Sex-Specific Variation in Deep Brain Shape is Attenuated in Schizophrenia - An ENIGMA Consortium Meta-Analysis

Delaina Brooke Cimmino
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Sex-Specific Variation in Deep Brain Shape is Attenuated in Schizophrenia –
An ENIGMA Consortium Meta-Analysis

Delaina Brooke Cimmino

A thesis submitted to the faculty of
Brigham Young University
in partial fulfillment of the requirements for the degree of

Master of Science

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ABSTRACT

Sex-Specific Variation in Deep Brain Shape is Attenuated in Schizophrenia – An ENIGMA Consortium Meta-Analysis

Delaina Brooke Cimmino
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Master of Science

Schizophrenia (SCZ) is characterized by a disconnect from reality that manifests as various clinical and cognitive symptoms, as well as consistent neurobiological abnormalities. However, unique sex-related differences have been observed regarding clinical presentation that imply separate brain substrates. The present study characterized deep-brain morphology using shape features to understand whether the neurobiology of schizophrenia varies as a function of sex.

This study analyzed multi-site archival data from 1,579 male (M) and 836 female (F) participants with SCZ, as well as 1,934 male and 1,828 female healthy controls (CON) from twenty-four cross-sectional study samples from the ENIGMA Schizophrenia Workgroup. Harmonized shape analysis protocols were applied to each site's data independently for bilateral caudate, putamen, globus pallidus, accumbens, amygdala, hippocampus, and thalamus obtained from T1-weighted structural MRI scans. Four separate contrasts were conducted: 1) Schizophrenia-Male/Control-Male; 2) Schizophrenia-Female/Control-Female; 3) Schizophrenia-Male/Schizophrenia-Female; 4) Control-Male/Control-Female.

For contrasts 1 & 2, mass univariate meta-analyses revealed more-concave-than-convex shape differences for the hippocampus, amygdala, accumbens, and thalamus, with more-convex-than-concave differences in the putamen and pallidum (d = -0.30 to 0.30, SE = 0.03 to 0.10, p<0.05) in SCZ for both male and female group comparisons. More extensive patterns of deformation were noted in right hippocampus and right thalamus for SCZ women. Contrasts 3 & 4 revealed more-concave-than-convex shape differences in the thalamus, pallidum, putamen, and amygdala among females compared to males, with mixed findings in the hippocampus and caudate in both SCZ and CON contrasts (d = -0.30 to 0.20, SE = 0.03 to 0.09, p<0.05). Pattern and extent of deformation was greater in dorsal, ventral, and lateral aspects of putamen, thalamus, amygdala, and pallidum in SCZ.

Findings are consistent with prior volume-based analyses in SCZ, as well as earlier studies on sex differences in the brain. Shape patterns reveal more extensive abnormalities in SCZ women relative to SCZ men that could aid in our understanding of clinical expression and treatment response differences between men and women.

Keywords: schizophrenia, sex differences, deep brain shape, meta-analysis, neuroimaging
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Sex-Specific Variation in Deep Brain Shape is Attenuated in Schizophrenia – An ENIGMA Consortium Meta-Analysis

Schizophrenia is characterized by a disconnect from reality that manifests in the presence of positive, negative, and cognitive symptoms that vary in intensity across the lifespan and cause significant impairment in multiple functional domains (Craighead et al., 2017). Neurobiological abnormalities have been observed as a key feature of schizophrenia including cortical, deep brain, and cerebellar regions (Egloff et al., 2018). The extent to which structural changes in deep brain regions map on to the clinical presentation of the disorder is still largely unclear. Key deep-brain nuclei that are consistently implicated in the pathophysiology of schizophrenia include the hippocampus, thalamus, hypothalamus, amygdala, basal ganglia, cingulate gyrus, and cerebellum, which play an important role in behavioral and emotional responses (Gutman et al., 2022). Overall, this presentation suggests a network-based neurobiological contribution to the etiology of psychosis given the inter- and intra-connected nature of these regions. Current research efforts continue to study how structural changes to various cortical-subcortical circuits influence the onset of the disorder, progress over time, and change the presentation of the disorder, which fluctuates in intensity and continues over the lifespan.

Schizophrenia presents differently in men and women. Age of onset is typically earlier in males, who may begin experiencing symptoms between 18 and 25 years old, compared to females, who demonstrate functionally impairing symptoms closer to 30 years old or even after 45 years of age (Li et al., 2016; Ochoa et al., 2012). As premorbid functioning is an important predictor of prognosis, it is important to note that females tend to exhibit higher premorbid adjustment and social support (Giordano et al., 2021; Ochoa et al., 2012). A more severe pattern of negative symptoms is generally observed in males, including blunted affect, avolition, and anhedonia, whereas females tend to present with increased mood disturbance and elevated manic symptoms (Giordano et al., 2021; Li et al., 2016; Irving et al., 2021). Among patients who are
actively taking antipsychotics, females tend to show better compliance and better outcomes with pharmacological interventions for psychosis, although they may also be at greater risk for side effects compared to males (Li et al., 2016). These differences may be mediated by the amount of the drug that enters the brain, as females require, on average, a lower dosage to achieve the desired effects (Seeman, 2021).

Recent studies have also begun to examine potential sex differences in brain abnormalities observed in schizophrenia, suggesting a reconceptualization of the disorder that may explain the different expressions of symptomatology between males and females (Guma et al., 2017; Gutman et al., 2022; Egloff et al., 2018). Lateralization of dysconnectivity appears to be a focus of current research, finding that males tend to show a pattern of connectivity deficits that are left-lateralized and highlighted in striato-cortical systems, while the deficits in females are primarily right-lateralized (Wang et al., 2019). In terms of structural abnormalities aside from dysfunctional connectivity, differences in shape deformation have been observed in the hippocampus and amygdala between males and females, although these results appear to be inconclusive as other studies have found no significant sex-based differences in the brain (Guma et al., 2017; Egloff et al., 2018). Furthermore, both males and females present with asymmetry in limbic structures including the hippocampus, amygdala, and thalamus compared to individuals without the disorder, highlighting the emotional and behavioral impairments that arise due to the limbic system’s basic survival functions in the brain (Gutman et al., 2022).

Researchers have hypothesized that there may be a significant relationship between brain abnormalities and the presentation of symptoms in schizophrenia, and differences in clinical presentation between males and females suggest neurobiological changes that could possibly be accounted for by sex (Guma et al., 2017; Li et al., 2016; Lang et al., 2018). Larger ventricles and
smaller frontal and temporal volumes have been observed in males with schizophrenia, whereas females have exhibited smaller volumes of the anterior cingulate cortex and insula (Turkozer et al., 2020; Goldsmith et al., 2018). Guma and colleagues (2017) found an association between the intensity of negative symptoms observed in males with schizophrenia and structural changes in the amygdala. Across men and women who present with psychosis, prominent biomarkers included enlarged ventricles and a reduction in hippocampal volume (Goldsmith et al., 2018). Although researchers have studied differences in the clinical presentation of psychosis between males and females, the underlying mechanisms contributing to these findings are unclear and warrant further research.

The present study sought to investigate sex differences in deep-brain structures implicated in the pathophysiology of schizophrenia using high-dimensional brain mapping procedures. Shape deformation of deep-brain regions was quantified using surface metrics in men and women with and without schizophrenia from multiple worldwide datasets. Using a meta-analytic approach, four contrast models were constructed: 1) men with vs. without schizophrenia; 2) women with vs. without schizophrenia; 3) men vs. women with schizophrenia; and 4) men vs. women without schizophrenia. It was hypothesized that patients with schizophrenia would demonstrate abnormal shape deformation in the amygdala, hippocampus, thalamus, hypothalamus, and basal ganglia (i.e., caudate, putamen, globus pallidus, and nucleus accumbens) compared to healthy controls. Furthermore, it was hypothesized that abnormal shape deformation in the amygdala, hippocampus, thalamus, and basal ganglia would vary among males and females with schizophrenia, such that greater caudate and hippocampal deformation would be observed in males, but greater deformation of the amygdala in women.
An examination of potential sexual dimorphisms in deep-brain regions in schizophrenia will aid in our understanding of the unique neurobiological contributions, as well as underlying mechanisms, of the disorder as they specifically relate to biological sex. The application of new insights from this work can strengthen assessment, improve diagnostic approaches, and allow for more effective personalized treatment of schizophrenia patients.

**Methods**

**Study Samples**

This study included archival data on 6,177 participants from twenty-three cross-sectional study samples. In total, 2,415 individuals with schizophrenia (1,579 males and 836 females) and 3,762 healthy controls (1,934 males and 1,828 females) were included in the meta-analysis, with data collected through the ENIGMA Schizophrenia Working Group. Measurement of clinical symptoms of the schizophrenia group was based on the Scale for the Assessment of Positive Symptoms (SAPS), the Scale for the Assessment of Negative Symptoms (SANS), and the Positive and Negative Symptom Scale (PANSS), as well as report of duration of illness and symptom severity (Andreasen, 1984a; Andreasen, 1984b; Kay & Opler, 1987). Participants provided written informed consent approved by local Institutional Review Boards prior to participating in their respective studies. The characteristics of this sample, including age, age of illness onset, duration of illness, and symptom severity, are provided in Table 1. A breakdown of the individual cohorts, including number of schizophrenia patients and controls as well as age and sex, is provided in Table 2. The average age of schizophrenia participants was approximately 35.2 years (SD = 12.4), whereas the average age of healthy controls was 33.2 years (SD = 13.2). The total scores across data sets were 63.9 for the PANSS (SD = 19.4), 16.4 for the SAPS (SD =
13.5), and 19.5 for the SANS (SD = 16.6). For data sets that recorded current antipsychotic type and dose, the average chlorpromazine dose was equivalent to 366.8 milligrams (Woods, 2003).

**Image Acquisition and Processing**

1. **FreeSurfer Segmentation:** High-resolution structural T1-weighted brain scans were acquired from each participant. Deep brain surface measures were characterized using the validated ENIGMA-Shape pipeline (Gutman et al., 2022). Deep-brain regions of interest (ROI) were initially defined using the FreeSurfer segmentation protocol, which includes the thalamus, hippocampus, amygdala, pallidum, caudate, accumbens, and putamen from both the right and left hemispheres.

2. **Surface Triangulation:** In each subject, segmented ROIs were tessellated with a triangulated surface model with vertices that corresponded to a standard template surface (Wang et al., 2011). The resulting surfaces underwent visual quality control by individual raters at each participating site according to the ENIGMA-Shape Quality Control Guide and local quality control by the University of Southern California Imaging Genetics Center.

3. **Surface Registration:** The ENIGMA shape atlas provided a single template for all studies that contributed to the data set, averaging surface models of 200 unrelated individuals from the Queensland Twin Imaging Study.

4. **Shape Computation:** Global brain volume measures (cortical gray matter, cerebral white matter, and cerebellar gray and white matter for covariate purposes), as well as deep brain shape deformation, were extracted from each individual. A medial curve was computed for individual shape models, and one measure of shape was calculated at each vertex: thickness was calculated as the distance to the medial curve (Gutman
et al., 2022; Wang et al., 2011) and group differences were assessed by comparing vertex-wise maps.

5. Statistical Analyses: All statistical analyses were performed using the R statistical package (v4.2.2; R Core Team 2022). Vertex-wise mass univariate analysis per shape measure were performed first, followed by the aggregation of effect sizes, regression parameters, and confidence intervals for mass univariate meta-analysis. The meta-analysis was conducted by using the inverse variance-based mixed effects sample weighting as implemented in the R metafor package. Linear model analyses were performed for participants with schizophrenia (SCZ) and healthy controls (CON), comparing males (M) versus females (F) with and without a diagnosis of schizophrenia to assess for sex differences, as well as a broader comparison of schizophrenia patients versus healthy controls per sex to determine the impact of psychosis on shape deformation of deep brain regions. To summarize, four separate contrasts were conducted: 1) SCZ-M/CON-M; 2) SCZ-F/CON-F; 3) SCZ-M/SCZ-F; 4) CON-M/CON-F. In all models, age was accounted for by including its linear and quadratic terms, and intracranial volume (ICV) was also included as a covariate. Maps of p-values were corrected for multiple comparisons across all structures and measures for each linear model using a modified searchlight false discovery rate (FDR) procedure (Langers et al., 2007).

Results

Effect of Diagnosis on Bilateral Shape Features in Males

Patterns of deep brain shape deformation were observed across several regions based on diagnosis in male participants, with a predominance of regions in the bilateral hippocampus, amygdala, accumbens, pallidum, caudate, putamen, and thalamus showing abnormal shape
deformation for males with schizophrenia as compared with healthy controls (see Figure 1). Within the bilateral hippocampus, amygdala, accumbens, and thalamus, there was a pattern of more concave-than-convex shape differences in males with schizophrenia compared with controls. Within the bilateral putamen and pallidum, there was a pattern of more convex-than-concave shape differences in males with schizophrenia. Findings were mixed when it came to the caudate, with increased thinning observed in the medial caudate and more thickening in the lateral regions of the caudate. More extensive patterns of deformation were observed in the dorsal putamen, lateral hippocampus, pallidum, and lateral regions of the thalamus among males with schizophrenia. The magnitude of the above effects ranges from small to moderate (d = -0.30 to 0.30, p<0.05).

**Effect of Diagnosis on Bilateral Shape Features in Females**

Patterns of deep brain shape deformation were also observed across multiple structures based on diagnosis in female participants, with a predominance of regions in the bilateral hippocampus, amygdala, caudate, putamen, accumbens, pallidum, and thalamus indicating shape deformation for females with schizophrenia as compared with healthy control (see Figure 2). Within the bilateral hippocampus, amygdala, accumbens, and thalamus, there was a pattern of more concave-than-convex shape differences in females with schizophrenia compared with controls. Within the bilateral putamen and pallidum, there was a pattern of more convex-than-concave shape differences in females with schizophrenia. Similar to males, findings were mixed when it came to the caudate, with greater thinning in the medial caudate and more thickening in the lateral regions. More extensive patterns of deformation were observed in the right thalamus and right hippocampus among women with schizophrenia, more so than what was observed in the SCZ-M vs. CON-M model. The magnitude of the above effects ranges from small to moderate (d = -0.30 to 0.30, p<0.05).
Effect of Sex on Bilateral Shape Features in Healthy Controls

Patterns of deep brain shape deformation were observed across all structures on the basis of biological sex in healthy controls, with a predominance of regions in the bilateral putamen, amygdala, thalamus, caudate, hippocampus, and pallidum indicating shape deformation in females as compared with males (see Figure 3). Within the thalamus, pallidum, putamen, and amygdala, there was a pattern of more concave-than-convex shape differences in females compared to male controls. Findings were mixed in the hippocampus and caudate, with medial regions of the caudate showing greater thickness in females compared to males and anterior regions of the hippocampus showing more thinning in females. Shape differences were not observed in the accumbens. More extensive shape differences were observed in the dorsal putamen, amygdala, left pallidum, and dorsal thalamus in healthy controls. The magnitude of the above effects ranges from small to moderate (d = -0.30 to 0.20, p<0.05).

Effect of Sex on Bilateral Shape Features in Participants With Schizophrenia

Patterns of deep brain shape deformation were also observed across all structures among males and females with schizophrenia, with a predominance of regions in the bilateral hippocampus, amygdala, caudate, putamen, pallidum, and thalamus showing shape deformation in females as compared with males (see Figure 4). Within the bilateral pallidum, putamen, and amygdala, there was a pattern of more concave-than-convex shape differences in females compared to males with schizophrenia. Similar to healthy controls, anterior regions of the hippocampus showed more thinning in females, with mixed findings in the caudate. Medial regions of the caudate showed greater thickness in females compared to males. Of note, while anterior regions of the thalamus showed more thinning in females compared to males, the posterior thalamus indicated greater thickness in females with schizophrenia, a pattern that was also observed in the CON-M vs. CON-F model but to a lesser extent. More extensive patterns of deformation were observed in dorsal, ventral, and lateral aspects of
putamen, thalamus, amygdala, and pallidum for participants with schizophrenia. The magnitude of the above effects ranged from small to moderate (d = -0.30 to 0.20, p<0.05).

**Discussion**

The overarching aim of this study was to conduct a meta-analysis of deep brain shape deformation among males and females with schizophrenia. Four separate contrasts were conducted: 1) SCZ-M/CON-M (i.e., males with schizophrenia vs. healthy controls); 2) SCZ-F/CON-F (i.e., females with schizophrenia vs. healthy controls); 3) SCZ-M/SCZ-F (i.e., males vs. females with schizophrenia); 4) CON-M/CON-F (i.e., male vs. female controls). Given the literature on brain pathways and functional impairment in schizophrenia, it was hypothesized that abnormal shape deformation in the amygdala, hippocampus, thalamus, and basal ganglia would vary among males and females with a diagnosis, such that decreased caudate and hippocampal volume, as well as enlargement of the amygdala, would be observed in males. Looking at the effect of disease, there was a predominance of regions showing more-concave-than-convex shape differences across the bilateral hippocampus, amygdala, accumbens, and thalamus, with more-convex-than-concave differences in the putamen and pallidum in both male and female comparisons of SCZ/CON. Pattern and extent of deformation was greater in the right hippocampus and right thalamus for SCZ women relative to male comparisons of SCZ/CON. Regarding sex differences, there was a predominance of regions showing more-concave-than-convex shape differences in the thalamus, pallidum, putamen, and amygdala among females compared to males, with mixed findings in the hippocampus and caudate in both SCZ and CON contrasts. More extensive patterns of deformation were observed in dorsal, ventral, and lateral aspects of putamen, thalamus, amygdala, and pallidum in SCZ.
Impact of Diagnosis and Sex on Shape Deformation

These findings are consistent with prior volume-based analyses of patients with schizophrenia compared to healthy controls (Gutman et al., 2022; Okada et al., 2016; Tu et al., 2022). In a study of overlapping subjects, greater shape deformation was reported in the bilateral hippocampus, amygdala, thalamus, and accumbens compared to healthy controls, whereas increased volumes were reported in the bilateral putamen, pallidum, and caudate (Gutman et al., 2022). A meta-analysis of 2,564 participants reported decreased volume in the bilateral hippocampus, amygdala, thalamus, and accumbens in patients with schizophrenia compared to healthy controls, whereas increased volumes were observed in the bilateral caudate, putamen, and pallidum (Okada et al., 2016). A single-site study of 160 participants with schizophrenia and 160 healthy controls reported a significant reduction in hippocampal and thalamic volumes, along with increased volume of the pallidum (Tu et al., 2022). Similarly, Goldsmith and colleagues (2018) highlighted enlarged ventricles and a reduction in hippocampal volume as potential biomarkers of psychosis.

Looking at sex differences in neuroanatomical organization for healthy individuals, broad findings in the literature have consistently revealed larger intracranial volume in males compared to females (Hines, 2020). The present study controlled for intracranial volume across all linear models, which is typical for shape analysis studies, and our meta-analysis still revealed sex differences in deep brain shape deformation. These results were consistent with prior volume-based analyses of sex differences in deep brain regions (Hines, 2020; Ritchie et al., 2018; Ruigrok et al., 2014). A single-site study of 5,216 participants reported increased volume of the amygdala, caudate, pallidum, putamen, and thalamus in males compared to females, with females showing increased volume of the accumbens (Ritchie et al., 2018). A meta-analysis of
sex differences in brain structure reported larger volumes and higher tissue densities in the bilateral amygdala, hippocampus, and putamen (Ruigrok et al., 2014). Hines (2020) observed smaller nuclei in the hypothalamus and stria terminalis in females compared to males, although findings vary across studies and stage of development.

Considering both structural abnormalities based on diagnosis and differences based on biological sex, the present study observed patterns of deep brain shape deformation that appear to align with previous research in that more extensive deformation was observed in patients with schizophrenia, and greater thickness observed in males compared to females. However, the present study is one of the first to observe sex-based dimorphisms in structural organization among patients with schizophrenia. Given the variability in findings regarding sex differences in the brain, future research is necessary to replicate the finding that sex-specific variation in deep brain shape is attenuated in schizophrenia.

Theories of Brain Development and Clinical Presentation

Early studies on structural abnormalities and pathophysiological implications for patients with schizophrenia suggest that shape deformation could be influenced by environmental and genetic risk factors, course of illness, and treatment (Buckley, 2005). Specifically, deformation of the caudate nucleus is thought to be associated with whether the patient is treated with typical or atypical antipsychotic medication, as patients who switched to clozapine treatment saw greater shape deformation in the thalamus, caudate, putamen, and hippocampus (Buckley, 2005; Tronchin et al., 2020). Gaser and colleagues (2004) studied the effects of ventricular enlargement on focal atrophy of the brain (Gaser et al., 2004). Given the location of deep brain regions including the thalamus, hippocampus, and corpus callosum adjacent to the ventricles, it is possible that patterns of deformation observed in the present study are associated with enlargement of the ventricles. While effect sizes for genetic variants are small, epigenetic...
research has reported possible interactions with environmental factors, including antenatal maternal virus infections or hypoxia during neurodevelopment, that can contribute to shape deformation of the hippocampus in patients with schizophrenia, a pattern that was consistently observed between males and females in the present study (Schmitt et al., 2014).

Studies on the underlying mechanisms contributing to sex differences in neuroanatomical organization has included potential contributions of evolutionary, genetic, and environmental influences (DeCasien et al., 2022). Researchers have focused on the impact of gonadal steroids and sex chromosome dosage on brain organization. Specifically, increases in surface area of the dorsal caudate, dorsal thalamus, and rostro-caudal extremes of the hippocampus, as well as decreases in volumes of the pallidum and amygdala and decreases in cortical thickness, have been associated with carriage of supernumerary X chromosomes compared to karyotypically normal males and females (Arnold, 2020; Nadig et al., 2018). Given the present study’s findings that showed a pattern of greater thickness across most regions of interest in males compared to females, it is possible that sex chromosome dosage could be a potential mechanism of action contributing to these sex-based dimorphisms, although it does not provide a comprehensive explanation of differences in the caudate, thalamus, and hippocampus. Sex differences in total brain volume appear to hold over development and include both gray and white matter volume (Mills et al., 2016). While sex differences in global and regional brain anatomy are reproducible, researchers are still uncertain of their causal factors or potential connections with human behavior (DeCasien et al., 2022).

Given the extensive patterns of shape deformation observed in males and females with schizophrenia, these findings warrant consideration of how structural abnormalities map on to clinical presentation. Limbic dysfunction is believed to contribute to the affective symptoms of schizophrenia, as the neurocircuitry of fear-related behaviors involve the critical roles of the
amygdala and hippocampus (Butler et al., 2012). The interconnectedness of the frontal and temporal lobes has been associated with language, memory, and emotional processes that are impaired in patients with schizophrenia due to shape deformation in cortical and deep brain regions. Furthermore, significant relationships have been found between subcortical volumes and deformation in first-episode schizophrenia, specifically among the bilateral amygdala and hippocampus (Shi et al., 2022). The caudate and putamen, on the other hand, form the striatum and are thus implicated in cognitive and motor functioning (Williams, 2016). Specifically, the nigrostriatal pathway is often associated with severity of psychotic symptoms due to the origin of dopamine neurons in the substantia nigra. The nucleus accumbens is believed to play an important role in the presynaptic dopamine pathway (McCollum & Roberts, 2015). Furthermore, corticopallidal dysfunction is associated with functional impairments in schizophrenia due to its intermediate role in many cognitive, affective, and motor processes (Tarcijonas et al., 2020).

Given the literature on neuroanatomical organization and functional impairment in psychosis, further research will be necessary to investigate how patterns of deformation contribute to differences in clinical presentation of schizophrenia symptomatology.

Regarding sex differences in the clinical presentation of schizophrenia, males tend to present with more severe negative symptoms, including blunted affect, avolition, and anhedonia, whereas females present with more affective symptoms, including increased mood disturbance and mania (Giordano et al., 2021; Li et al., 2021). While females with schizophrenia are often diagnosed later than males with the disorder and less likely to be prescribed long-acting antipsychotics, there is no significant difference in number of hospitalizations (Sommer et al., 2020). While both males and females with schizophrenia showed decreased thickness of deep brain regions compared to healthy controls, the difference in shape deformation between males
and females were not consistent with the initial hypothesis of this study. Examination of aggregate surfaces showed greater thickness of most deep brain structures in males compared with females with schizophrenia. These differences were also observed in healthy controls, suggesting a pattern of shape deformation that is based on biological sex rather than the presence of psychosis. Findings from the present meta-analysis revealed extensive patterns of deformation that exhibited stronger vulnerability in women. Given our understanding of the relationship between limbic dysfunction and clinical symptomatology, increased mood disturbance and manic symptoms in females could be related to structural abnormalities in schizophrenia.

Study Limitations and Future Directions

The present study had several limitations that should be considered in future studies. Given the neuroimaging and clinical data was collected from multiple sites, a meta-analytic approach was used to generate consensus maps. Meta-analysis is limited in that the data may not be homogeneous, and there is a potential for nonlinear correlations. To target these concerns, all subcortical shape measures were processed using the validated ENIGMA-Shape pipeline where a set of standardized scripts were used on data from all contributing sites to compute mass univariate statistics. Furthermore, methodological considerations, in part, accounted for this limitation by aggregating effect sizes across sites. Another approach for a study that reviews data from multiple sites is mega-analysis, which pools raw data across studies. In this sense, site-level effects are modeled as random effects. Meta-analyses do not assume that data from contributing sites have the same mean and variance. Another consideration is the noise that is generated by the FreeSurfer software, which can impact shape measurements that are based on vertex-wise information. This limitation was mostly addressed through quality assurance procedures that were completed by individual raters and the USC Imaging Genetics Center.
This meta-analysis observed sex differences in deep brain shape deformation in patients with schizophrenia and healthy controls. Recent theories have explored the different subtypes of schizophrenia based on predominant symptoms experienced by the client. Further research exploring the underlying mechanisms of these schizophrenia subtypes may lead to insights regarding the differences in clinical presentation among males and females. Additionally, the present study did not analyze the potential impact of medication on shape deformation, which can be an important area of future research given the literature on the effects of antipsychotics in the brain. Furthermore, the lack of research on distal and proximal influences of sex differences in the brain lead to challenges when it comes to interpreting patterns of shape deformation. Future research should focus on the environmental and biological correlates of differences in brain organization, as well as their connection to changes in human behavior. Although the present study observed patterns of shape deformation among males and females with schizophrenia, it is still uncertain whether these differences map on to clinical symptomatology or response to treatment, which is a focus of future research.

**Conclusion**

In conclusion, compared to prior studies, our meta-analysis of deep brain regions revealed strong patterns of shape deformation that provide stronger insights into sex differences in healthy individuals and patients with schizophrenia. Findings from our meta-analysis suggest that sex-based patterns of deep brain shape deformation in schizophrenia reveal a particular vulnerability in females. There are several mechanisms that may contribute to surface contraction and thinning across deep brain regions, with more nuanced differences that may be dependent on the participant’s sex. These results can enhance our understanding of the unique neurobiological contributions and underlying mechanisms of psychosis as they pertain to biological sex, the application of which can strengthen assessment, improve diagnostic approaches, and allow for more effective personalized treatment of patients with schizophrenia.
References


### Table 1

**Sample Characteristics**

<table>
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<tr>
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<th>SCZ-M</th>
<th>SCZ-F</th>
<th>CON-M</th>
<th>CON-F</th>
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<td>1,579</td>
<td>836</td>
<td>1,934</td>
<td>1,828</td>
</tr>
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<td>Age, years</td>
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<td>33.3 (SD = 12.8)</td>
<td>33.1 (SD = 13.3)</td>
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<td>Age at onset, years</td>
<td>23.1 (SD = 6.8)</td>
<td>-25.9 (SD = 9.1)</td>
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<td>Duration of illness, years</td>
<td>24.9</td>
<td>-21.0</td>
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<td>PANSS total</td>
<td>65.8 (SD = 19.8)</td>
<td>-59.9 (SD = 17.9)</td>
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<td>SAPS total</td>
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<td>-15.0 (SD = 12.5)</td>
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<tr>
<td>SANS total</td>
<td>20.7 (SD = 16.8)</td>
<td>-16.7 (SD = 15.9)</td>
<td>-</td>
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<td>Chlorpromazine dose equivalent</td>
<td>382.3 (SD = 473.2)</td>
<td>-335.7 (SD = 370.5)</td>
<td>-</td>
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</tbody>
</table>

**Note:** PANSS = Positive and Negative Syndrome Scale, SANS = Scale for the Assessment of Negative Symptoms, SAPS = Scale for the Assessment of Positive Symptoms; Range of mean ages across sites were 16.3-43.9 for SCZ and 16.2-43.6 for CON; Chlorpromazine dose equivalent shows group average.
Table 2

Sample Demographics by Cohort

<table>
<thead>
<tr>
<th>Site</th>
<th>Schizophrenia</th>
<th>Healthy Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>M/F</td>
<td>Age</td>
</tr>
<tr>
<td>Basel SCORE1</td>
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<td>117/44</td>
</tr>
<tr>
<td>CAMH2</td>
<td>117</td>
<td>70/47</td>
</tr>
<tr>
<td>Dublin1</td>
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<tr>
<td>FBIRN3</td>
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<td>139/46</td>
</tr>
<tr>
<td>FIDMAG3</td>
<td>160</td>
<td>124/36</td>
</tr>
<tr>
<td>Galway1</td>
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<td>58/20</td>
</tr>
<tr>
<td>Hubin1</td>
<td>94</td>
<td>70/24</td>
</tr>
<tr>
<td>Indiana</td>
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<td>74/10</td>
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<tr>
<td>KASP SZ2</td>
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<tr>
<td>MPRC</td>
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<td>Marburg1</td>
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</tr>
<tr>
<td>NARSAD2</td>
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<td>17/9</td>
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<tr>
<td>Wellcome2</td>
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<td>41/20</td>
</tr>
</tbody>
</table>

1 Sites used the SAPS/SANS to measure clinical symptoms (n = 1,310)  
2 Sites used the PANSS to measure clinical symptoms (n = 948)  
3 Sites used the SAPS/SANS and PANSS to measure clinical symptoms
Figure 1

Deep Brain Shape Deformation in SCZ Males vs. CON Males

Note: Color bar represents magnitude of effect sizes that represent greater inward deformation (cooler colors) or outward deformation (warmer colors) of shape features in males with schizophrenia compared to healthy controls.
Figure 2

*Deep Brain Shape Deformation in SCZ Females vs. CON Females*

*Note:* Color bar represents magnitude of effect sizes that represent greater inward deformation (cooler colors) or outward deformation (warmer colors) of shape features in females with schizophrenia compared to healthy controls.
Figure 3

Deep Brain Shape Deformation in CON Females vs. CON Males

Note: Color bar represents magnitude of effect sizes that represent greater inward deformation (cooler colors) or outward deformation (warmer colors) of shape features in female controls compared to males.
**Figure 4**

*Deep Brain Shape Deformation in SCZ Females vs. SCZ Males*

*Note:* Color bar represents magnitude of effect sizes that represent greater inward deformation (cooler colors) or outward deformation (warmer colors) of shape features in females with schizophrenia compared to males