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Honors Thesis

EXAMINING LIMBIC SEXUAL DIMORPHISMS IN SCHIZOPHRENIA

by
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Submitted to Brigham Young University in partial fulfillment
of graduation requirements for University Honors

Neuroscience Center
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ABSTRACT

EXAMINING LIMBIC SEXUAL DIMORPHISMS IN SCHIZOPHRENIA

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Schizophrenia is a mental disorder that affects a significant number of individuals in the United States and can have numerous different symptoms. Recently, interest in the differences between the neuroanatomy of individuals with schizophrenia and individuals without schizophrenia has emerged, specifically the sexual dimorphism in individuals with schizophrenia. This study aimed to gain a better understanding of the sexual dimorphisms of two structures in the limbic system: the hippocampus and amygdala. Data was harmonized and analyzed from two datasets to determine the sexual dimorphic factor of these structures in healthy controls and individuals with schizophrenia. Demographic features were also taken into consideration for all subjects. It was found that women with schizophrenia exhibited an inward deformation in both the hippocampus and amygdala, whereas men with schizophrenia exhibited an outward deformation in the hippocampus. These results suggest that men and women with schizophrenia do possess differences between the hippocampus and amygdala and that these differences may impact symptom manifestation and potential treatments.

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Examining Limbic Sexual Dimorphisms in Schizophrenia

Schizophrenia is a psychiatric disorder that alters an individual's behavior, emotional response, and thought process (National Institute of Mental Health, 2022). This disorder is complex yet not uncommon, as it affects around 1% of the United States' population (McCutcheon et al., 2020). The complexity of schizophrenia stems from different factors that impact its emergence and subsequent development. Some of these factors may include neurodevelopmental complications, environmental responses, and hormonal anomalies (Mendrek & Mancini-Marïe, 2016). Although multiple factors can influence schizophrenia, research into these factors is critical to gaining a better understanding of schizophrenia in general and how it can manifest differently in individuals.

Background of Schizophrenia

Schizophrenia can be traced back to a classification of "dementia praecox" (roughly translated as "premature dementia" or "precocious madness") by psychiatrist Benedict Augustine Morel (Lavretsky, 2008). Émil Kraepelin viewed dementia praecox as an illness caused by anatomical processes, progressing schizophrenia towards a neurodegenerative classification (Ebert & Bär, 2010). From this classification, psychiatrist Eugen Bleuler coined the term "schizophrenia" and explained that schizophrenia was a psychological disorder (Ebert & Bär, 2010; Lavretsky, 2008). He categorized the symptoms into two groups: fundamental (cognitive disturbances) and accessory symptoms (delusions and hallucinations) (Lavretsky, 2008). Additionally, Bleuler described the features of schizophrenia as alogia, autism (the desire to avoid reality by replacing reality with hallucinations or fantasies) ambivalence, and affect

blunting (Arantes-Gonçalves et al., 2018; Evans, 2013). It is through this development of schizophrenia that our understanding and diagnosis standards have altered.

In the DSM-I, "schizophrenic reactions" contained nine subtypes of schizophrenia-like disorders; these include hebephrenia, catatonic, schizoaffective, and paranoid schizophrenia (Bhati, 2013). In the DSM-II, the term "schizophrenia reactions" was then changed to "schizophrenia," which made it distinct from other forms of psychosis (Bhati, 2013). With the DSM-III, "schizophrenia" was changed again to "schizophrenic disorder" and required an onset age of 45 (Bhati, 2013). According to Keefe and Fenton (2007), the DSM-IV did not include impairments to function and biology within schizophrenia, yet highlighted the cognitive disturbances seen in schizophrenia. For the DSM-5, the edition sought to cover more information about the nature of schizophrenia and resolve the limitations of the DSM-IV (Tandon et al., 2013).

The lifetime prevalence of schizophrenia is between 0.3% and 0.7% (American Psychiatric Association, 2013), and the incidence rate of schizophrenia is around 15.2 cases for every 100,000 individuals in a population (McGrath et al., 2008). More men are diagnosed with schizophrenia than women, with a male to female ratio of 1.4:1 (McGrath, 2006). The changes in prevalence and incidence of schizophrenia are difficult to pinpoint because of the intricacy of the disorder and potential disorder overlapping (National Institute of Mental Health, n.d.). An increase in awareness about schizophrenia and advancements in research may have contributed to the current prevalence and incidence rates and possible increases in these rates.

The clinical symptoms of schizophrenia can be divided into three categories: positive, negative, and disorganized symptoms. Positive symptoms include symptoms

that are an exaggeration of normal functions of an individual, such as hallucinations and delusions (Correll & Schooler, 2020), whereas negative symptoms, "refer to a diminution or absence of normal behaviors related to motivation and interest (e.g., avolition, anhedonia, asociality) or expression (e.g., blunted affect, alogia)" (Correll & Schooler, 2020, pp. 519-520). Disorganized symptoms are symptoms that disrupt the capability of organizing and expressing thoughts, behaviors, and speech (Kemp et al., 2021).

Biopsychosocial Model of Schizophrenia

On the biological side of schizophrenia, neurotransmitters are a critical aspect of understanding schizophrenia. The main neurotransmitter that is in association with schizophrenia is dopamine. Dopamine is an inhibitory neurotransmitter that regulates motor, cognitive, and emotional functions (Syvälahti, 1994). The "dopamine hypothesis" of schizophrenia states that hyperactivity of dopamine release causes positive symptoms and negative symptoms seen in individuals with schizophrenia (Brisch et al., 2014). From a genetic perspective, schizophrenia is considered heritable. In twin studies, the heritability rate was found to be around 33% in monozygotic twins and about 7% in dizygotic twins (Hilker et al., 2018). In families, the chance of inheriting schizophrenia is over 80% (Avramopoulos, 2018). In addition to biological factors, psychological factors can also play a role in better understanding schizophrenia.

One psychological factor of schizophrenia is personality. A personality aspect that increases the likelihood and severity of schizophrenia is neuroticism (negative emotions such as depression, anxiety, and self-consciousness) (Camisa et al., 2005; Widiger & Oltma, 2017). If an individual has a higher level of neuroticism on a personality test, they are more likely to develop positive symptoms of schizophrenia (Shi et al., 2018).

Neuroticism increases the risk of schizophrenia and positive symptoms because it increases the vulnerability of distress, a risk factor for schizophrenia (Shi et al., 2018). In addition to personality markers that can affect the likelihood of schizophrenia, comorbidities also affect the progression of the disorder.

The prevalence rate of depression in individuals with schizophrenia is around 40% (Upthegrove et al., 2016), and the prevalence rate of anxiety in individuals with schizophrenia is about 38% (Temmingh & Stein, 2015). These comorbidities of schizophrenia can lead to a higher risk of suicide and poorer outcomes for schizophrenia (Emsley et al., 2013; Upthegrove et al., 2016). Depression can increase some symptoms associated with schizophrenia and lead to a higher probability of committing suicide, such as paranoid delusions and negative symptoms (Ventriglio et al., 2016). Furthermore, according to Temmingh and Stein (2015), the more severe the anxiety one has, the more likely one will experience positive symptoms of schizophrenia. Overall, psychological factors like comorbidities and personality affect the severity and progression of schizophrenia.

Social factors also give insight into the etiology and progression of schizophrenia. One social marker of schizophrenia is socioeconomic status. There is a higher incidence of schizophrenia in areas with a large population of low socioeconomic individuals (Weyerer, 1994). Individuals born into a community or family with low socioeconomic status are also at a higher risk of having schizophrenia (Werner et al., 2007). The reasoning behind this correlation could be the resources an individual has depending on their social status. If someone is in a situation with low access to proper networks and

resources to get treatment, they may have a higher risk of developing schizophrenia (Werner et al., 2007).

Trauma may also influence schizophrenia manifesting in an individual. Childhood trauma, in general, affects both social and functional impairments seen in adults with schizophrenia (Gil et al., 2009). Additionally, childhood abuse can cause suffering into adulthood and increase the distress an individual experiences (Morgan & Fisher, 2007). This distress, as previously mentioned, can contribute to a higher risk of developing schizophrenia into adulthood. Lastly, sexual abuse causes a higher risk of an individual being diagnosed with psychosis as it affects the hypothalamic-pituitary-adrenal axis, making individuals susceptible to stress (Morgan & Fisher, 2007). The trauma an individual experiences and its effects on stress increases the susceptibility to developing schizophrenia (Morgan & Fisher, 2007). In general, social factors such as community and trauma play a significant role in understanding how social factors contribute to the diagnosis of schizophrenia.

Research Interests in Schizophrenia

One factor that is of a strong interest in schizophrenia research is the neuroanatomical differences in individuals with schizophrenia. Compared to healthy individuals, individuals with schizophrenia generally possess differences in brain structure at all stages of the illness (Kambeitz et al., 2015). Some of the regions of interest implicated in patients with schizophrenia include a wide range of regions, such as the prefrontal lobe, temporal cortex, parietal cortex, cerebellum, and various subcortical areas (Ahmed et al., 2013). Although many studies have successfully highlighted the neuroanatomical differences in patients with schizophrenia compared to healthy

individuals, one aspect that needs further research is whether these changes are different between men and women with schizophrenia.

The differences between men and women, or sexual dimorphisms, are an area of interest in the research field concerning neurodevelopmental differences. Currently, research in sexual dimorphism utilizes neuroimaging resources to understand how the male and female brains show differences on an anatomical level (Sacher et al., 2013). Some of these findings included men having a larger overall brain volume compared to women and women having an overall increase in grey matter (2013). It is imperative to understand how sexual dimorphisms may affect individuals with mental disorders like schizophrenia since sexual dimorphisms are present in healthy individuals. Additionally, sex differences are becoming apparent in the symptom manifestation of schizophrenia. For example, women with schizophrenia tend to exhibit more positive symptoms of schizophrenia at the onset of schizophrenia, whereas men with schizophrenia tend to present more negative symptoms (Fernando et al., 2020). Understanding the differences in brain anatomy between men and women diagnosed with schizophrenia can open a discussion on how sexual brain dimorphisms affect individuals with schizophrenia and how these differences may impact future treatments.

One of the areas of the brain that needs to be further researched is the hippocampus. The hippocampus is of interest due to its connection with some of the symptoms observed in individuals with schizophrenia. Individuals with schizophrenia may exhibit deficits in memory, such as declarative memory (Zierhut et al., 2010), which is a main function of the hippocampus. In a recent study on how emerging psychosis affects the brain anatomy of men and women, two main ideas were presented. First, men

with schizophrenia exhibited a reduction in hippocampal volume compared to healthy controls (Egloff et al., 2018). Second, women with schizophrenia had a larger hippocampal volume than males with schizophrenia (2018). However, there is conflicting information regarding the hippocampal volume found in women diagnosed with schizophrenia.

Females with schizophrenia can exhibit hippocampal volume reduction as well. In an article investigating the hippocampal size in patients with schizophrenia, women with schizophrenia demonstrated a smaller hippocampus the longer the individual was diagnosed with schizophrenia compared to males with schizophrenia (Irle et al., 2011). In the study, women with schizophrenia exhibited normal hippocampal volume at the onset of schizophrenia, but the reduction of hippocampal emerged as the years of the illness progressed (2011). Based on the conflicting information presented concerning the hippocampus, it is imperative to research further into the sexual dimorphic factors of the hippocampus regarding schizophrenia.

Besides the conflicting information concerning the hippocampus, the sample sizes in each study were also small, which leads researchers to suggest further research to solidify the validity of their results. In Egloff et al. (2018), the sample sizes for individuals with schizophrenia were 48 males and 17 females for those with at-risk mental states and 37 males and 13 females for those with first-episode psychosis. These numbers are compared to 27 male controls and 43 female controls. In Irle et al. (2011), the sample size included 23 males with schizophrenia and 23 females with schizophrenia compared to 23 male controls and 23 female controls. Both studies present small sample

sizes for their subjects, and it is urged by the researchers for further research to be done to prove the validity of their results

The amygdala is also of importance when understanding sexual dimorphisms in schizophrenia. Individuals with schizophrenia may have impaired emotion recognition, which correlates to the amygdala (Pinkham et al., 2011). In a study concerning the amygdala and individuals with schizophrenia, researchers found that when looking at MRI scans of 14 males and 14 females with schizophrenia, both exhibited a significant decrease in amygdala volume (Kalus et al., 2004). In another study concerning the amygdala and schizophrenia, two main findings were highlighted. First, the amygdala overall was smaller in individuals with schizophrenia compared to controls (Niu et al., 2004). Second, when comparing the gender of the patient with schizophrenia, it was shown that males with schizophrenia had a smaller left amygdala volume than controls; females with schizophrenia exhibited a reduced right amygdala compared to controls (2004). Although research has been carried out concerning the sexual dimorphic factors of the amygdala in individuals with schizophrenia, the topic is still of interest to further research due to the confounding factors found in past research.

One main reason to continue researching the amygdala is the methods utilized in previous studies. In Kalus et al. (2004), manual region of interest tracing was utilized to segment the amygdala in MRI scans; a similar method was also utilized in Niu et al. (2004). By tracing the amygdala, over-segmentation or under-segmentation can occur and affect the results of the findings. Another variable that may affect the results and may need further research is the sample size. In both studies, a small sample size was utilized

to obtain the results (Kalus et al., 2005, Niu et al., 2004). Utilizing small sample sizes may affect the validity of the results and requires further research to verify findings.

The overarching aim of this study was to characterize the shape features of the hippocampus and amygdala and determine whether they are different between men and women with schizophrenia. Understanding the differences in brain anatomy between men and women diagnosed with schizophrenia, specifically the hippocampus and amygdala due to their involvement with the pathology of schizophrenia, can open a discussion on how sex-related neuroanatomical differences can affect the manifestation of symptoms and, eventually, lead to better disease management and effectively treat unique symptom profiles.

Methods

This study utilized archival data collected from the Conte Center for the Neuroscience of Mental Disorders (CCNM) at Washington University of St. Louis and the Center for Biomedical Research Excellence (COBRE) through the Mind Research Network and the University of New Mexico. The data was obtained from the online open-access repository SchizConnect (http://schizconnect.org), which was anonymized before the incorporation of this study.

Participants

All participants were screened and excluded if they presented the following characteristics: 1) history of an intellectual disability (of all severities), 2) had a past head injury that resulted in the loss of consciousness, and 3) history of substance abuse disorder or substance dependence (Delawalla et al., 2006; Mayer et al., 2013). Subjects with schizophrenia were diagnosed through the criteria outlined in the Diagnostic and

Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) (Delawalla et al., 2006; Mayer et al., 2013). The diagnosis of the subjects was determined by utilizing a Structured Clinical Interview to solidify diagnoses (Delawalla et al., 2006; Mayer et al., 2013).

A total of 388 subjects were collected from both data sets. The total subjects were separated into four categories: 1) control female (CONF, n = 68), 2) schizophrenia female (SCZF, n = 52), 3) control male (CONM, n = 121), and 4) schizophrenia male (SCZM, n = 147). The ages of all subjects ranged from ages 14 to 68. Informed consent for each data set was collected from all participants according to the guidelines from both institutions (Cobia et al., 2021; Mayer et al., 2013).

Imaging Processing

For the CCNM data, magnetic resonance images were collected on a Siemens Magnetom 1.5T scanner utilizing a turbo-FLASH sequence (repetition time = 20msec, echo time = 5.4msec, flip angle = 30°, 180 slices, FOV (field of view) = 256mm, matrix = 356 x 256, time = 13.5 min) (Cobia et al., 2021). For the COBRE data, all magnetic resonance images were collected on a Siemens 3T scanner utilizing a five-echo multiecho MPRAGE sequence [TE (echo times) = 1.64, 3.5, 5.36, 7.22, 9.08 ms, TR (repetition time) = 2.53 s, inversion time = 1.2 s, 7° flip angle, number of excitations = 1, slice thickness = 1 mm, FOV = 256mm, resolution = 256 x 256] (Mayer et al., 2013).

The raw T1-scans of the magnetic resonance images were first processed using the neuroimaging toolkit FreeSurfer v6.0 (https://surfer.nmr.mgh.harvard.edu/). The images were edited according to established protocols (Dale et al., 1999; Beelen et al., 2020), which include fixing skull stripping errors, fixing intensity normalization errors to

increase white matter surface, fixing topological errors, fixing white matter errors, and fixing pial errors (Beelen et al., 2020). Characterization of the shape feature of the amygdala and hippocampus was accomplished using a high-dimensional brain mapping procedure known as Large Deformation Diffeomorphic Metric Mapping (LDDMM; Csernansky et al., 2004; Khan et al., 2008). First, the subcortical segmentation output from FreeSurfer was used for the initial rigid registration of both structures. Then atlases of both the hippocampus and amygdala were warped into each subject space with diffeomorphic procedures. Finally, a tessellated graph was superimposed on each structure, with matching coordinates based on template maps.

Data Analysis

To analyze the demographic variables of the data (race, sex, age, first- and second-generation antipsychotic usage, and handedness), chi-square and ANOVA analyses were used to examine group differences. The socioeconomic status of each subject was excluded from the overall data analysis due to the different measures used to characterize it from each cohort as outlined by Mayer et al. (2013) and Delawalla et al. (2006). The data from the chi-square and ANOVA analyses, including ANOVA F-test results, degrees of freedom (df), and p-values, for these variables are outlined in Table 1.

Imaging data from both COBRE and CCNM cohorts were harmonized using neuroComBat procedures (Fortin et al., 2018) to eliminate or account for the effects of the use of different scanners in both datasets and its potential effects on further analysis of the regions of interest. The surface output of the harmonized data was reviewed and subjects that did not possess surface data were eliminated from the overall analysis. Differences between groups in the surface shape of both the amygdala and hippocampus

were accomplished by constructing vertex-wise t-maps for each group comparison. Deformation values at each vertex along the surface were compiled per group and evaluated using t-tests. The resulting t-values were mapped onto an average map of each structure and assigned a color representing the strength of significance. All comparisons were corrected for multiple comparisons using random field theory (Brett et al., 2003).

Results

Demographics Table

The mean age of the SCZ group was 34.7 for SCZM and 38.9 for SCZF, with a standard deviation (SD) of 13.3 and 12.8 respectively. For the CON group, the mean age for CONM was 35.5 and 33.5 for CONF, with an SD of 13.6 and 13.2 respectively. There was no statistical significance between the groups on age (F_{df}=3, p = 0.145). The first-generation and second-generation antipsychotic drug usage was analyzed between SCZF and SCZM subjects. Reviewing the first-generation antipsychotic usage, the mean dosage (in mg) was 121.3 in males and 122.8 in females, with an SD of 381.6 and 361.1 respectively (F_{df}=1, p = 0.981). For the second-generation antipsychotic dosage, SCZM had a mean of 276.4 and SCZF had a mean of 287.4, with an SD of 460.5 and 257.4 respectively (F_{df}=1, p = 0.871). Both first- and second-generation antipsychotics did not significantly differ between groups (see Table 1).

The percentages of right-handedness, medication use, and race were also analyzed between all groups. There was no statistically significant difference in handedness between all groups (χ^2_X = 1.56, p = 0.955). Additionally, the percentage of medication usage did not show statistical significance between SCZF and SCZM subjects (χ^2_X = 0.832, p = 0.362) (Table 1). Lastly, race was statistically significant between SCZM and

CONM ($\chi^2_X = 14.964$, $p = 0.021$) and SCZF and CONF ($\chi^2_X = 14.964$, $p = 0.021$) (Table 1).

Table 1. Demographic Characteristics of Study Sample

	SCZ (n = 199)		CON (n = 189)		Omnibus Statistic		
	Male (n=147)	Female (n=52)	Male (n=121)	Female (n=68)			
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	*F*-test	df	*p*
Age (years)	34.7 (13.3)	38.9 (12.8)	35.5 (13.6)	33.5 (13.2)	1.811	3	0.145
1st-Gen Antipsychotic (mg)	121.3 (381.6)	122.8 (361.1)			0.001	1	0.981
2nd -Gen Antipsychotic (mg)	276.4 (460.5)	287.4 (257.4)			0.027	1	0.871
	N	N	N	N	X^2	df	*p*
Sex Percentage	74%	26%	64%	36%	388	3	**<0.001**
Right-Handed (%)	88.4%	87.5%	90%	92.5%	1.56	6	0.955
Medication Use (% yes)	92.5%	96.2%			0.832	1	0.362
Race (% White)	68%	58%	81%	78%	14.964	6	**0.021*+**

* Significant difference between SCZM and CONM
+ Significant difference between SCZF and CONF

Imaging Analysis

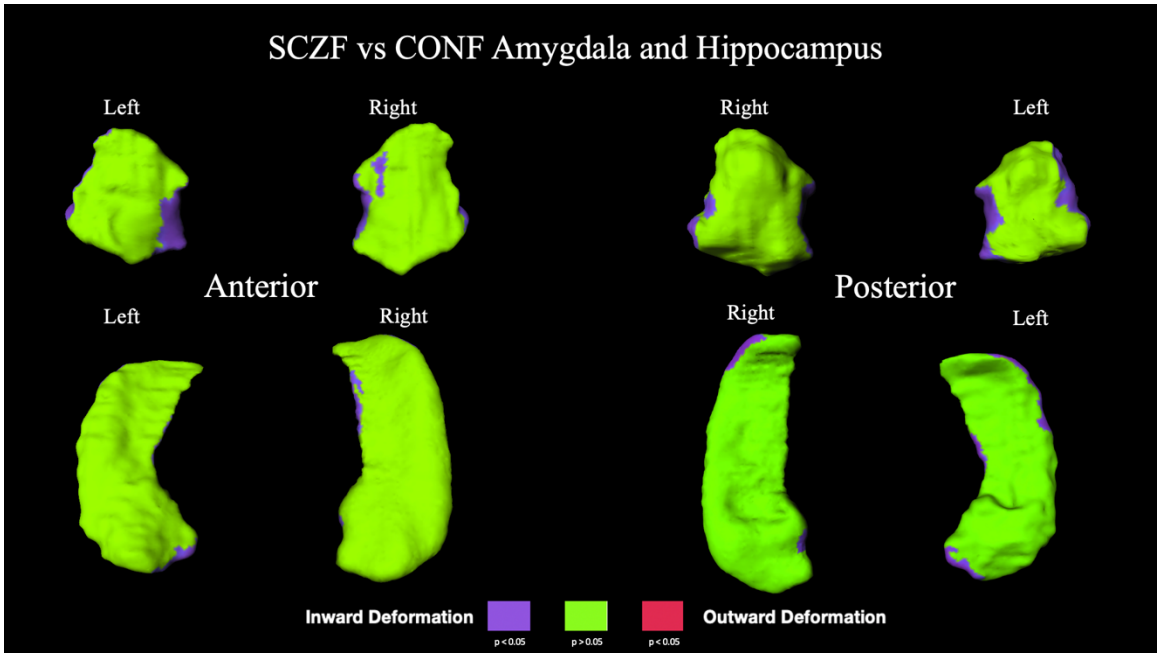
The following group contrast vertex-wise t-maps were generated for both the amygdala and hippocampus: SCZM vs CONM, SCZF vs CONF, CONM vs CONF, and SCZM vs SCZF. Significant differences between groups were observed for all contrasts, with the exception of SCZM vs CONM, in which no differences survived multiple comparison corrections.

Examination of the amygdala contrast map between SCZF and CONF subjects revealed significant inward deformations in the lateral and medial aspects of the amygdala for SCZF (Figure 1). Looking at hippocampus shape differences of SCZF and CONF, significant inward deformation was seen in SCZF in both the medial and lateral aspects of the hippocampus, namely the subiculum and CA1. These results suggest

localized volume loss, as represented by an abnormal surface shape, is present and unique in females with schizophrenia relative to healthy females.

Figure 1

Amygdala and Hippocampal Differences Between SCZ and CONF



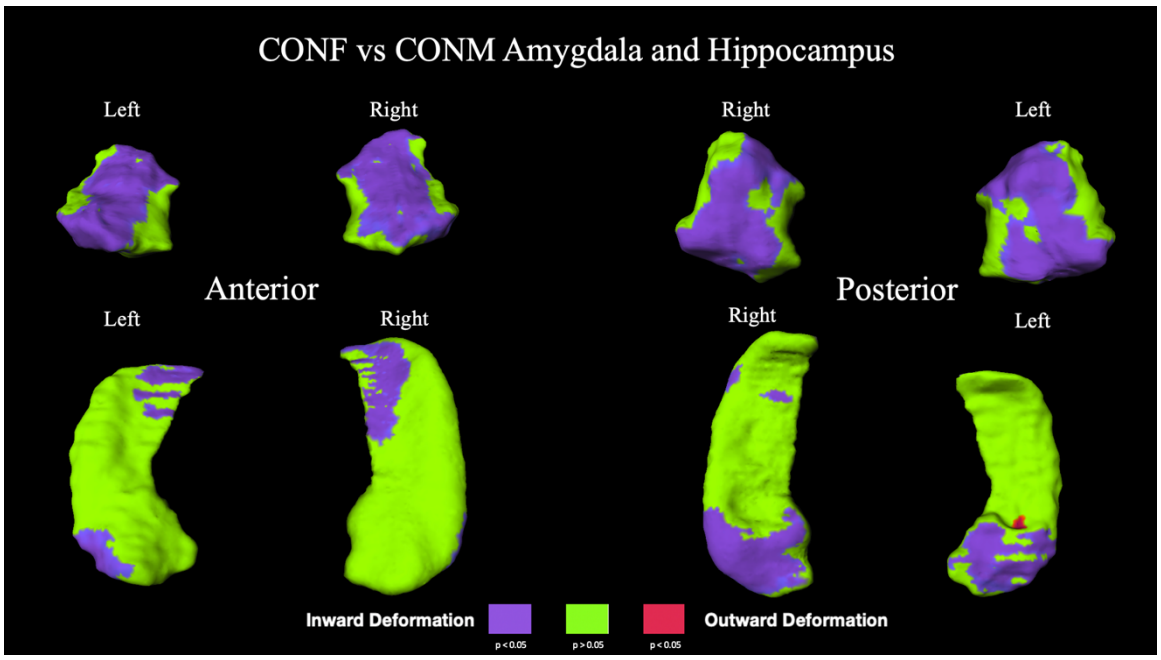
Note. This figure demonstrates anterior and posterior views of the left and right amygdala and hippocampal vertex-wise t-maps between female controls and females with schizophrenia. Cooler colors demonstrate an inward deformation in relation to females with schizophrenia ($p < 0.05$). Warmer colors demonstrate an outward deformation in relation to females without schizophrenia ($p < 0.05$). Green indicated no significant inward or outward differences between the two groups. All maps were corrected using an application of random field theory.

Examining results from amygdala mapping between CONF and CONM subjects, a significant shape difference was noted in the amygdala as an inward deformation in healthy females relative to males (Figure 2). These differences were manifested along the dorsal and ventral aspects of the amygdala. Looking at the hippocampus, two results were illustrated. First, healthy females exhibited an inward difference in the posterior and

anterior regions of the hippocampus, namely the CA1 and subiculum regions. Second, a modest outward deformation was noted in healthy male subjects compared to healthy female subjects. This outward deformation was seen in the left hippocampus posterior to the head of the hippocampus (red region in Figure 2). These results suggest localized volume loss is present in healthy females and a localized volume gain in healthy males.

Figure 2

Amygdala and Hippocampal Differences Between CONF and CONM



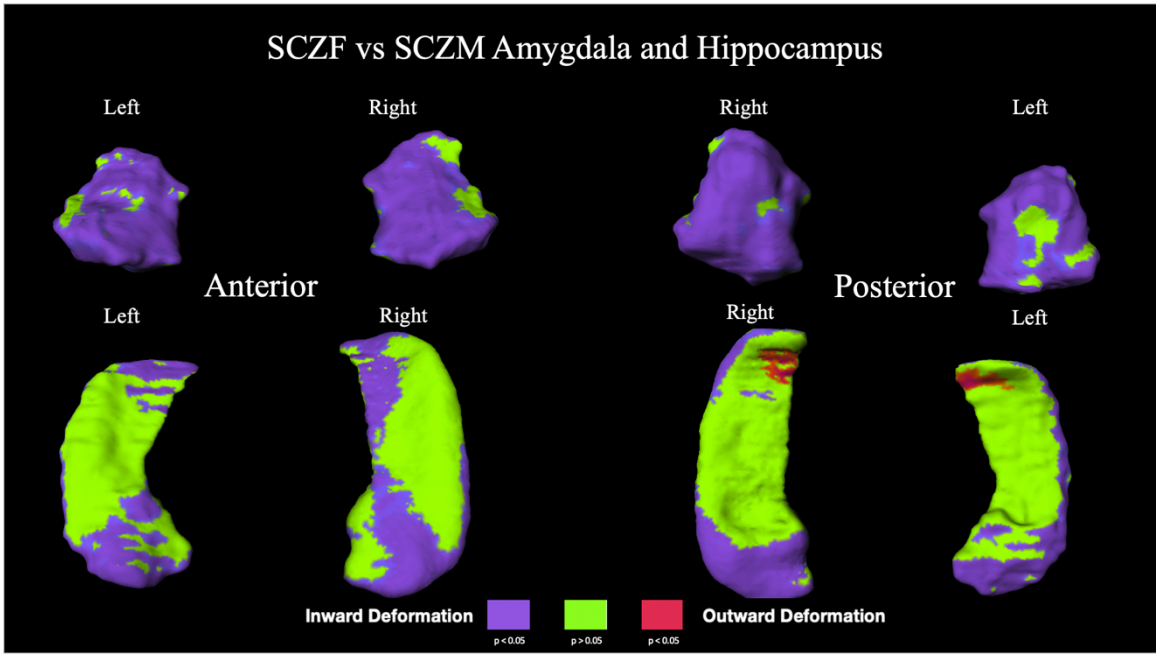
Note. This figure demonstrates the anterior and posterior views of the left and right amygdala and hippocampal vertex-wise t-maps between female controls and male controls. Cooler colors demonstrate an inward deformation in relation to female controls ($p < 0.05$). Warmer colors demonstrate an outward deformation in relation to male controls ($p < 0.05$). Green indicated no significant inward or outward differences between the two groups. All maps were corrected using an application of random field theory.

Finally, examination of t-maps between SCM and SCZF revealed a broad inward shape in both the left and right amygdala in women with schizophrenia that encompassed almost the entirety of the amygdala (Figure 3). Examination of the hippocampus revealed

two main results illustrated in the vertex-wise maps. First, an inward shape deformation was exhibited in females with schizophrenia and broadly distributed across the anterior and posterior regions of the hippocampus. Specifically, these inward differences were demonstrated in the CA1 region and the subiculum. Second, there was a modest outward difference in men with schizophrenia noted in the dorsal aspects of the tail of the hippocampus bilaterally (Figure 3). These results suggest localized volume loss is present in females with schizophrenia and a localized volume gain in males with schizophrenia.

Figure 3

Amygdala and Hippocampal Differences Between SCZF and SCZM



Note. This figure demonstrates the anterior and posterior views of the left and right amygdala and hippocampal vertex-wise t-maps between females with schizophrenia and males with schizophrenia. Cooler colors demonstrate an inward deformation in relation to females with schizophrenia ($p < 0.05$). Warmer colors demonstrate an outward deformation in relation to males with schizophrenia ($p < 0.05$). Green indicated no significant inward or outward differences between the two groups. All maps were corrected using an application of random field theory.

Discussion

The overarching aim of this study was to characterize the shape features of the hippocampus and amygdala and determine whether they are structurally different between men and women with schizophrenia. Based on analyses of the amygdala and hippocampus the findings revealed inward shape deformations were observed in SCZF relative to CONF subjects, as well as a slight inward shape deformation in the hippocampus between these two groups.

Between men and women with schizophrenia, it was illustrated that there is a significant inward shape deformation in the amygdala in women with schizophrenia in comparison to men with schizophrenia. This correlates with the idea that individuals with schizophrenia have reduced amygdala volumes compared with individuals without schizophrenia (Mahon et al., 2013; Niu et al., 2004). Additionally, the visualizations of the hippocampus shape deformations exhibited an inward shape difference in women with schizophrenia compared to men with schizophrenia as well as a modest outward difference in hippocampal shape deformation in men with schizophrenia in comparison to females with schizophrenia. This finding corresponds with the literature that individuals with schizophrenia have a decreased hippocampal volume compared to individuals without schizophrenia (Arnold et al., 2015). The outward shape deformation in the hippocampus of individuals with schizophrenia demonstrates that there may be an increased hippocampal volume in individuals with schizophrenia, but it is not as significant as the decreased hippocampal volume seen in the hippocampus. One possibility of the outward shape deformation could be with the heredity of schizophrenia; those that have ancestral evidence of schizophrenia may have increased hippocampal

volume than those who have non-inherited schizophrenia (Harris et al., 2002). Taking this into consideration, it may be that the male subjects with schizophrenia could have had familial evidence of schizophrenia, causing the outward deformation seen in the results.

The regions in the amygdala and hippocampus that exhibited shape deformations correlate with specific functions in the brain and may give probable reasonings behind the symptom manifestation of schizophrenia. With the amygdala, some regions that were noted were the lateral and medial amygdala. In healthy individuals, the medial nucleus of the amygdala is crucial for initiating innate emotional behavior responses (Keshavarzi et al., 2014). The medial nucleus does this by sending olfactory responses and signals to the regions of the hypothalamus that are responsible for defense and reproductive behaviors (Keshavarzi et al., 2014). Additionally, the lateral nucleus of the amygdala correlates with Pavlovian fear-conditioning and plays a role in retrieving fear memories (Erlich et al., 2012). An inward shape deformation in this region, as seen with females with schizophrenia, may correlate to the symptom manifestation of blunted affect or absence of emotional responses.

In the hippocampus, the most prevalent shape deformations seen was an inward shape deformation in the CA1 and subiculum regions. For the CA1 region, one of the functions of this area is autobiographical memory, a form of episodic memory (Bartsch et al., 2011). For the subiculum, one of the functions of this area is the reconciliation of the interaction between the hippocampus and the cortices surrounding the hippocampus (O'Mara et al., 2001). Additionally, the subiculum can also play a role in inhibiting the hypothalamic-pituitary-adrenal axis and the processing of space, movements, and

memory (O'Mara, 2005). An inward shape deformation in these regions may relate to the potential deficit of memory that can be exhibited in schizophrenia. Concerning the head and tail deformations seen in the results, the head, body, and tail of the hippocampus play a role in passing information to the cortices of the hippocampus (Hackert et al., 2002). The head of the hippocampus is involved in verbal memory and individuals with larger hippocampal head volumes have a score increase in verbal memory tests (Hackert et al., 2002). The outward shape deformations seen in the head of the hippocampus may help explain potential memory functions in males with schizophrenia; more research should be conducted on if men with schizophrenia have more memory consolidation. More research needs to be conducted to understand if the body and tail of the hippocampus have a specific memory function and how that translates to the data collected from this thesis.

An interesting pattern found in the analyzed data was that the manifestations of shape differences in the hippocampus and amygdala in healthy individuals were similar to the differences seen in the hippocampus and amygdala of individuals with schizophrenia. For example, the inward differences that were seen in healthy females (Figure 2) exhibit the same patterns seen in females with schizophrenia (Figure 3). These differences, however, seem amplified in females with schizophrenia. Similarly, healthy females showed a similar pattern of inward differences in the hippocampus (Figure 2) that is also seen in females with schizophrenia (Figure 3). These hippocampal differences are also amplified in females with schizophrenia compared to controls. These findings present an avenue for future research into if there is an amplification in the inward amygdala and hippocampal difference in volumes in females with schizophrenia compared to healthy controls and why, if present, is this amplification present.

The one measure that was not included in the overall analysis of the shape deformation of the hippocampus and amygdala were the figures comparing the amygdala and hippocampus between men with and without schizophrenia. The low significance of the differences between men with and without schizophrenia may result in females with schizophrenia contributing to the shape differences seen in the SCZM versus SCZF shape analysis of the amygdala and the hippocampus. This would be in line with the literature stating that women with schizophrenia have a reduced hippocampal volume in comparison to males with schizophrenia (Egloff et al., 2018). However, literature also states that men and women with schizophrenia have decreased amygdala volume but in different hemispheres (Niu et al., 2004). The results from the harmonized data showed that women particularly have an inward difference in the amygdala, which may correlate with the decreased amygdala volume seen in the literature.

Sexual dimorphism can be a pathway to understanding how schizophrenia affects men and women differently. Highlighting the differences between the hippocampus and amygdala in individuals with schizophrenia could allow further research to progress to gain a better knowledge of if the volumetric reductions presented in past literature and the shape deformations exhibited in this study correlate to the different symptoms men and women with schizophrenia may present. Doing so would bring a better understanding of schizophrenia in general and how it differs between men and women diagnosed with this disorder. For example, research has shown that hippocampal dysfunction can be linked to positive symptoms of schizophrenia (Zierhut et al., 2010). The information gathered from this study about the hippocampal differences in individuals with schizophrenia can help further understand how hippocampal shape deformation can contribute to different

symptoms seen in individuals with schizophrenia and if these symptoms are sex-specific. This research can also help further the discussion on how differences in the hippocampus and the amygdala can provide an explanation of symptom manifestations in individuals with schizophrenia and open new discussions on treatment options for schizophrenia.

Currently, there are two main types of treatments for schizophrenia symptoms. The primary treatment option for individuals with schizophrenia is pharmacological interventions such as antipsychotic medications (Patel et al., 2014). A secondary treatment option is nonpharmacological techniques like such as cognitive behavioral therapy, group therapies, and individualized therapies that target different symptoms of a patient and prevent relapse (2014). Both types of treatment options progressively assist with decreasing any relapse symptoms and assist in helping individuals with schizophrenia integrate into society as smoothly as possible.

However, an aspect of treatments for schizophrenia that is overlooked is the sex-specific possibilities for treatments and therapies. Currently, clinical treatments for individuals with schizophrenia do not focus on the sex-specific differences in individuals with schizophrenia (Fernando et al., 2020). Clinical treatments can be developed to include a sex-specific focus using the evidence presented. By connecting different aspects of the brain in men and women with schizophrenia, current methods can be tailored to compensate for volume growth and reduction in an individual with schizophrenia.

A limitation of this study is the lack of socioeconomic status of the participating subjects. Lower socioeconomic status and the father and mother's education are risk factors for schizophrenia (Werner et al., 2007). Since socioeconomic status was calculated differently between the COBRE and CCNM datasets, it was not included to

keep consistency between the data. Including this factor may give more explanation between schizophrenia within the studied population and if socioeconomic status correlated with schizophrenia prevalence.

Conclusion

There is a sexual dimorphic factor of the amygdala and hippocampal shapes between men and women with schizophrenia, specifically with women with schizophrenia. Men with schizophrenia did not show a significant difference between controls, which can make women with schizophrenia the main component of the significant volume changes seen between men and women with schizophrenia. Sexual dimorphism can pave the way to a better understanding of schizophrenia and will need further research. Implementations of different therapeutic methods, such as counseling and antipsychotics, will need to be further researched in terms of sexual dimorphism and what treatments or interventions could be beneficial for men and women depending on neuroanatomical differences.

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