Original

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Insula volumes in patients with schizoaffective disorder

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ABSTRACT

We aimed to investigate insula volumes in patients with schizoaffective disorder with the motivation that schizoaffective disorder has strong resemblance of clinical presentaion with schizophrenia and bipolar disorder and that there have been studies on insula volumes in patients with schizophrenia and bipolar disorder but not in patients with schizoaffective disorder. We hypothesized that patients with schizoaffective disorder would have similar alterations in regard to insula volumes. Eighteen patients with schizoaffective disorder and nineteen healthy controls were included into the study. Insula volumes were measured by using the MRI. the mean volumes of the insula region for both sides were statistically significant smaller in patients with schizoaffective disorder compared to those of healthy ones (P<0.001). In conclusion, our findings suggest that patients with schizoaffective disorder had reduced volumes of the insula region. Beacuse of some limitations, it is required to replicate our present results in this patient group.

Key words. Schizoaffective disorder; MRI; volumes; insula

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VOLÚMENES DE LA ÍNSULA EN PACIENTES CON TRASTORNO ESQUIZOAFECTIVO

RESUMEN

Nuestro objetivo era investigar los volúmenes de la ínsula en pacientes con trastorno esquizoafectivo con la motivación de que el trastorno esquizoafectivo presenta una gran similitud de manifestación clínica con la esquizofrenia y el trastorno bipolar, además de que ha habido estudios sobre los volúmenes de la ínsula en pacientes con esquizofrenia y trastorno bipolar, pero no en pacientes con trastorno esquizoafectivo. Nuestra hipótesis era que los pacientes con trastorno esquizoafectivo tendrían alteraciones similares en cuanto a los volúmenes de la ínsula. Se incluyó en el estudio a dieciocho pacientes con trastorno esquizoafectivo y a diecinueve sujetos de control sanos. Los volúmenes medios de la región de la ínsula para ambos lados fueron estadísticamente significativos en los pacientes con trastorno esquizoafectivo en comparación con los sujetos de control sanos (P<0,001). En conclusión, nuestros hallazgos sugieren que los pacientes con trastorno esquizoafectivo tenían volúmenes reducidos de la región de la ínsula. Debido a algunas limitaciones, se requiere replicar nuestros resultados actuales en este grupo de pacientes.

Palabras clave. Trastorno esquizoafectivo; IRM; volúmenes; ínsula

INTRODUCTION

One of psychotic disorder, schizoaffective disorder is a psychiatric disorder characterized by abnormal thought processes and accompanying mood swings. The Diagnostic and Statistical Manual of Mental Disorders, version 5 revealed the most frequemtly used diagnostic criteria for the schizoaffective disorder in daily psychiatry practice[1]. In the DSM 5, clinical picture of the schizoaffective disorder includes both schizophrenia and other psychotic disorders and a mood disorder, however, it does not meet the diagnostic criteria for schizophrenia or a mood disorder separately[1]. The DSM 5 describes the essential clinical dimension of the schizoaffective disorder to have the presence of psychotic symptoms for at least two weeks, in a seperate illness period, without any mood symptoms present[1]. In daily clinical practice of psychiatry, since their clinical presentations resemble to each other, it is usually so difficult to discriminate schizophrenia, schizoaffective disorder and bipolar disorder with psychotic features. Moreover, for a longtime, it has been raised a question that schizoaffective disorder is a real separate clinical entity from schizophrenia and bipolar disorder with psychotic characteristics. In the DSM 5, schizoaffective disorder has been described in two types, first type is the bipolar one in which manic episodes are seen. Depressive episodes can be accompanied with to manic episodes. Depressive type is

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the second type in which the disorder has major depressive episodes, without manic, hypomanic, or mixed episodes. It has been questioned whether the schizoaffective disorder is a different diagnosis from bipolar disorder with psychotic features or schizophrenia itself, or a variant clinical antity of schizophrenia[2,6] The etiology of schizoaffective disorder has not been investigated enough. In fact, in psychiatry, some disorders have been studied well in terms of etiopathogenesis while some other have been ignored a bit. According to us, schizoaffective disorder seems to include in latter group. A little thing has been studied in the pathophysiology of schizoaffective disorder [7-10]. When looking at a glance to structural brain imagings, in bipolar disordered patients showed just a minimal total brain and regional volume alterations whereas in patients with schizophrenia it has been found that there was a remarkable volume reductions up to 2% of volume loss particularly in frontal lobe and hippocampal areas[11-20]. There are several investigations on patients with schizoaffective disorder in terms of neuroimaging ones.

Insula region of the brain has an important role on processing of emotions and organizations of sensorial stimulations[21]. On the other hand, human awares of interoceptive sensations, internal situation of the body, via the insula. In patients with schizophrenia, it has been demonstrated to be gray matter alterations, abnormalities in cortical thickness and cellular architecture, and disturbances in protein expressions[21]. We did not come across any magnetic resonance imaging (MRI) investigation on the insula region in patients with schizoaffective disorder in the screen of medicine literature. However, there have been limited number of studies in patients with schizophrenia and bipolar disorder which resemble clinically to schizoaffective disorder. Borgwardt et al. reported that monozygotic twins with schizophrenia showed reduced grey matter volumes of the insula in both sides[22]. In addition, in people who had high risk for the development of schizophrenia, it was demonstrated that there was a bilateral decrease in insular grey matter volumes[23,24]. Furthermore, in this people, individuals who developped a psychotic state had reduced insular grey matter volumes initially compared to those who did not demonstrate any psychotic state[23,25]. In one of several meta-analyses on the insula region in patients with schizophrenia, out of investigations evaluating insula, decreases gray matter volumes were reported in a half of them. Two of them repoorted that there was a deficit situated in the right side, while one determined that there was left-sided localization, and four revealed a bilateral deficit[26]. In other meta-analyses, it was reported gray matter volumes to be bilaterally in the insula in patients with schizophrenia[24,27-29]. In patients with bipolar disorder, another psychiatric disorder resembling to schizoaffective disorder in terms of clinical presentation, there have been limited number of studies evaluating insula volumes. In a cross-sectional designed study, Bechdolf et al. examined eleven individuals clinically at ultra-high risk of development of psychotic state, who all developed bipolar I and II disorder by follow-up, same number of matched ultra-high risked participants, without any psychiatric disorder at least twelve months of follow-up, and eleven matched healthy controls[30]. The authors reported amygdala and insula volume decreases were more pronounced in people at ultra-high risk of development of psychotic state, who all developed bipolar I and II disorder by follow-up compared to those with ultra-high risked participants, without any psychiatric disorder and healthy control subjects, suggesting that these could help to distinguish people who would develop bipolar disorder from those who would not, at least in symptomatically enriched samples.

Given the information aforementioned, in the present study, we aimed at investigating the insula volumes in patients with schizoaffective disorder with the motivation that schizoaffective disorder has strong resemblance of clinical presentation with schizophrenia and bipolar disorder and that there have been studies on insula volumes in patients with schizophrenia and bipolar disorder but not in patients with schizoaffective disorder. We hypothesized that patients with schizoaffective disorder would have similar alterations in regard to insula volumes.

MATERIALS AND METHODS

We have described all study details to patients with schizoaffective disorder and healthy control subjects before starting the investigation. After this definition, we obtained the written informed consents from all of them. As in our all previous studies, we were in accordance with the insructions of the Helsinki Declaration of 1975, as revised in 1983. All subjects were taken from the Firat University, School of Medicine, Department of Psychiatry and suffered from structural imaging protocols at Department of Radiology, Neuroradiology section, Elazig, Turkey. We should mention that the subjects of the present study were those of our previous study on pituiatry volumes (Atmaca et al. unpublished study). There were eighteen patients with schizoaffective disorder (ten females and eight males) and nineteen healthy control subjects (nine females and ten males) in that study. The mean age of patient group was 35.00±9.43 while it was 27.11±5.86. There was a significant difference regarding age between the groups (P<0.001). We obtained the approval of the Firat University School of Medicine Local Ethics Committee. We discriminated potential participants to include in our study who applied to Firat University School of Medicine Department of Psychiatry and was diagnosed as schizoaffective disorder by using the Structured Clinical Interview for DSM-IV Disorders in the Turkish version[31]. By this way, we included eighteen

patients with schizoaffective disorder and nineteen healthy control subjects in the study. To identify medical conditions which was be able to study results, whole patient group was examined in regard to medical history, and physical examination including neurological one. Same exclusion criteria with our previous study (Atmaca et al. unpublished study) were administered to patients with schizoaffective disorder. As in that study, we meticulously differentiated from schizophrenia, and bipolar disorder which can be easily mistaken for the diagnosis of schizoaffective disorder. In this context, we should note that twenty-one patients were not included in the present study since they had included in clinical presentation of schizophrenia, delusional disorder, pscyhotic disorder not other specified, or bipolar disorder with psychotic features or without psychotic features. If a clinician was hesitant about the diagnosis, the two clinicians decided together. In this way, fifteen patients were interviewed together to verify the exact diagnosis. They included in any medical contraindications for an MRI evaluation such as the presence of cardiac stent, cerebrovasculary stent, or joint apparatus, any neurological disorder such as cerebrovasculary accedant, the presence of serious current medical troubles, any past or actual history of traumatic brain injury because of different reasons, presence of any comorbid psychiatric disorder excluding depression, alcohol and/or substance abuse within the 6 months preceding the study, utilization of unstable dose of psychoactive agents within four weeks of the study. In the present investigation, we examined also nineteen healthy control comparisons. We applied several exclusion criteria to the healthy control comparisons, too. They needed not to have the DSM-IV Axis I disorders in self or in a first-degree relatives, as detected by the SCID non-patient version, traumatic brain injury, any neurologic and severe medical illnesses, or any history of psychiatric disorder. In addition, we evaluated any medical contraindications for an MRI investigation such as cardiac, cerebrovasculary stent, or joint apparel. Patients with schizoaffective disorder were not different in terms of gender, education, or handedness, but age. It was administered the Brief Psychiatric Rating Scale[32] and Scales for the Assessment of Positive and Negative Symptoms (SAPS and SANS) to patients with schizoaffective[33].

MRI PROCEDURE

A 1.5-Tesla General Electric (GE) signa Excite high speed scanner (Milwakuee, WI, USA) with a 3-D gradient-echo yielding 160–180 contiguous T1-weighted slices of 1.0-mm thickness in the sagittal plane was used to scan of brains of patients with schizoaffective disorder and healthy control subjects. We offered an option to take an anti-anxiety drug for their phobic avoidance before one our suffering from the MR examination if required. When scanning patients with schizoaffective disorder and healthy control cıomparisons, some parameters of MRI were used. They were: bandwidth=20.8, field of view [FOV]=240 mm, flip angle=20^0, [TR]=2000 ms, echo time [TE]=15.6 ms, slice thickness=2.4 mm, echo spacing=15.6 ms, with resolution of 0.9375×0.9375×2.4 mm. By the way, to get a good measurement stability, in every weeks, the scanner was calibrated with the same phantom.

To trace the landmarks of the insula region, it was benefited from the standard neuroanatomical atlases[34,35] and from methods and definitions adapted from neuroimaging studies on the pituitary which were performed by some investigators[14, 36,37]. **Measurement was performed first in the sagittal plane for the determination of boundaries. Anterior limits were accepted as orbitofrontal cortex. Posterior limit was determined as the point that gray matter ends. Superior boundary was accepted as superior cicular sulci. Ann finally, and lower liinferior limit was recognized as inferior circular sulci. Boundaries were re-evaluated and marked in coronal plane. Grey matter-white matter differentiation was used in the determination of medial and lateral limits.** As mentioned in our our previous study on pituitary volumes in patients with schizoaffective disorder (Atmaca et al., unpublished study), the measurements of the insula region were performed by an expert research neuroradiologist who was blind to the diagnosis, other information, and identities of the study subjects. All images obtained by manual tracing were transferred to Voxtool 4.6 semi-automated program to get volumetric results. Imagings belonging to the insula are presented in the Figure 1. Meanwhile, all volumes we have written were given in cubic milimeters.

Statistical Analysis

In the Results section, we gave all results in the manner of mean±standard deviation. To perform the statistical analyses, it was utilized the Statistical Package for Social Sciences (SPSS for Windows, version 22.0, SPSS, Chicago, IL, USA). Effect sizes were calculated, by using the Cohen's d. For comparing relative volumes of insula region, we used independent sample *t* test. In addition, for the comparison of categorical variables, chi-square test was chosen. We also used Analysis of Covariance (ANCOVA) in General Linear Model in the SPSS to exclude the effects of age, total brain volumes and gender distribution on insula region. To obtain correlational analyses, Spearman's rank test was chosen. Statistical significance was accepted as $P<0.05$ by a two-tailed test.

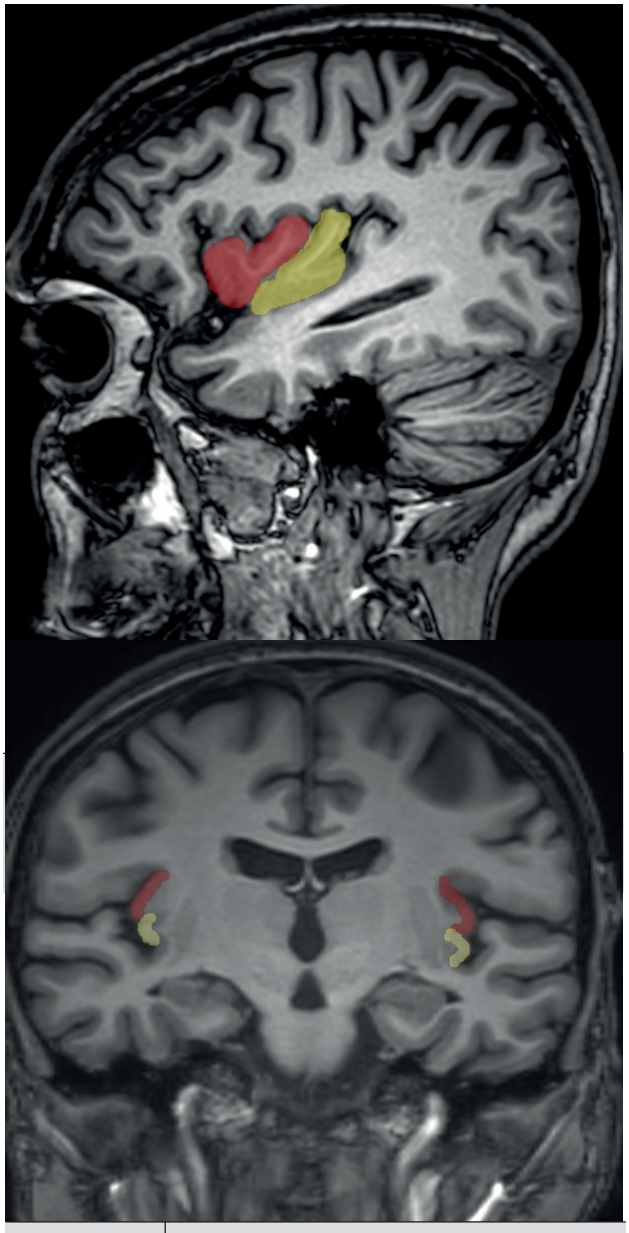

Figure 1 Sample images for tracing the insula*

*Red represents the anterior insula and yellow represents the posterior insula

RESULTS

The results for patients with schizoaffective disorder and healthy control comparisons are presented in the Table 1. As much there was an effort to preselect to be matched for gender, or handedness, unfortunately the groups could not be adjusted for age. Because of the fact that given the exclusion criteria particularly comorbid diagnoses, for the diagnosis of schizoaffective disorder it is very hard to include in available patients meeting the obligatory exclusion criteria. On the other hand, we did not detect any difference in terms of the whole brain volumes between patients with schizoaffective disorder and healthy control subjects (P>0.05). In addition, total white and gray matter volumes of patients with schizoaffective disorder were not different from those of healthy control subjects (P>0.05).

When we compared the insula volumes of patients with schizoaffective disorder to the healthy control comparisons by using independent samples t test, there was a statistically significant difference (P<0.05). As can be seen in the Table 1, the mean volumes of the insula region for both sides were statistically significant smaller in patients with schizoaffective disorder compared to those of healthy

Table 1 Demographic, volumetric and clinical data for patients with schizoaffective disorder and healthy subjects

	Healthy comparisons (n=19)	Patients with schizoaffective disorder (n=18)	*p*
Gender (Female/ Male)	9/10	10/8	>0,05
Age (years)	27.11±5.86	35.00±9.43	<0.001
Handedness (right/left)	19	18	>0.05
SANS	3.47±2.41	47.15±19.90	<0.001
SAPS	0.00±0.00	35.00±20.16	<0.001
BPRS	5.37±3.65	27.35±12.11	<0.001
Insula volumes			
Left			
Anterior	3.54±0.09	3.26±0.08	<0.001
Posterior	1.47±0.05	1.32±0.04	<0.001
Right			
Anterior	3.54±0.11	3.24±0.08	<0.001
Posterior	1.48±0.05	1.30±0.05	<0.001

*Los volúmenes presentados se expresan en mm^3.

ones (for left anterior, 3.26±0.08 cm^3 in the patient group vs. 3.54±0.09 cm^3 in the control group, $P<0.001$; for left posterior, 1.32±0.04 cm^3 in the patient group vs. 1.47±0.05 cm^3 in the control group, $P<0.001$; for right anterior, 3.264±0.08 cm^3 in the patient group vs. 3.54±0.11 cm^3 in the control group, $P<0.001$; for right posterior, 1.30±0.05 cm^3 in the patient group vs. 1.48±0.05 cm^3 in the control group, $P<0.001$). When controlling for total brain volumes, age, or gender which could have a potential to affect our results as covariates in the ANCOVA, it was seen that statistical significance lasted under control for those variables ($P<0.001$, for whole brain volumes as covariate, $P<0.001$, for age as covariate, $P<0.001$, for gender distribution as covariate). In addition to comparisons, it was also done correlational analyses to reveal that there would be any relationships between the insula volumes and clinical and demographical variables in patients with schizoaffective disorder and healthy compariosons, separately. We did not detect any relationship between these analyeses ($P>0.05$).

DISCUSSION

As far as we know, taking into consideration medicine literature that we can access, this is the first study that evaluates the insula volumes in patients with schizoaffective disorder. Because of its unique nature, we would like to emphasize important results of the present study. When we compared the insula volumes of patients with schizoaffective disorder to the healthy control comparisons by using independent samples *t* test, there was a statistically significant difference ($P<0.05$). Insula volumes of patients with schizoaffective disorder were statistically significant smaller in patients with schizoaffective disorder compared to the healthy control subjects ($P<0.05$). When controlling for total brain volumes, age, or gender which could have a potential to affect our results as covariates in the ANCOVA, it was observed that statistical significance continued under the control for those variables ($P<0.05$, for whole brain volumes as covariate, $P<0.05$, for age as covariate, $P<0.05$, for gender distribution as covariate). When looking at a glance to insula region, it is established that it has an important role on processing of emotions and organizations of sensorial stimulations[21]. On the other hand, human beings aware of interoceptive sensations, internal situation of the body, via the insula. It has been shown to be gray matter changes, alterations in cortical thickness and cellular architecture, and disturbances in protein expressions in patients with schizophrenia[21]. There have been so limited number of studies on structural brain alterations in patients with schizoaffective disorder. There has not been any study examining insula volumes in patients with schizoaffective disorder. However, limited number of studies exist on patienmts with schizophrenia and bipolar disorder. In a study performed by Borgwardt et al., it was found that monozygotic twins with schizophrenia showed reduced grey matter volumes of the insula in both sides[22]. In addition, it was shown that there was a bilateral decrease in insular grey matter volumes in individuals who had high risk for the development of schizophrenia[23,24]. In that study, it was also reported that ones who developed a psychotic state had reduced insular grey matter volumes initially compared to those who did not develop any psychotic condition[23,25]. In one of several meta-analyses on the insula region in patients with schizophrenia, out of investigations examining the insula, reductions in gray matter volumes were reported in a half of them. Two of them revealed that there was a deficit situated in the right side, whereas one determined that there was left-sided localization, and four revealed a bilateral deficit[26]. Other meta-analyses emphasized bilaterally gray matter volume reductions to be in the insula in patients with schizophrenia[24,27-29]. As for patients with bipolar disorder, another psychiatric disorder resembling to schizoaffective disorder in terms of clinical presentation like schizophrenia, there have been limited number of studies evaluating insula volumes. Bechdolf et al. investigated eleven individuals who were clinically at ultra-high risk of development of psychotic state, who all developed bipolar I and II disorder by follow-up, same number of matched ultra-high risked participants, without any psychiatric disorder at least twelve months of follow-up, and eleven matched healthy controls[30]. The authors found that amygdala and insula volume decreases were more pronounced in people at ultra-high risk of development of psychotic state, who all developed bipolar I and II disorder by follow-up compared to those with ultra-high risked participants, without any psychiatric disorder and healthy control subjects, suggesting that these could help to distinguish people who would develop bipolar disorder from those who would not, at least in symptomatically enriched samples, suggesting that imaging investigations could provide a support to distinct individuals who would subsequently develop bipolar disorder from those who would not, at least in symptomatically enriched samples. Our present results demonstrating that insula volumes were statistically significant reduced in patients with schizoaffective disorder are in accordance with those both on patients with schizophrenia and bipolar disorder. We consider that this main result of the present investigation supported the notion that schizoaffective disorder could be a different diagnostic category consisting of some neuroanatomical features of schizophrenia and bipolar disorder.

Before covering the Discussion section, we would like to mention some limitations of the present study to offer several projections for individuals who wished to perform future studies on same diagnostic group in terms of structural neuroimaging. First of all, the present study included in small sample size. This was a limitation of the study. However, it should be taken into consideration that confusing diagnostic side of schizoaffective disorder could

make this condition accepted. We also considered that validity of clinical diagnosis of schizoaffective disorder might be another problematic isuue when commenting the results of our study. In addition, it was not evaluated any other neuroanatomic area apart from the insula region. This can be accepted as another limitation of the study. As mentioned in the Introduction section, the clinical picture of the schizoaffective disorder includes both schizophrenia and other psychotic disorders and a mood disorder, however, it does not meet the diagnostic criteria for schizophrenia or a mood disorder separately. So, patients with schizophrenia and bipolar disorder could have been included in the present study for comparing with schizoaffective disorder. Novel studies with these groups together can be considered in furture studies. Finally, we determined that there was a age difference between groups, this could have affected the results.

In conclusion, our findings suggest that patients with schizoaffective disorder had reduced volumes of the insula region and that this finding was in accordance with those both on patients with schizophrenia and bipolar disorder. Beacuse of some limitations aforementioned, it is required to replicate our present results in this patient group.

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