Clinical and Experimental Health Sciences

The Corpus Callosum in Schizoaffective Disorder: A Shape Analysis Study

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Received: 06.07.2023 **Accepted:** 10.06.2024

ABSTRACT

Objective: The corpus callosum is the largest white matter structure in the human brain that connects the cortical regions of both hemispheres. Diseases could lead to degenerative alterations in brain structures such as the corpus callosum (CC). Studies have associated CC abnormalities with Schizoaffective Disorder (SAD) symptoms. We predicted that there may be differences in the CC, an important structure connecting the two halves of the brain, in patients with SAD. The present study aims to analyze the CC of patients with statistical shape analysis (SSA) and compare the findings with healthy controls.

Methods: Thirty-nine SAD patients and 39 healthy individuals (11 females and 28 males) of similar age that included subjects participated in the study. CC landmarks were marked on the mid-sagittal images of each participant. The mean 'Procrustes' point was determined, and shape deformations were analyzed with thin plate spline analysis.

Results: Significant differences were observed between the shapes of CC in the two groups, and maximum CC deformation was observed in the posterior regions of SAD patients. There was no significant difference between the CC area of the SAD patients and the controls.

Conclusion: In the present study, the maximum deformation was observed in the posterior region (isthmus and splenium) and the rostrum of the CC. The first CC region, the rostrum (+genu), connects prefrontal and premotor regions, which are associated with cognitive information (landmarks = 1, 7, 8, 9, 13, 15, and 12). The second area, the splenium, connects temporal and occipital cortical areas. These predominantly have auditory, peripheral, and central visual stimulation functions (landmarks = 5, 3, and 4). The current study could assist future studies on the etiology, diagnosis, and treatment of SAD.

Keywords: Corpus callosum, schizoaffective disorder, magnetic resonance imaging, neuroimaging, computer-assisted imaging.

1. INTRODUCTION

Schizoaffective disorder (SAD) is a chronic, potentially disabling psychotic disorder common in clinical settings. SAD has been often used as a diagnostic tool for individuals with an admixture of mood and psychotic symptoms and without a certain diagnosis. Its hallmark is the presence of major mood episode symptoms (either a depressive or manic episode) concurrent with schizophrenia symptoms such as delusions, hallucinations, or disorganized speech (1). When psychotic symptoms are observed exclusively during a mood episode, DSM-5 indicates that the diagnosis should be an adequate mood disorder with psychotic properties; however, when a psychotic condition includes at least two weeks of psychosis without prominent mood symptoms, the diagnosis could be either SAD or schizophrenia. According to the DSM-5, SAD can only be diagnosed if full mood disorder episodes are present during the majority of the total active and residual course of illness, from the psychotic symptom onset until the diagnosis (2).

The corpus callosum is the largest white matter structure in the human brain that connects cortical regions in both hemispheres (3). They contain numerous intra-hemispheric and interhemispheric myelinated axonal projections. Patients who undergo complete or partial corpus callosotomy and callosal lesion intervention have provided further data on their function over the years (3). Corpus callosum shape deformation could reflect a midline neurodevelopmental abnormality (4).

Corpus callosum (CC) size was associated with cognitive and emotional deficits in several neuropsychiatric and mood

DOI: 10.33808/clinexphealthsci.1323653

disorders (5). Morphological abnormalities in the corpus callosum were associated with cognitive impairments or abnormal behavior in patients with mental disorders such as schizophrenia and bipolar disorder (6).

Quantitative morphologic analysis of each brain structure commonly entails segmentation observed with volumetric measures in neuroimaging. Volumetric alterations are intuitive markers since they could explain disease-induced atrophies or enlargements. On the other hand, structural alterations such as bending/flattening or changes in a specific section of a structure, for example, thickening of the occipital horn of ventricles, have not been adequately reflected in global volume measurements (7).

Statistical shape analysis, a relatively new method in biological research, compares body forms with specific landmarks determined by anatomical prominence (8). Knowledge of the biological variations of anatomical objects is essential for statistical shape analysis and discrimination between healthy and pathological structures (7).

In addition to schizophrenia and bipolar disorder (6,9,10,11), shape alterations in the corpus callosum (CC) were investigated in various diseases such as Multiple Sclerosis (12), mild cognitive impairment, and Alzheimer's disease (13) , autism subtypes (14), restless leg syndrome (15), and Behçet's Disease (16) with statistical shape analysis (SSA). Our study employed statistical analysis to determine the presence of a correlation between shape changes in the CC in SAD patients.

To our knowledge, this is the first study where statistical analysis was employed to determine whether there was a correlation between shape changes in CC and SAD patients.

2. METHOD

2.1. Participants and study design

The present cross-sectional retrospective study included the data collected from patients, who were diagnosed with SAD based on the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria (17) and admitted to the outpatient or inpatient clinics in a Psychiatric Training and Research Hospital between January 2018 and July 2022. The local ethics committee approved the study (IRB: 07/07/2022–2022.07.177). The images of 39 SAD cases diagnosed based on the DSM-5 criteria, met the participation criteria, and underwent cranial MRI examination were identified in the Hospital Information System (HIS) and examined by a radiologist to determine whether they were suitable for the study. Cases with additional diseases were not included in the study. Participation criteria included age between 18-65, the presence of no other psychiatric diagnosis, mental retardation, a neurological or physiological disease, and no history of alcohol or substance use during the last 6 months based on HIS data and patient statements. The control group included age – and gender-equivalent healthy individuals who met the above-mentioned study criteria, who did not have a psychiatric diagnosis, or who underwent brain MRI examinations for other reasons. In the power analysis performed Post Hoc by comparing it with similar studies (18–20) in the literature, the power was found to be 100 % .

2.2. Data collection and image analysis

All participants were scanned in the same 1.5T Philips Ingenia scanner (Philips Medical System, Best, NL) with an 8-channel array head coil. T2 Turbo Spin Echo MRI images were obtained.

2.3. Determination of the Two-Dimensional Landmarks

Mid-sagittal T2-weighted two-dimensional digital MRI images of each individual that clearly reflected the cerebral aqueduct, CC, and superior colliculus were identified (Figure 1). Corpus callosum was marked (Figure 1) on TpsDig2 version 2.32 software on each image with standardized anatomical landmarks (20–22) for data collection (23).

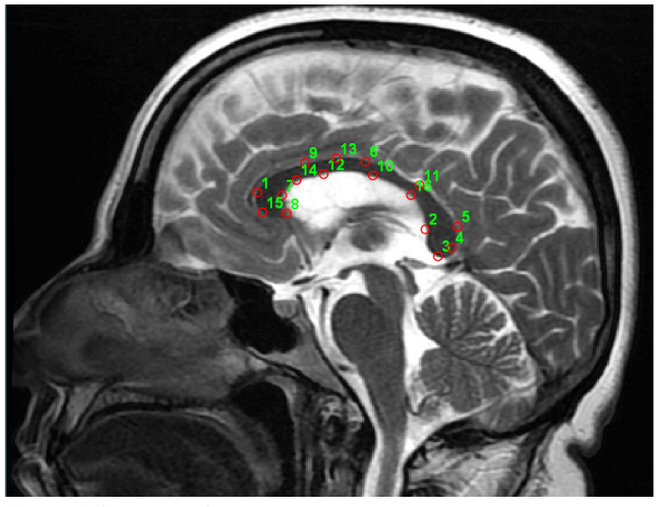

Figure 1. *'Procrustes' landmarks in a midline sagittal image.*

2.4. Statistical Deformation Analysis

The mean 'Procrustes' landmark was calculated and shape deformations were analyzed with thin plate spline (TPS) analysis with Past version 4.10 software (24) Areas with the most significant expansion or contraction were marked with different colors to indicate deformations in this analysis. The homogeneity of the variance-covariance matrices was analyzed with the Box-M test (24, 25) Due to the non-homogeneity of the matrices, the James F_J test based on a resampling procedure was employed to compare the CC shape between the control and SAD groups (25, 26) Furthermore, the root means square of Kendall's Riemann distance rho was compared with the mean to determine the overall shape variation in both groups. The allometric analysis was conducted with multivariate regression analysis of the centroid size (CS, the square root of the sum of the square of the Euclidean distance between each sign and the center) and

tangent coordinate. Model significance was determined with Wilks' lambda test. Model fit was determined based on the mean square error (MSE) and coefficient of determination (R^2) (27, 28).

2.5. Landmark Reliability

A single rater manually defined all landmarks in the present study. Intra-rater reliability was not calculated, since the high reliability of the landmark selection by the same rater was demonstrated in previous studies (28, 15).

2.6. Statistical analysis

Shapes version 1.2.6 software with R version 4.2.0, and PAST version 4.10 were employed for statistical shape analysis (24, 25) Statistical analyses were conducted on SPSS for Windows version 26 (IBM Corporation, Armonk, New York, USA) software. Data are presented in mean±standard deviation. The normal distribution of the data was analyzed with the Kolmogorov-Smirnov test, and adequate tests were employed to compare the groups based on the test results. A p-value of < .05 was considered statistically significant.

3. RESULTS

Eleven out of the 39 patients and 11 out of the 39 controls were female, and the rest were male, and there was no significant difference between the groups based on gender. The mean patient age was 42.08±11.22 and the mean control age was 41.94±12.30, and there was no significant difference between the groups based on age (p= .958).

Since the Box-M test identifies inhomogeneous matrices (F=3.3054, p< .001), the James F_J test was conducted, and it was determined that the CC shapes of SAD patients were significantly different when compared to the controls (T^2=3767.8684, p< .001) (Figure 2). The root means square of Kendall's Riemann distance (rho) to the main shape was 0.06763486 in controls, 0.07620406 in SAD patients, and 0.09275064 for all (Figure 3).

The effect of size-dependent shape changes and mean shape deformations on graphs (shrinkage) was demonstrated and compared for both groups with TPS (Figure 4). Maximum deformation was observed at the landmarks in the rostrum, anterior corpus, and splenium regions of the CC (landmarks 5, 13, 4, 6, 9, 3, 7, 8, 1, 12, 15, 10, 14, 16, 11, and 2 in descending order) (Table 1).

Multivariate regression analysis was conducted to determine the correlation size and shape in allometric analysis, and a statistically significant model (p=4.48E-246, R^2=0.1685, MSE=0.03072, and Wilks' lambda=7.913E-12) was developed.

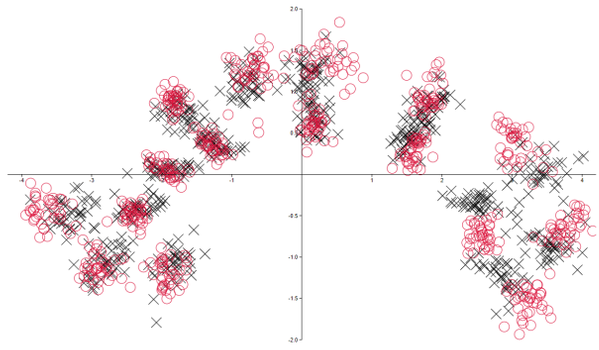

Figure 2. *Landmark scatter plot for controls (O) and schizoaffective disorder patients (X)*

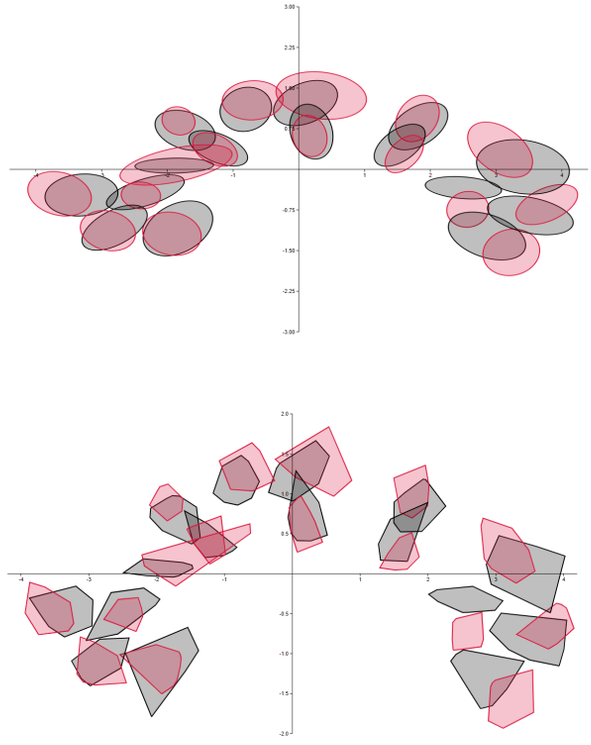

Figure 3. *%95 ellipse/convex hull graph for landmark scatter of controls (grey) and schizoaffective disorder patients (red).*

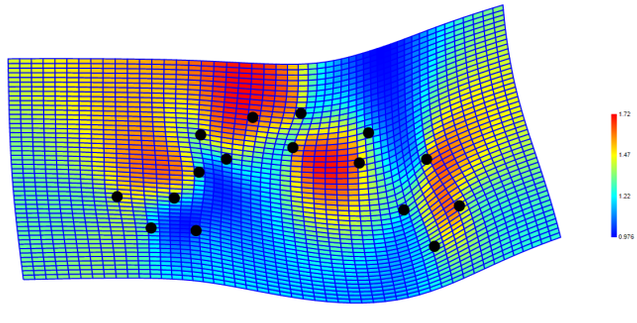

Figure 4. *Thin-plate spline transformation grid with expansion factors of the transformation from the control group to the schizoaffective disorder group.*

Table 1. *Average dissimilarities and contribution rate of the landmarks.*

Landmark	Average dissimilarity	Contribution %	R/p
1	1,9182E+13	2,96	0.5115/< .001
2	2,0122E+12	0,31	
3	3,66E+13	5,66	
4	8,181E+13	12,65	
5	1,5303E+14	23,65	
6	7,069E+13	10,93	
7	3,1194E+13	4,82	
8	2,39E+13	3,69	
9	5,41165E+13	8,37	
10	1,7166E+13	2,65	
11	9,851E+12	1,52	
12	1,8242E+13	2,82	
13	8,3762E+13	12,95	
14	1,61143E+13	2,49	
15	1,8128E+13	2,80	
16	1,1104E+13	1,72	

p-value of < .05

4. DISCUSSION

In the current study, the maximum deformation was identified in the posterior region (isthmus and splenium) and the rostrum of the CC. The first CC region, rostrum (+genu), connects prefrontal and premotor areas, which were associated with cognitive information (landmarks = 1, 7, 8, 9, 13, 15, and 12). The second region, splenium, connects temporal and occipital cortical areas. These areas predominantly have auditory, peripheral, and central visual stimulation (landmarks = 5, 3, and 4) functions (29–32).

Studies on brain structures such as the corpus callosum (CC) are limited in schizoaffective disorder. To our knowledge, there is no study where patient CCs were analyzed with statistical shape analysis (SSA), the results of which were compared with healthy controls. We think that our study will contribute to the literature in this respect.

Morphological abnormalities in the corpus callosum were associated with cognitive impairments or abnormal behavior in patients with mental disorders such as schizophrenia and bipolar disorder(6).

Only one study employed statistical analysis to determine whether there was a correlation between CC shape alterations in schizophrenia patients (SZ) (deficit syndrome (DS) and non-deficit syndrome (NDS)) and healthy controls (HC). The comparison of CC Procrustes shapes between HC and SZ revealed a statistically significant difference. The present study demonstrated callosal shape variations in SZ patients in both the DS and NDS subgroups based on the topographic distribution in CC (9).

In a study where corpus callosum abnormalities were determined based on anatomical signs in autism, no significant difference was reported in the landmark forms between patients and controls; however, the distance between the interior genu and the most posterior section was significantly shorter in the patient group. Thin-plate spline analysis demonstrated significant differences between the landmark configurations of the groups in terms of the diversion from the overall mean. Significant global shape differences were observed in the anterior lower body and posterior bottom, and a local shape difference was determined in the anterior bottom (33).

In a study where corpus callosum was investigated with statistical shape analysis in restless legs syndrome, a statistically significant shape difference was reported between the groups. The highest deformation was determined at the posterior midbody of the corpus callosum. Growth curve analysis demonstrated that an increase in disease duration and severity led to a decrease in the CC size (15).

Morphological analysis of the corpus callosum shape in normal, schizophrenic, and bipolar patients did not reveal significant global shape differences between these mental disorders. The highest differences were observed in the genu-rostrum, posterior body, isthmus, and splenium of schizophrenia and bipolar patients. Sample group comparisons revealed significant differences between all groups and global measurement parameters in various sub-regions. The present study findings suggested that the CC differed significantly in schizophrenia and bipolar disorder when compared to healthy controls, specifically in the anterior body and isthmus in schizophrenia and only in the isthmus in bipolar disorder (6). In our study, the maximum deformation was observed in the posterior region (isthmus and splenium) and rostrum of the CC in SAD patients.

In a previous study, CC area and shape were analyzed in first-episode schizophrenia and affective disorder patients, and the findings were compared with healthy controls with two-dimensional shape analysis. No differences were reported between the corpus callosum areas of the three groups, although differences were observed between the CC shapes of the schizophrenia patients and the controls. Furthermore, as the corpus callosum width narrowed, the angle decreased and led to a more curved shape only in the affective disorder group (4). In our study too, there was no significant difference between the CC area of the SAD patients and the controls.

In a study on CC, subregional volumes and the correlations between these and cognition, psychotic symptoms, and age were investigated in schizophrenia, psychotic bipolar disorder (PBD), SAD patients, their first-degree relatives, and healthy controls, and it was reported that anterior and posterior splenial volumes were significantly reduced in all groups. The schizophrenia and PBD probands exhibited robust and significant reductions, while significant reductions were of intermediate severity in the relatives group. There was a positive but differential correlation between splenial volumes and cognition in the probands and relatives. Proband groups exhibited a significant age-related decrease in the anterior splenium volume when compared to the controls.

The splenial volume was significantly reduced across the psychosis groups (34).

In a study where the morphology of the corpus callosum was compared in various stages of schizophrenia, no significant differences were reported between the total area of the groups. Similarly, in our study, there was no significant difference between the CC area of SAD patients and controls. Reductions in callosal width were observed in the anterior genu region in first-episode disorders. Similar reductions were observed in the anterior genu, as well as the posterior genu and isthmus in the chronic schizophrenia group. Reductions were present in anterior callosal regions that connect the frontal cortex at the onset of schizophrenia, and these were accompanied by changes in other callosum regions that connect cingulate, temporal, and parietal cortices in established illness (35).

In another study, structural-T1 and diffusion magnetic resonance images of SAD patients and healthy controls were obtained to determine surface-based brain morphometry and conduct diffusion tensor imaging analysis. In grey matter, SAD patients exhibited abnormalities in the frontal and temporal lobes, striatum, fusiform, cuneus, precuneus, lingual, and limbic regions. White-matter abnormalities were identified in tracts that connect these areas, including the corpus callosum, superior and inferior longitudinal fasciculi, anterior thalamic radiation, uncinate fasciculus, and cingulum bundle. The spatial overlap of abnormalities across different imaging techniques suggested widespread and consistent brain pathology in SAD. The abnormalities were mainly observed in areas that were commonly reported as abnormal in schizophrenia and, to some extent, in bipolar disorder, which could explain the clinical and etiological similarities in these disorders (36).

According to a systematic review of neuropsychological and neuroimaging studies in schizoaffective disorder, neurocognitive and neuroimaging abnormalities in schizoaffective disorder resembled schizophrenia more when compared to bipolar disorder. This could suggest that schizoaffective disorder could be a subtype of schizophrenia or part of a continuum psychosis spectrum model. schizoaffective disorder patients are more prone to schizophrenia when compared to bipolar disorder (37).

5. CONCLUSION

In the present study, SSA and CC analyses conducted on MRI images revealed significant differences between SAD patients and healthy controls. The maximum deformation was identified in the posterior region (isthmus and splenium) and rostrum of the CC. The study findings emphasized abnormal white matter distribution and subregional variations in the CC of the SAD patients. Future studies that would be conducted with larger samples could contribute to further elucidation of the present study findings.

One limitation of the study was the small sample size. Furthermore, the duration of illness for the patients is not the same. Patients take antipsychotic and/or mood stabilizers and antidepressant medications. One of the limitations of the study is that a clinical scale was not used in the study and whether there was a relationship between anatomical findings and clinical symptoms was not evaluated.

Acknowledgements: *We would like to thank Marmara University for providing access to academic databases.*
Funding: *The author(s) received no financial support for the research.*
Conflicts of interest: *The authors declare that they have no conflict of interest.*
Ethics Committee Approval: *This study was approved by Ethics Committee of Bakirkoy Dr. Sadi Konuk Training & Research HospitalNoninvasive Clinic Ethics Committee (Approval date:* 07/07/2022*; Number:* 2022.07.177*)*
Peer-review: *Externally peer-reviewed.*
Author Contributions:
Research idea: MNN,MB;ÖG
Design of the study: MB,SB
Acquisition of data for the study: ÖG,MB;MNN
Analysis of data for the study: SB,MB
Interpretation of data for the study: SB,MB
Drafting the manuscript:ÖG,MB
Revising it critically for important intellectual content: ÖG,SB,MNN,MB
Final approval of the version to be published: ÖG,SB,MNN,MB

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How to cite this article: Gül Ö, Baykara S, Namlı MN, Baykara M. The Corpus Callosum in Schizoaffective Disorder: A Shape Analysis Study. Clin Exp Health Sci 2024; 14: 691-697. DOI: 10.33808/clinexphealthsci.1323653