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Research Article

Orbitofrontal Cortex Volumes in Patients Diagnosed with Somatic Symptom Disorder

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Abstract

Aim: Somatic symptom disorder (SSD) is a psychiatric disorder with unknown etiopathogenesis that is still under investigation. The results of neuroimaging studies on SSD have shown that some brain regions may be associated with it. In this connection, this study aims to explore the orbitofrontal cortex (OFC) morphometric changes in patients with SSD to better comprehend the etiopathogenesis.
Material and Methods: The study enrolled 20 patients and 20 healthy controls. All study participants were administered a sociodemographic and clinical questionnaire, the Hamilton Depression Rating Scale (HAM-D) and the Hamilton Anxiety Rating Scale (HAM-A). The volumes of total brain, OFC, total white matter, and total gray matter were measured by a magnetic resonance imaging (MRI)-based method in studied patients.
Results: Orbitofrontal cortex volume was significantly smaller in the patient group than in healthy controls ($p<0.05$). No significant difference between the two groups could be observed in total brain, white matter and gray matter volumes ($p>0.05$).
Conclusions: The OFC was markedly smaller in SSD patients than in healthy controls, suggesting that the OFC may be associated with SSD pathophysiology. Future studies examining the functional features of the OFC using imaging and cognitive function tests will likely shed more light on this issue.

Keywords: Somatic symptom disorder, volume, orbitofrontal cortex, MRI

INTRODUCTION

Somatic symptom disorder (SSD) is a mental disorder characterized by disproportionate thoughts about the severity of one or more somatic complaints that significantly impair functionality (1). It was classified into the somatoform disorder group and included in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (2). It was then renamed "somatic symptom disorder" (1) in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) (1). Prevalence rates for SSD in general population varies from 5% to 7% (3).

Several efforts have been directed towards elucidating the etiology of SSD, but it remains one of the mental disorders about whose biological basis we have very little information. Somatic symptoms may result from a tendency to interpret certain bodily sensations as signs of disease because of an increased perception of these sensations (4). The limited number of neuroimaging studies in SSD patients is based on relatively old data. According to these data, some brain regions become prominent in the physiopathogenesis of SSD. Some studies have shown that SSD patients have non-dominant hemispheric dysfunction in the cerebral hemispheres and dominance of the right hemisphere (5). In other studies, SSD symptoms were thought to be related to the caudate nucleus, hippocampus, and putamen, and volume changes were found in the right and left amygdala (6,7). Bilateral amygdala volume has been reported to be decreased in SSD patients (7). In a functional magnetic resonance imaging (fMRI)-based study examining patients with somatoform pain disorder, it was observed that patients had atypical activation of the precentral gyrus at rest compared with healthy controls (8). In another fMRI study, lower activity was observed in the bilateral parahippocampal gyrus and cerebellum and the left

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amygdala, postcentral gyrus, superior temporal gyrus, and posterior insula in SSD patients compared to control subjects (9). A 2016 study found that the medial prefrontal cortex and anterior cingulated cortex may provoke emotional dysregulation in SSD patients (10).

The orbitofrontal cortex (OFC) has enhanced connections to the basal ganglia and amygdala. The OFC additionally has a key role in cognitive function assessment. Various literature studies have confirmed that the OFC is impaired not only in patients with SSD but also in many psychiatric disorders, including hypochodriasis, body dysmorphic disorder, panic disorder, anorexia nervosa, and obsessive-compulsive disorder (11-15).

It has been suggested that SSD patients respond similarly to relevant and irrelevant stimuli and that their selective attention deteriorates (5). Accordingly, it was hypothesized by the authors of this study that the OFC, the region associated with cognitive function, may be important in SSD patients.

SSD is a disease that is sometimes difficult to diagnose, and therefore it is not uncommon for SSD patients to spend a long time going door to door to find an answer to their condition. The use of imaging, along with the necessary diagnostic tools, can both help diagnose patients early and reduce unnecessary healthcare costs (16). The results of neuroimaging studies in SSD show certain differentiations that may be related to etiology. Therefore, these implications are very important for diagnosing and treating SSD patients. The present study aim is to assess the total brain, OFC, total gray matter, and total white matter volumes in SSD population to determine neuroanatomical causes of SSD etiology. Detection of these regions may offer insight into disease etiology, allowing further studies to determine MRI as a reliable and efficient screening tool for these patients.

MATERIAL AND METHOD

The patient group enrolled in the study consisted of 20 patients admitted to the Psychiatric Clinic of Fırat University, Faculty of Medicine Hospital, diagnosed with SSD based on DSM-IV-TR diagnostic criteria, treated as inpatients or outpatients, and who fulfilled the study inclusion criteria. In addition, 20 healthy subjects who fulfilled the study inclusion criteria and conformed to the patient group in age and gender were classified as a control group. Exclusion criteria for the patient group were the presence of a comorbid personality disorder, the presence of a neurological disorder or a history of a neurological disorder or treatment for a neurological disorder, a history of head trauma, a contraindication to MRI examinations, the presence of significant somatic pathology that could affect the distribution of the patient's ongoing psychiatric disturbances, and a history of alcohol or substance abuse disorder in the past six months. Exclusion criteria for healthy controls were the presence of psychiatric disorders, neurological diseases, and psychoactive drug use in the participants or their first-degree relatives. All participants were administered a sociodemographic and clinical questionnaire designed by the study's authors in agreement with the aims of this study and in agreement with clinical experience and knowledge from the literature. The sociodemographic and clinical questionnaire is a semi-structured form that collects sociodemographic characteristics such as age, marital status, educational level, occupation, gender, place of residence, economic status, and family structure, and clinical data such as duration of disease, number of hospitalizations, and psychosocial stressors at disease onset. Participants' depressive symptoms were measured with the Hamilton Depression Rating Scale (HAM-D) (17), whereas anxiety scores were measured with the Hamilton Anxiety Rating Scale (HAM-A) (18). Signed informed consent was given by all participants.

A power analysis performed with G*Power 3 with a power of 80% for the minimum sample size within the 95% confidence interval (CI) indicated that the study group had to consist of 32 participants, of whom 16 were patients and 16 were controls (19).

Fırat University Ethics Committee (2010/07) granted ethical approval for the study. The current study was undertaken between April 2012 and September 2012 in line with the tenets of Helsinki Declaration.

MRI Procedure and Volumetric Measurement

Procedure: For the imaging studies, a 1.5 Tesla scanner GE SIGNA (GE Medical System) was used to acquire three-dimensional (3D) T1-weighted MRI images with the following parameters: 1.5 mm sagittal cross sections, echo time (TE): 15.6 ms; repetition time: 14.4 ms; excitation number: 1; field of view (FOV): 240 mm; rotation angle: 20 degrees; bandwidth: 20.8; cross-sectional thickness: 2.4 mm; and resolution: 0.9375 x 0.9375 x 2.4 mm. Images achieved with these parameters were processed in the workstation software.

Volumetric Measurements: Volumetric measurements of the total brain, gray matter, white matter, and orbitofrontal regions of each patient and control subject were obtained by MRI. The area of the orbitofrontal cortex was examined in coronal, sagittal, and axial planes using the workstation GE. First, coronal slices were visually inspected and marked, and then they were measured.

The line running from the anterior commissure to the posterior commissure also forms the anterior region of the corpus callosum genu with its superior boundary. Alternatively, a horizontal line can be used to define more posterior sections showing most of the lateral OFC. Fixed geometric boundaries were created by using all sections on the line of the anterior commissure posterior commissure forming its upper boundary. Thus, the upper dimension of the lateral orbital sulcus was also included in the OFC. The posterior OFC boundary was localized with coronal images in sections starting from the first visible sulcus

olfactorius. The inferior boundary was mostly determined considering the inferior portion of the cortex (20, 21). The drawing was completed in the coronal plane to include the temporafrontal junction. Two different evaluators who were blinded to participant gender and diagnosis made the drawing and volumetric measurements.

Some examples of the volumetric measurements are shown in Figures 1 and 2.

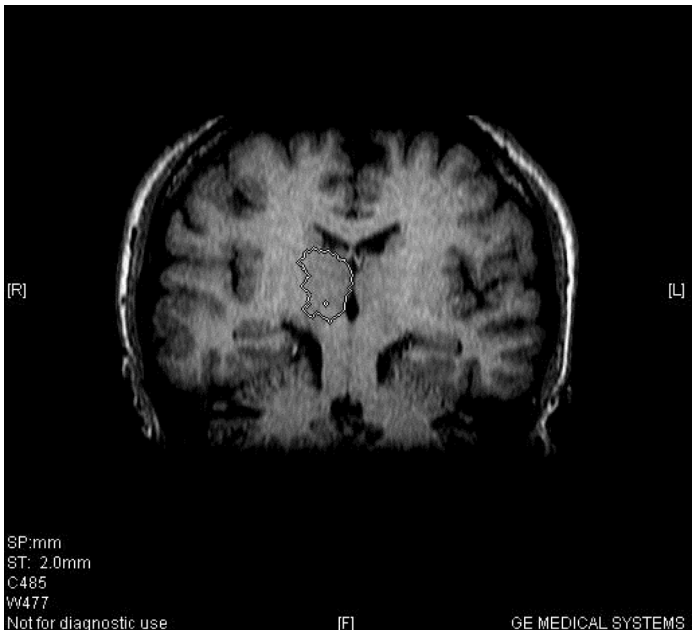

Figure 1. OFC MRG image

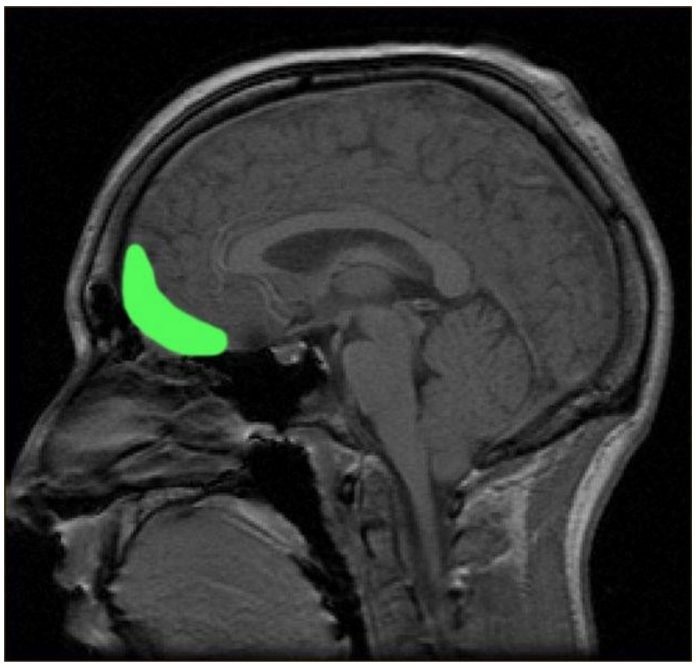

Figure 2. OFC MRG image, sagittal cross-section

Statistical Analysis

Study group data were presented as mean ± standard deviation (mean ± SD). Analysis of covariance (ANCOVA), Student's t-test, and chi-square tests were performed for statistical analysis. The association of volumetric values observed in the groups with age and disease duration was tested using Spearman correlation analysis. The SPSS 13.0 software package was applied for statistical analyses. Statistical significance was regarded as $p < 0.05$.

RESULTS

Twenty female patients were enrolled in the patient group. The study participants were between 30 and 62 years, presenting a mean age of 43.6±8.032. The control group also consisted of 20 healthy female subjects. The mean age of the control subjects was 40.0±3.90, ranging between 24 and 40 years. The patient and control groups had no significant differences regarding age ($p>0.05$). Most patients had either an elementary or middle/high school degree, were married, and had a middle or low socioeconomic status. The distribution of sociodemographical data among the study groups is shown in Table 1.

Table 1. Sociodemographic Characteristics of Patients and Controls

	Control (n=20)	Patient (n=20)
Age	43.6±8.32	40.0±3.90
Gender (M/F)	0/20	0/20
Disease duration		
0-5 y	-	9
6-10 y	-	2
11-15 y	-	5
≥16 y		4
Educational status		
Illiterate	-	2
Literate	-	2
Primary school	3	12
Secondary School	6	4
University	11	-
Marital Status		
Married	8	17
Single	12	3
Socioeconomic status		
Good	15	-
Moderate	5	16
Poor	-	4
Residency		
County	15	16
District	3	2
Village/Town	-	2

M: male, F: Female

The mean HAM-D scores in the patient and control groups were 15.35±3.32 and 7.85±1.92, respectively. In addition, the mean HAM-A scores in the patient and control groups were 11.15±2.97 and 6.15±2.20, respectively. HAM-D and

HAM-A scores did not vary significantly between groups (p>0.05 for both cases). The mean disease duration was 4.14±2.97 years. Statistical tests could not reveal any significant differences between the patient and control groups in total brain, gray matter, and white matter volumes (p > 0.05).

Volumetric measurements yielded that the mean OFC volume in the patient group was 13.21±0.90 ml on the right and 12.76±2.55 ml on the left, whereas in the control group it was 15.48±2.55 ml on the right and 16.16±2.06 ml on the left. Accordingly, statistically significant differences existed between the studied groups in OFC volume, both right and left (p<0.05 for both cases). No laterality was observed in both groups in terms of OFC volume. The distribution of the OFC measurement results between the patient and control groups is presented in Table 2. Some samples taken from sections during the volumetric measurements are illustrated in Figure 1 and Figure 2.

Table 2. OFC Volume in Patient and Control Groups

	Control (n=20)	Patient (n=20)	p
OFC Volume (ml)			
Right	15.48±2.55	13.21±0.90	p<0.05
Left	16.16±2.06	12.76±2.55	p<0.05

OFC: orbitofrontal cortex, ml: milliliter, p: probability statistic

DISCUSSION

Due to the limited number of studies on this issue, we would like to start the discussion by presenting our main study results. These results include that the mean OFC volume in SSD patients was 13.21±0.90 ml on the right and 12.76±2.55 ml on the left and was significantly smaller than in healthy controls.

A meta-analysis suggested that somatoform disorders are characterized by selective alterations in large-scale brain networks involved in cognitive control, emotion regulation and processing, stress, and somatic-visceral perception (22). Valet et al. found a decrease in orbitofrontal cortex volume in patients diagnosed with SSD, similar to our study (23). Perez et al. (24) stated that the orbitofrontal cortex is associated with SDD due to its emotional processing and recognition task. Considering fMRI methods in patients with SSD, there have been few studies on this topic. In this regard, neuroimaging studies with SSD have mentioned slow metabolism in the frontal lobes and non-dominant cerebral hemispheres (25). In a study conducted with SSD patients, regional blood flows in the brain were examined and hyperactivity was determined in the right parietal lobe. This brain region is thought to contain important cortical networks for the control of attention to external stimuli, and in this context, increased attention to external stimuli has been indicated in SSD patients (26). In a study conducted in Northern Finland, significantly higher levels of somatic anxiety were found in patients with right hemispheric tumors than in patients with left hemispheric tumors. Dizziness and palpitations were the most frequent specific signs in patients with right hemispheric tumors (27). Of studies that used structural neuroimaging methods, the 2004 study by Hakala et al. (6), which used MRI to examine 10 female patients with SSD and undifferentiated somatoform disorders and 16 healthy female controls, measured the volume of the caudate nucleus, hippocampus, and putamen, finding an increase in the volume of the putamen, a decrease in the volume of the hippocampus, and a significant increase in the volume of the caudate nucleus. Similarly, the Atmaca et al. study (7), conducted with 20 SSD patients and 20 control subjects, determined that the volume of the right and left amygdala was significantly smaller in patients than in healthy controls. In conjunction with previously reported related data, the present study results suggest that morphological changes in these regions, which are associated with stress and emotion regulation, may lead to alterations in emotional perception in these patients.

Regarding the findings related to the orbitofrontal cortex, this study found a significant reduction in OFC volume in SSD patients compared with control subjects. In comparison, studies from the related literature reported changes in the OFC not only in SSD patients but also in patients with somatoform disorders. In a 2009 study of 16 patients and 16 control subjects, patients with hypochondriasis were concluded to have smaller left and right OFC volumes and larger left thalamic volume than control subjects (11). These results have been reported to suggest that the OFC and thalamus may play an essential role in hypochondriasis pathophysiology. In an MRI study, it was pointed out that the volume of the OFC was smaller, whereas the volume of the white matter was larger in patients with body dysmorphic disorder than in controls. In addition, an association of disease duration with OFC volume was shown in the aforementioned study (12). In another study, single photon emission computed tomography (SPECT) detected elevated blood flow in the cingulum in a patient with body dysmorphic disorder (28).

The SSD patients included in this study had mild depressive symptoms. Somatic symptom disorder can often co-exist with depressive disorder. Moreover, SSD patients may often have symptoms that overlap with depressive disorder symptoms. In parallel, a reduction in OFC volume and a 7.2 % reduction in frontal lobe was observed in patients with depressive disorders compared with healthy control subjects, which was also the case in SSD patients (29). The results of another study, which found a volume reduction of approximately 8.6 %, are consistent with the aforementioned study (30). In a meta-analysis by Koolschijn et al. (31), which included studies with depression patients, it was found that the volume decrease of the prefrontal, anterior cingulate, and OFC regions was higher than the volume decrease of the hippocampal region. This finding suggests that frontal lobe structures and cingulate cortex play a role in or may be affected by the pathophysiology of

depression at least as much as the hippocampus. In light of the above stated, it can be speculated that OFC functions play as important a role in the etiology of SSD as they do in the etiopathogenesis of depression. However, further studies, such as functional neuroimaging studies in SSD patients, are needed to reach more definitive conclusions.

The current study has some potential limitations. First, the low sample size limits the power of our results. In addition, differences in measurement methods between our study and other studies may have affected our results. Another factor that complicates the interpretation and generalizability of our results is that few volumetric studies have been performed on SD patients.

CONCLUSION

In conclusion, the findings of this study indicated the abnormalities pertaining to OFC, which might also be related to the pathophysiology of SSD. Employing imaging modalities such as MRI may reduce the potential clinical diagnostic burden in cases where SSD can be bypassed. However, further studies with larger sample groups are needed to corroborate the findings of this study.

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Conflict of Interest: *The authors declare that they have no competing interest.*

Ethical approval: *The study protocol was approved by The Ethics Committee of Fırat University, Faculty of Medicine (Approval Date: January 20, 2012; Approval Number: 2012/14).*

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