ORIGINAL ARTICLE

Psychiatry and Clinical Psychopharmacology 2022;32(1):28-32
DOI:10.5152/pcp.2022.21239

Pituitary Volume in Individuals with Social Anxiety Disorder

Mustafa Koç[1], Osman Mermi[2], Sabriye Aslan[2], Murad Atmaca[2]

[1]Department of Radiology, Fırat University School of Medicine, Elazığ, Turkey; [2]Department of Psychiatry, Fırat University School of Medicine, Elazığ, Turkey

ABSTRACT

Background: There are no volumetric magnetic resonance imaging studies on the pituitary gland in individuals with social anxiety disorder. The present study aimed to investigate pituitary volume in individuals with social anxiety disorder compared to healthy controls due to the correlation between pituitary gland volume and stress response and the hypothalamic-pituitary-adrenal axis and hypothesized that pituitary gland volume would be different in these individuals.

Methods: In this study, 21 individuals with social anxiety disorder based on fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and 20 healthy controls were included. Both patient and control groups were scanned with a 1.5-Tesla General Electric (GE) Magnetic Resonance Imaging scanner. Pituitary volume was measured with the manual tracing method.

Results: The statistical analysis revealed that the mean pituitary gland volume of the individuals with social anxiety disorder was significantly smaller when compared to that of healthy controls, statistically, as presented in Table 1 [594.10±104.56 mm^3 for individuals with social anxiety disorder and 818.01±215.25 mm^3 for healthy controls] when it was done by using the analysis of covariance controlled for age ($F=12.979$, $df=1$, $P < .001$), sex ($F=11.448$, $df=1$, $P < .001$), and total brain volume ($F=10.772$, $df=1$, $P < .001$), demonstrating that smaller pituitary volume in social anxiety disorder, when compared to healthy subjects, was an important finding independent of age, sex, or total brain volume.

Conclusion: We suggest that social anxiety disorder may be associated with smaller pituitary volume, supporting the notion that anxiety itself could reduce the pituitary volume.

ARTICLE HISTORY

Received: September 20, 2021
Accepted: December 2, 2021

KEYWORDS: HPA, MRI, pituitary, social anxiety disorder, volume

INTRODUCTION

Social anxiety disorder (SAD) is an anxiety disorder also known as social phobia, classified in the fifth edition of *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*.[1] It was described as a persistent fear of one or more social situations or performances where the individual is exposed to unfamiliar patients or scrutiny by other individuals. The individual fears that he or she will behave in an embarrassing and humiliating way (or demonstrate anxiety signs). The anxiety would almost always be provoked in individuals with SAD when they are in a feared situation, despite the knowledge that the fear is unreasonable and clearly unwarranted. Patients also exhibit physiological symptoms such as nausea, palpitations, sweating, shaking, trembling, and blushing when faced with feared social situations. Certain studies on the epidemiology of SAD demonstrated that the disorder was prevalent in the population.[2] Furthermore, in a national field study, it was estimated to reach 13.3%.[3] In fact, similar to other psychiatric disorders, the exact reason for SAD is still obscure. Neurobiological changes have been reported in individuals with SAD, even at the molecular level.[4-6] Although SAD is a prevalent disorder, the number of studies conducted with structural magnetic resonance imaging (MRI) in patients with SAD in comparison with affective or other anxiety disorders is quite limited. In an initial study,[7] the authors reported that there was no statistically significant volume difference between SAD and healthy controls. Later, other researchers studied the amygdala and hippocampus volumes of patients with SAD with the manual tracing method and reported that amygdala and hippocampus volumes were reduced with SAD and there were negative correlations between The Liebowitz Social Anxiety Scale (LSAS) scores and right hippocampus volumes and between State-Trait Anxiety Inventory score and right amygdala volumes.[8] Others reported significant subcortical volume alterations in thalamus sides, right precuneus, right amygdala, and a negative correlation between right amygdala volume and duration of the disorder.[8]

Corresponding author: Mustafa Koç, e-mail: mkoc44@yahoo.com

Cite this article as: Koç M, Mermi O, Aslan S, Atmaca M. Pituitary volume in individuals with social anxiety disorder. *Psychiatr Clin Psychopharmacol*. 2022;32(1):28-32.

Kawaguchi et al[9] investigated the insula volume with SAD,compared the findings with controls, and reported that insula volume was significantly reduced in SAD when compared to healthy groups.[9] Previously, we conducted an MRI study on amygdala and hippocampus volumes in 22 SAD patients and healthy controls and found that the volumes of both sides of the hippocampus were significantly larger than those of the controls. However, we did not determine any volumetric differences in bilateral amygdala volumes between the 2 groups.[10]

The pituitary gland is a pea-sized mid-brain structure weighing 0.5 g. It is a protrusion from the bottom of the hypothalamus at the base of the brain and is an upper center that modulates endocrine glands and hormones. It is also called the "master gland in human body." The pituitary gland is an important part of the hypothalamic-pituitary-adrenal (HPA) axis that plays an important role in stress response. The increased HPA axis activity that induces high cortisol levels could affect the pituitary volume.[11] In our previous study, the pituitary gland volume of patients with obsessive-compulsive disorder (OCD), another disorder associated with anxiety, was investigated, and it was found that their gland volume was smaller when compared to healthy controls.[4] On the other hand, similar results were determined in a study conducted by us with panic disorder patients and in another study with anxiety patients.[12] Furthermore, the same team conducted an MRI study on patients with hypochondriasis, another disorder associated with anxiety, to measure the pituitary gland volume and reported that the gland volume of the patients with hypochondriasis was reduced when compared to healthy individuals.[4] Despite the relationship between anxiety and pituitary gland structural alterations, to date, no more volumetric MRI study was conducted on the pituitary gland of the SAD patients. In our study, due to its correlation with stress response and the HPA, pituitary volume in SAD was investigated and compared with healthy control subjects and hypothesized that pituitary gland volume differed between these groups.

MAIN POINTS

- Social anxiety disorder (SAD) is an anxiety disorder also known as social phobia.
- It was described as a persistent fear of one or more social situations.
- The number of studies conducted with structural magnetic resonance imaging in individuals with SAD in comparison with affective disorders or other anxiety disorders is quite limited.
- It could be suggested that anxiety itself could have an impact on reduced pituitary gland volume structurally.
- When taking into consideration that SAD is so related to the anxiety itself and is classified in the Anxiety Disorders in the *DSM 5*, it seems that anxiety itself to be associated with pituitary gland structural changes.

METHODS

The present investigation was conducted on 21 patients who were 18 and 65 years old with SAD and admitted to the department of psychiatry. Since the study was started before the completion of the Turkish validity and reliability study of The Structured Clinical Interview for DSM-5 (SCID-5), all patients were diagnosed with SAD based on The Structured Clinical Interview for DSM-IV (SCID).[13] In the study, 20 healthy control subjects were included. The present study subjects were the same with a previously published study conducted by the same team.[14] Diagnosis of SAD was conducted by a senior psychiatrist. The mean age (±standard deviation (SD)) of the patients with SAD was 27.9±4.9, while the healthy control group was 25.7±4.7. Certain exclusion criteria were employed, including any current or history of endocrinological conditions, neurologic problems, endocrinological pharmacological treatment history, previous treatment for pituitary functions, the presence of any severe medical problem, mental disability, and any existing problem that may lead the patient to suffer during imaging as a joint or cardiac apparel, low education level that could prevent a healthy interview, and also alcohol/substance use within 6 months. Patients with comorbidities were not included excluding depressive disorder that is a common comorbidity in SAD. Only 1 patient met a *DSM*-IV major depressive disorder and it did not affect the statistical analysis. No one had met criteria for any anxiety disorders other than SAD.

Similar to our previous MRI studies, healthy controls neither have any *DSM*-IV axis I disorders as proposed in the SCID non-patient version nor any current, endocrinologic, psychiatric, or neurologic history, or psychoactive medication use in 2 weeks of the study. Approval from the Ethics Committee of Fırat University was obtained. Furthermore, written informed consent was obtained from both SAD and healthy controls. All study applications were in accordance with the instructions described in the Helsinki Declaration.

All MRIs were taken with a 1.5-Tesla (GE, Milwaukee, Wis, USA) scanner. No intravenous contrast agent was used in patients or healthy controls. An 8-channel head coil was used. All patients were asked whether they wanted to take an anxiolytic agent for reducing avoidance during the process. The structural high-resolution T1-weighted MRI images were obtained with sagittal 3D spiral fast spin-echo. Cross sections of 1.5 mm were obtained on sagittal, coronal, and axial planes. The following MRI parameters were used: echo time: 15.6 ms, excitation number: 1, time of repetition: 14.4 ms, field of view: 240 mm, diameter of the band: 20.8, rotation angle: 20°, resolution: 2.4×0.9375 mm, and cross-sectional thickness: 2.4 mm. All measurements were determined on an advanced workstation running the General Electric

Volume Viewer Vox tool 4.6 software (GE, Milwaukee, Wis, USA). Tracing was performed by 1 researcher blinded to subject diagnosis and independently verified by a second blinded investigator. The interrater reliability (intraclass correlation coefficient), established on tracing by 2 different evaluators, was r = 0.90 for pituitary. During tracing, pituitary gland boundary and tracing methods were determined with a standard neuroanatomical atlas (the volume of an object may be estimated by sectioning it with a set of uniformly spaced parallel planes and measuring the cross-sectional area of the object on each plane),[15,16] methods and descriptions adapted from neuroimaging studies on pituitary gland[17,18] proposed by Macmaster et al.[19] Infundibular recess of the third ventricle and optic chiasm were accepted as the superior boundary of the pituitary gland, as mentioned in reference studies. The inferior boundary was accepted as the sphenoid sinus. Sample images of the pituitary gland are presented in Figure 1. In the results section, all volumes are presented in cubic millimeters.

Statistical Analysis

Statistical analyses were conducted using Statistical Package for Social Sciences, version 22.0 (IBM Inc., Armonk, NY, USA). Demographics were analyzed by using an independent t-test and chi-square test. Volumes were analyzed by using analysis of covariance (ANCOVA) under the control of age, sex, and total brain volumes. Correlations between age, length of illness, and pituitary volumes were detected using Spearman's correlation. Bonferroni test was used for correcting multiple comparisons for all analyses. To calculate the effect size, Cohen's d test was used. $P < .05$ was accepted as statistically significant with a 2-tailed test.

Ethics

Ethical committee approvals for the study were obtained from the Fırat University Scientific Research and Publication Ethics Committee (date April 22, 2019, session number 2019/4).

RESULTS

Demographic and diagnostic attributes of individuals with SAD and healthy subjects are summarized in Table 1. Based on age (mean age±SD = 27.9±4.9 for patients with SAD and mean age±SD = 25.7±4.7 for healthy controls), education level, handedness, or sex, there were no statistically significant differences between the groups (Table 1). The statistical analysis revealed that the mean pituitary gland volume of the patients with SAD was significantly smaller when compared to that of healthy controls, statistically, as presented in Table 1 (594.10±104.56 mm^3 for patients with SAD and 818.01±215.25 mm^3 for healthy controls) when it was done by using the ANCOVA controlled for age ($F = 12.979$, $df = 1$, $P < .001$), sex ($F = 11.448$, $df = 1$, $P < .001$), and total brain volume ($F = 10.772$, $df = 1$, $P < .001$), demonstrating that smaller pituitary volume in SAD, when compared to healthy subjects, was an important finding independent of age, sex, or total brain volume (effect size value by using Cohen's d test: -1.32; r = -0.55).

Spearman's correlation test was employed in correlation analyses. No statistically significant correlation was determined between pituitary gland volume and age (for the patient group, r = 0.09, P = .56; for control group, r = 0.12, P = .45), sex (for the patient group, r = 0.28, P = .07; for control group, r = 0.25, P = .08), HDRS score (for the patient group, r = 0.12, P = .45; for control group,

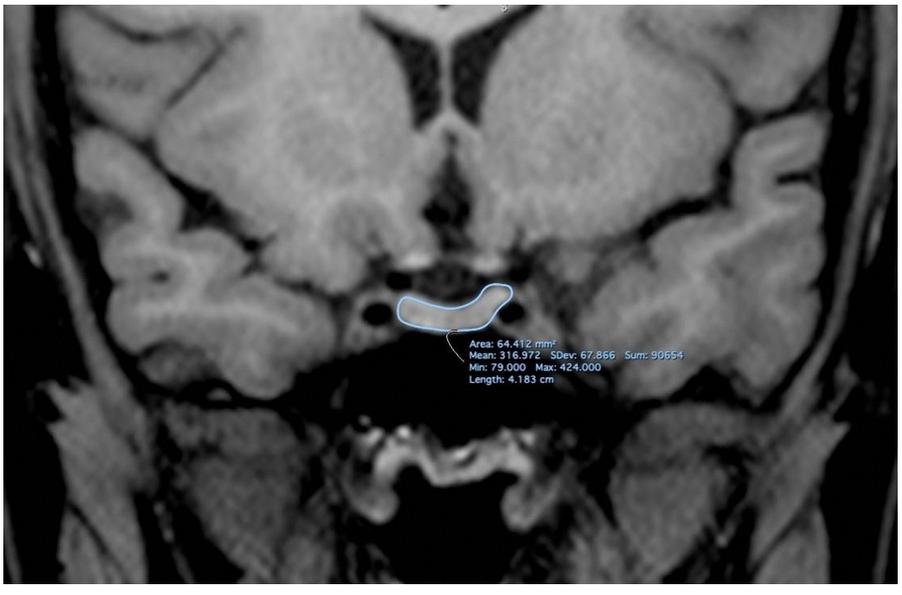

Figure 1. Sample trace of the pituitary gland in MRI.

Table 1. Pituitary Volume in Individuals with SAD Versus Healthy Controls

	Individuals with SAD (n = 21)	Healthy Controls (n = 20)	P
Sex (F/M)	13/8	11/9	>.05
Age (years)	27.9±4.9	25.7±4.7	>.05
HDRS score	11.7±3.0	7.1±1.9	<.001
Handedness (L/R)	0/21	0/20	>.05
Length of illness (years)	3.79±2.78	-	
Pituitary volume	594.10±104.56	818.01±215.25	<.001

Volume is presented in cubic centimeters (cm^3).

r = 0.10, P = .42), and length of illness (for the patient group, r = 0.20, P = .09) ($P > .05$).

DISCUSSION

As far as we know, the present study is the first research where the pituitary volume was measured in SAD individuals. Thus, although the findings are preliminary, the present study results could be considered significant. Further studies would benefit from the present study findings. The main finding of the study was the statistically significant smaller pituitary gland volume determined in individuals with SAD when compared to healthy controls [(594.10±104.56 mm^3 in individuals with SAD and 818.01±215.25 mm^3 in healthy controls (t = -4.185, $P < .001$)]. The ANCOVA controlled for age, sex, and total brain volume revealed that reduced pituitary gland volume lasted, demonstrating that smaller volume of the pituitary gland in individuals with SAD, when compared to healthy controls, was a significant finding independent of age, sex, or total brain volume.

Pituitary gland regulates a variety of activities of other endocrine glands each of that is associated with emotions and mood regulation in part or complete, for this reason, it is known as the master gland. On the one hand, the activated HPA axis modulates peripheral functions of the body, for example immunological functions and metabolism. On the other hand, glucocorticoid hormones have regulatory effects on neurogenesis, surviving neurons, the acquisition of new memories, the emotional appraisal of events lived, and the volumes of some brain structures like hippocampus, and it has profound effects on the brain.[20] The role of HPA axis in anxiety and fear is well established. Because under stress, hypothalamic corticotropin-releasing hormone production rises, stimulating the pituitary release of adrenocorticotropin hormone. Consequently, cortisol secretion by the adrenal cortex increases. On the other hand, in depression, the role of dysregulation of the HPA axis is well known. Its close relationship with the aforementioned psychiatric disorders led the authors to investigate the morphometry of the pituitary gland, as in other parts of the brain.

In the present study, we do not exactly know whether smaller pituitary gland volume in SAD individuals was associated with this physiologic process. However, it was determined that pituitary gland volume was reduced in patients with various anxiety disorders. The present study team investigated pituitary gland volume with OCD and reported that patients with OCD had a smaller pituitary gland volume.[21] In panic disorder patients, similar findings were reported.[12] On the other hand, in another study, we investigated the pituitary volume in post-traumatic stress disorder patients (PTSD) and found that patients with PTSD exhibited statistically significant smaller gland volume when compared with the healthy controls.[22] Furthermore, we also determined smaller pituitary volume in somatization disorder patients and hypochondriasis, which are both associated with anxiety.[23,24] It could be suggested that anxiety itself could have an impact on reduced pituitary gland volume structurally. When taking into consideration that SAD is so related to the anxiety itself and is classified in the Anxiety Disorders in the *DSM*-5, it seems that anxiety itself to be associated with pituitary gland structural changes. Furthermore, increased HPA axis activity that leads to high cortisol levels could influence the pituitary gland volume, as mentioned in the Introduction section.[11] Also, we previously investigated another brain region associated with anxiety, namely the amygdala, and hippocampus in individuals with SAD,[10] and reported that patients had similar amygdala volume; however, reduced hippocampus volume was determined in the patients when compared to healthy controls, suggesting that brain regions associated with anxiety could be affected in patients with a variety of anxiety disorders.

Similar to our previous neuroimaging studies on anxiety disorder patients, the main limitation of our study was the relatively small sample size. However, when it is considered that it is difficult to access individuals with SAD without any comorbidity, this limitation could be exempted. Second, we did not study pituitary gland hormones that simultaneously implicate endocrinologic patient levels. Third, although we excluded patients who were on any psychotropic drug within 4 weeks prior to the present study, most patients with SAD have a history of previous psychopharmacological treatment. This could have affected our results. Finally, we employed a manual tracing method. This method itself has certain significant limitations such as measurement bias.

CONCLUSION

Thus, we suggest that SAD may be associated with smaller pituitary gland volume, supporting the notion that anxiety itself could reduce pituitary volume.

Ethics Committee Approval: Ethics comittee approval was received from the Ethics Committee of Fırat University (April 22, 2019; 2019/4).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.K., S.A., M.A.; Design – M.K., M.A.; Supervision – M.K., O.M., M.A.; Resource – M.K., S.A.; Materials – M.K., S.A., O.M.; Data Collection and/or Processing – M.K., S.A., O.M.; Analysis and/or Interpretation – M.K., M.A., Literature Search – M.K., M.A.; Writing – M.K.; Critical Reviews – M.K., O.M., S.A., M.A.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The study is supported by Scientific Research and Project Support Unit of Fırat University (FUBAP), and we would like to thank FUBAP for financial support.

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