a voxel value is more than half less the left intracalcarine cortex. The right planum temporale and the left occipital lobe both have similar co-activation voxel values. Overall, these four areas are the most significantly different in co-activation with the piriform cortex among patients and the control groups.

Figure 3 shows the image results of the voxel-wise statistical analysis. The figure shows the regions demonstrating statistically significant difference ($p<0.01$) in functional connectivity from the piriform cortex between patients and the control group superimposed on the MNI standard brain.

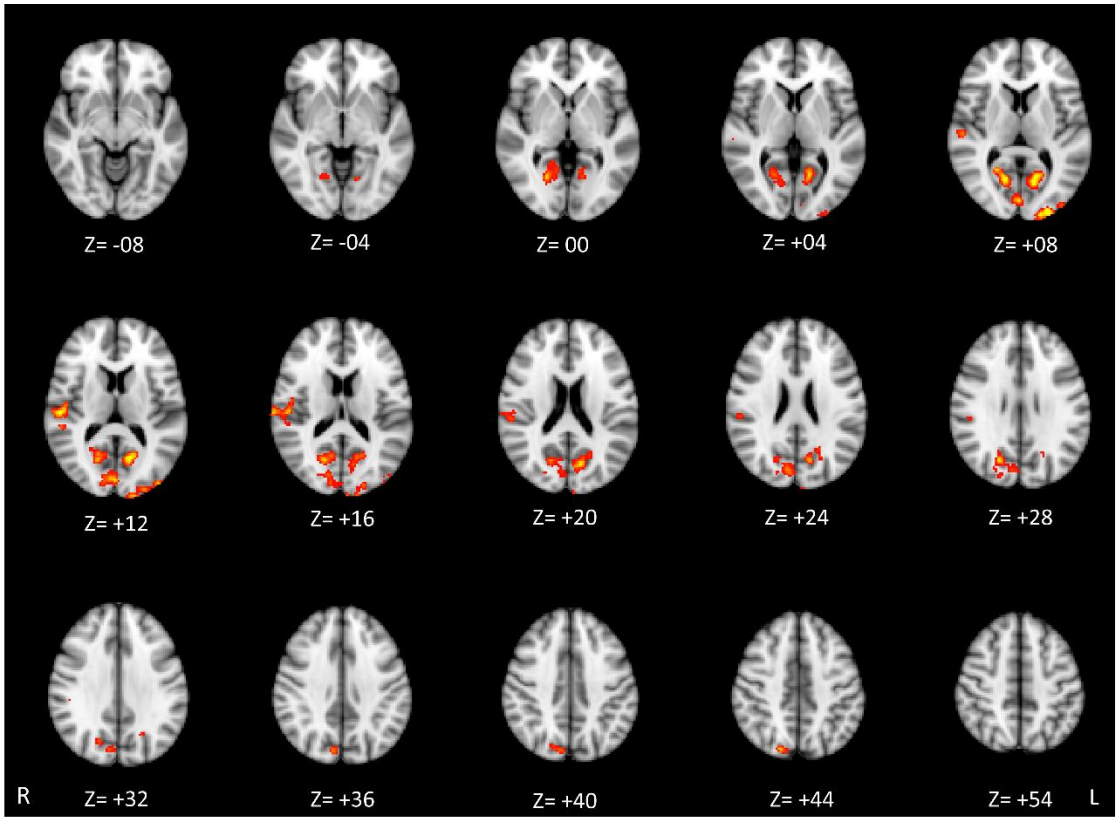

Figure 3: Image Results of Voxel-Wise Statistical Analysis

Discussion

The results of the present study found that patients with schizophrenia showed lower functional connectivity from the piriform cortex to four distinct areas associated compared to a control group. The four brain areas included the right intracalcarine cortex, the left intracalcarine cortex, the right planum temporale, and the left occipital lobe. The lower connectivity among these areas and the piriform cortex suggests that the lack of connectivity in patients may correspond to the symptoms associated with schizophrenia, especially symptoms of olfactory dysfunction.

The current results suggest that functional connectivity from the piriform cortex show reduced connectivity in schizophrenia. The lack of functional connectivity in patients suggests that olfaction in schizophrenia patients is not affecting the brain enough. Therefore, this finding supports the claim of other studies that identify olfactory dysfunction in schizophrenia patients (Nguyen et al., 2010).

In order to better understand the significance of co-activation of the piriform cortex with these four particular areas, we examine the independent role of each brain area.

Specifically, the intracalcarine cortex (lingual cortex) is where most of the V1 visual cortex is concentrated. The intracalcarine cortex is located in the occipital lobe and functions as the main site of input of signals coming from the retina (Lalli et al., 2006). The intracalcarine cortex is separated in the right and left cortices which receive inputs from the left and right visual fields, respectfully. The highest activation significance associated with the right intracalcarine cortex suggests that piriform activation affects the right intracalcarine cortex more than the left. The lowered co-activation associated with

this area and its functions could be used to explain the positive visual symptoms of patients with schizophrenia. The lack of connectivity could be the reason for the positive schizophrenia symptoms.

Independently, the right planum temporale is the primary auditory cortex, involved in perceiving auditory stimulation. The planum temporale is located in the posterior temporal lobe and carries out analysis of auditory stimuli which is crucial for the production of speech. Overall, the planum temporale seems to be involved in a bottom up processing mechanism of auditory attention. Specifically, studies show that the right planum temporale plays a large role in stimulus selection during dichotic listening. This further supports the notion that the right planum temporal is involved in stimulus driven auditory processing (Hirnstein, Westerhausen, & Hugdahl, 2013).The lower co-activation seen in patients within this area could suggest a cause for the auditory hallucination symptoms present in some schizophrenia patients.

The fourth region of lower co-acitvation among the piriform is the left occipital lobe. Independently, the left occipital lobe is responsible for visual processing and contains most of the anatomical visual cortex. The occipital lobe is associated with disorders such as visual hallucinations and occipital epilepsies (Knopman et al., 2014). The lack of co-activation of this area with the piriform cortex has the lowest significance of the other three particular brain areas studied. This lowest significance of difference among patients and non-patients could be explained by the occipital lobe's various functions. Because the occipital lobe is very active and working constantly to process many levels of information, it doesn't express the same lack of connectivity trends.

Combining the independent functions of these four particular areas along with the functions of the piriform cortex suggests a complex interconnection among different senses. Our results have found that this complex interconnection among the senses is less co-activated in patients with schizophrenia.

Although the results are conclusive, there is a weakness in this study that requires further research. Currently, it is not clear whether the symptoms of schizophrenia are causing the lower co-activation patterns or whether the lower co-activation patterns are causing the symptoms of schizophrenia. It is clear however, that patients with schizophrenia have a lack of connectivity between olfaction, auditory, and visual processing regions when compared to healthy patients.

In summary, the functional connectivity from the piriform cortex was significantly smaller to primary visual and auditory cortices in schizophrenia. The functional lack of connectivity among these areas can be used to further study the causes and symptoms of schizophrenia. If we assume that these patterns of lower co-activation of the brain cause schizophrenia, perhaps we can find ways of early diagnosis. On the other hand, if we assume that schizophrenia itself causes the lower co-activation patterns, we can come up with novel therapies such as drug treatments with nasal delivery. The functional connectivity of the piriform cortex significantly differs in schizophrenia patients and further studies could lead to more specific treatments.

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