

## Evidence for the changes of pituitary volumes in patients with post-traumatic stress disorder



Murad Atmaca<sup>a,\*</sup>, Omer Ozer<sup>a</sup>, Sevda Korkmaz<sup>a</sup>, Ismail Taskent<sup>b</sup>, Hanefi Yildirim<sup>b</sup>

<sup>a</sup> Firat University School of Medicine Department of Psychiatry, Elazig, Turkey

<sup>b</sup> Firat University School of Medicine Department of Radiology, Elazig, Turkey

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### ABSTRACT

In pubertal and postpubertal patients with post-traumatic stress disorder (PTSD), significantly greater pituitary gland volumes have been reported. Moving from this point, in the present study, we aimed to investigate pituitary gland volumes in patients with PTSD and hypothesized that volumes of the gland would be structurally changed. Volumetric magnetic resonance imaging of the pituitary gland was performed among sixteen patients with PTSD and fifteen healthy control subjects. We found that the mean volume of the pituitary gland was statistically significant and smaller than that of healthy subjects ( $0.69 \pm 0.08 \text{ cm}^3$  for patient group and  $0.83 \pm 0.21$  for control subjects). Consequently, in the present study, we found that patients with PTSD had smaller pituitary gland volumes than those of healthy controls like other anxiety disorders. It is important to provide support for this finding in future longitudinal investigations.

### 1. Introduction

Posttraumatic stress disorder (PTSD) is classified under anxiety disorders in Diagnostic and Statistical Manual of Mental Disorders–Edition IV (DSM-IV), a unique disorder described with its etiology in DSM-IV. It is highly associated with other psychiatric disorders. For this reason, comorbidity is frequent when a diagnosis of PTSD was performed [4,27]. In DSM 5, the disorder was separated from Anxiety Disorders and was classified under the completely different title, Trauma- and Stressor-Related Disorders.

As much as a traumatic event alone is an important precipitating factor in the beginning of the PTSD, important neurobiological factors contribute the occurrence and maintenance of the disorder. In the neurobiology of PTSD, it has been emphasized hypothalamic-pituitary-adrenal (HPA) axis in addition to a variety of neurotransmitters and neuropeptides such as catecholamines, serotonin, corticotropin-releasing factor, gamma-aminobutyric acid (GABA), glutamate, neuropeptide-Y and endogenous opioids [19]. In addition, immunological factors have been reported. We previously examined neopterin levels and suggested that patients with PTSD had increased dexamethasone suppression test (DST) non-suppression and that PTSD might be associated with neopterin [4].

There have been obviously limited neuroimaging studies on patients with PTSD. Especially, during the last decade, various studies have been performed to focus on the relationships between specific

brain regions linked to PTSD, with the purpose of determining whether there have been volumetric and functional differences in patients with PTSD, particularly in the brain regions related to anxiety and stress. In this context, it has been more focused on the hippocampus, amygdala, and anterior cingulate cortex (ACC). The studies evaluated the role of the amygdala and its relationship with the disorder, with results demonstrating increase in activation in PTSD and the results demonstrated an increase in these regions in patients with PTSD [11,24,29,32,40]. In addition, volumetric investigations were performed [10,31,39]. Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies have revealed that the ACC might be involved in the regulation of negative feedback of the hypothalamic-pituitary axis (HPA) during emotional, behavioural inhibition and the regulation of emotion distress [22,23,28,30]. On the other hand, because of the fact that hippocampus has an important role in memory processing and moderation of the HPA [2,14,34], this region has been particularly dealt with neuroimaging of the PTSD. Firstly, Bremner et al. found decreased hippocampus volumes in patients with PTSD compared to those of healthy controls [12]. Many investigations that followed this study supported the results [2,11,13,18,25,38,42]. However, it is obscure whether the reduced volumes of the hippocampus are the result of PTSD itself or it is the reason of PTSD. There is only one study about pituitary volumes in patients with PTSD [36]. In that study, authors examined pituitary volumes in pediatric PTSD patients and found that pituitary volumes

\* Corresponding author.

E-mail address: [matmaca\\_p@yahoo.com](mailto:matmaca_p@yahoo.com) (M. Atmaca).

were significantly greater in pubertal and postpubertal maltreated subjects with PTSD than control subjects while were similar in prepubertal maltreated subjects with PTSD and control subjects, suggesting that there might be a developmental changes in pituitary gland volumes in patients with maltreatment-related pediatric PTSD.

In people with a history of the traumatic event, alteration in the limbic-hypothalamic-pituitary-adrenal (LHPA) axis with increased values of corticotrophin releasing hormone (CRH) was reported [15,33]. In this context, hippocampus volume abnormalities were reported in patients with PTSD, as mentioned above. In addition, in pubertal and postpubertal patients with PTSD, significantly greater pituitary gland volumes have been reported [36]. Moving from this point, in the present investigation, we aimed to investigate pituitary gland volumes in patients with PTSD and hypothesized that volumes of the gland would be structurally changed.

## 2. Materials and methods

In total, 16 patients with PTSD according to DSM-IV-TR and the same number of healthy control subjects were investigated in the present study. Patients with PTSD were selected among those who had applied to the Firat University School of Medicine Department of Psychiatry out-patient or in-patient clinics and had met the criteria for inclusion on the study. Patients who were 18–65 years old were accepted. Diagnosis of PTSD was performed by a senior psychiatry assistant (O.O) by using the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) diagnostic criteria for PTSD based on the Structured Clinical Interview for DSM-IV (SCID) [16]. In addition, Turkish version of the Beck Depression and Anxiety Scales [7,8], and to solely patients Turkish version of the Clinician-Administered Post-Traumatic Stress Disorder Scale (CAPS) [9] were administered to patients and healthy control subjects [1,20,37]. Following criteria were used to exclude patients from the study: The existence of other Axis I DSM-IV diagnoses apart from depression, alcohol/substance abuse before the inclusion of the present study, being under eighteen years old, the existence of any congenital brain abnormalities, the existence of mental retardation which might prevent a good communication, current severe medical problems, history of head trauma, any condition that might prevent to suffer from MRI investigation such as cardiac stent. Some of the patients ( $n=6$ ) were undergoing stable dose of treatment with different antidepressants. Among them, three patients were taking paroxetine, with the dose range of 20–40 mg per day, two were taking sertraline, with the dose range of 50–100 mg per day, and one was using citalopram, with a dose of 20 mg per day. On the other hand, we included sixteen healthy control subjects into the investigation. Some criteria were administered to the healthy control subjects as well. Our study team used these criteria in a variety of MRI studies. They were the existence of any Axis I DSM-IV in themselves and in any first-degree relatives, any history of head trauma, any condition that prevent to suffer from MRI investigation such as cardiac stent, alcohol/substance abuse before the inclusion of the present study, being under eighteen years old, the existence of mental retardation to prevent a good communication, and the existence of any current major medical problems. We obtained an approval from the Local Ethics Committee at Firat University School of Medicine. All the study procedures were in accordance with the 1983 version of Helsinki Declaration of 1975. The informed consent was given to all participants included in the present study. All subjects returned their written informed consent, with a document signed. As in our previous investigations, for the anonymity of patients, attention was paid.

### 2.1. MRI procedure

All the MRI scannings of the subjects were performed at Neuroradiology section at Firat University School of Medicine Department of Radiology by using 1.5-Tesla GE Signa Excite high-

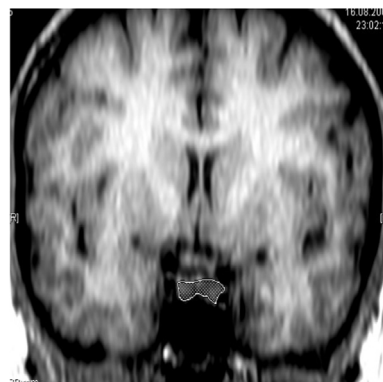


Fig. 1. Manual tracing for pituitary gland.

speed scanner (Milwaukee, USA), with a comfortable position of the subjects' head. To detect and exclude the participants with any morphological brain abnormalities during the scanning, a radiologist screened if there were any morphological alterations at first glance. MRI scanning we used had some specific measurement parameters as followings: Repetition time [TR]=2000 ms, echo time [TE]=15.6 ms, the field of view [FOV]=240 mm, bandwidth=20.8, flip angle=20°, slice thickness=2.4 mm, resolution=0.9375×0.9375×2.4 mm, echo spacing=15.6 ms, and 8 echoes. Tracings were performed manually by two radiologists who did not know the diagnosis of patients. After this process, manual tracings obtained were transferred to a computer advanced workstation with the GE Volume Viewer voxtool 4.2 program. To trace manually the boundaries of the pituitary gland, neuroradiologists benefited from neuroanatomical atlases [17,35]. In addition, they used tracing method of [26]. As described in our previous studies on a variety of psychiatric disorders [3,5,6,21,41], the boundaries were as follows. Superior boundaries of the pituitary gland were described as the optic chiasm and infundibular recess of the third ventricle. On the other hand, the sphenoid sinus was accepted as the inferior boundary of the gland. Scanning sample was presented in Fig. 1. All of the data on pituitary gland volumes were cubic centimeters. In addition, we determined the interrater reliability (intraclass correlation coefficient) to be 0.90 ( $r=0.90$ ) which indicates relatively high reliability.

### 2.2. Statistical analysis

For statistical analyses, the Statistical Package for the Social Sciences for Windows software (SPSS) version 16.0 was utilized (SPSS, Chicago, IL). In this context, analysis of covariance (ANCOVA), independent  $t$ -test and chi-square analyses were administered, when appropriate. Handedness, and gender distribution were compared by chi-square test. Scale scores, age and years of education were compared by using independent  $t$ . For comparing pituitary volumes, ANCOVA was used. In ANCOVA analyses, age, total brain volume, and gender were used as covariates. For various correlational relationships, Spearman's correlation analysis was used. An alpha level of  $p < 0.05$  was accepted as statistical significance.

## 3. Results

We found that there were no significant differences for age, education, and gender between groups ( $t=-1.33$ ,  $df=29$ ,  $p=0.193$ ; Chi-square=2.03,  $df=3$ ,  $p=0.056$ ). The mean duration of the illness of patients with GAD was  $7.40 \pm 5.59$  years. The mean Beck Anxiety Rating Scale scores were  $30.94 \pm 11.53$  in the patient group and  $6.07 \pm 2.22$  in controls ( $t=28.21$ ,  $df=29$ ,  $p=0.000$ ). Likewise, there were significant differences between the groups in regard to the Beck Depression Rating Scale scores ( $33.06 \pm 11.28$  for patient group and  $7.47 \pm 1.92$  for control subjects, ( $t=8.67$ ,  $df=29$ ,  $p=0.000$ ). CAPS total

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