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Gender dependent difference of hippocampus and amygdala sizes in relation to depression: A manual brain segmentation study

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ABSTRACT

Introduction: hippocampus and amygdala believed to be central to the cognitive deficits associated with depression. The former has a crucial role in declarative memory, whereas the latter is the center that is responsible for fear and anxiety. The present study examined their volumes depending on the patient's right and left sides, as well as gender, depression and controls. *Methods:* 50 controls (25 male, 25 female) and 50 patients with depression (25 male, 25 female) were involved in the study. The amygdala and hippocampal volumes were manually calculated using ImageJ brain segmentation software utilizing structural MRI. *Results:* The volume of right as well as left amygdala in a female patient with depression and control female (2.3648 cm3 and 2.2420 cm3) and (2.1352cm3 and 2.0724 cm3) (±SD 0.45704 and 0.41871) and (±SD 0.34923 and 0.31978), respectively. A patient with depression is higher than control, p. value < 0.05 (0.052); furthermore, the left amygdala has less volume than the right. *Conclusion:* depression is associated with the reduction of the volume of amygdala in females specifically the left side. Along with the amygdala, it could also cause abnormalities in hippocampus volume.

Keywords: Hippocampus, Manual Segmentation, Amygdala, Depression

1. INTRODUCTION

Over the past decade, researchers work hard to specify neuroimaging aspects of depression have assessed differences between depressed and non-depressed individuals in neural structures' volume (Kim et al., 2008). The hippocampus plays a critical role in declarative memory function, and the memory functions are affected by stress and depression disorder and schizophrenia (Ranganath et al., 2008; Bremner et al., 2000). Consequently, it has been speculated that the hippocampal volume and shape changes are seen in depression patients, it could lead to the well-documented memory

abnormalities seen in this disorder (Eichenbaum, 2004). Furthermore, fear and anxiety occur in the amygdala; in addition to functional differences in amygdala response such as in emotional memory and sleep physical activity disturbance (Parker et al., 2002; Gould et al., 2007), it is believed that symptoms of depression such as suicidal tendencies associated to alterations in the structure of amygdala, parahippocampal gyrus, inferior frontal and superior temporal gyri; as well as orbital frontal cortex (Osuch et al., 2014).

Studies in the past showed; significant gender-dependent differences in patients who have history of depression. These differences are assumed to be consequences of the stress hormones (glucocorticoids) along with psychosocial sex differences (Swaab et al., 2005; Van Praag, 2004). The target anatomical structures of the study have been broadly studied over the past decade in patients (Yin & Yuan, 2014; Habibi & Curran, 2012); this is considered as the first study conducted here in Sudan according to our knowledge. In the existing research, the volumes of the neurological structures were measured of patients with depression and normal comparison groups were evaluated using MRI and brain segmentation tool (ImageJ).

2. MATERIALS AND METHODS

The ethical committee gave its approval to the study of the National Ribat University/ Sudan (ethical approval number: REC-HSD-019-2020), depending on the statement of the ethical principles as developed on the World Medical Association Declaration of Helsinki (World Medical Association (WMA) 2008) (World Medical Association 2008).

Subjects

Fifty control subjects (25 males, 25 female) and 50 patients (25 males, 25 female) were involved in this study from October 15, 2020, to August 15, 2021. Patients with depression met the disease categorization on an international classification criterion, the tenth revision (ICD/10) (World Health Organization, 2010).

The patients were selected from Tigani Almahi Psychiatric hospital and private psychiatry clinics in Sudan. Sudanese volunteers served as controls. They had no history of psychiatric illnesses or drug use. Based on gender, control participants and patients were assigned. Both patients and controls were subjected to exclusion criteria, including head trauma, drug abuse, and central neurological disorders.

Patients and control have consented to all procedures; controls and patients filled out a descriptive questionnaire that includes socio-demographic data, physical data and the Beck of the Depression Inventory, which is a medical scale used to determine the degree and intensity of depression patients (Beck et al., 1996).

MRI Acquisitions

Structural MRI was done to both patients and healthy controls in the MRI section of the radiology department in the Al-Amal National Hospital. The scanner is Philips 1.5 Tesla Magnetom Avanto Vision System. T1- weighted Magnetization Prepared Rapid Acquisition (MP-RA) was used to create three-dimensional images; it generates good grey/white matter contrast in a short acquisition period. Slice distance is 1.0mm, the field of view is 250 read, 192mm phase, TR=1657ms, TE=2.95ms, bandwidth 180Hz/pixel, flip angle 30°, ECHO spacing=7.5ms, phase resolution=100%, slice resolution=50%, and acquisition time = 5 minutes and 18 seconds. The images were in the coronal section. This T1-weighted sequence is part of the standard clinical protocol for qualitative and quantitative analysis of the whole brain in patients with epilepsy. All subjects were scanned in the supine position. The subject lies on a couch without any metals and then slides into the scanner. When each picture is being taken, the subject needs to keep still for a few minutes; otherwise, the scan picture may be blurred. The scan itself is painless. The entire processes take six minutes, without contrast media.

Manual Brain Segmentation of the MRI

Manual mapping in ImageJ 64 bit downloaded from www.imageJ.com is done, using delineation technique. In this study, the region of interest (ROI) is mapped and delineated its boundaries. The accurate point is grey matter of the head of caudate nucleus, the white matter of the spinal cord and the CSF in the cavity of the lateral ventricle. The mapping direction is the poster- anterior, and the sampling strategy includes each slice.

Volume Measurement

In ImageJ, delineated ROI is converted volume to cm^3

Mapping of Hippocampus

In coronal view, the starting is from the most posterior slice. Then, moving anteriorly, the first slice in which the lateral ventricle looks as CSF in the middle of each hemisphere is identified. Keeping the same direction, the slice containing the grey matter in the lateral ventricle's inferomedial angle is then identified. This slice contains the tail of hippocampus. Finally, the grey matter between the cavity of lateral ventricle in the lateral and superior borders is delineated.

Similarly, the white matter separating the hippocampus from the parahippocampal gyrus in the medial and inferior borders is delineated. In the most anterior slices, a bulk of grey matter appears, overriding the superior border of hippocampus. This is the amygdala. The superior border of hippocampus in these slices is a thin white line (the fimbria), separating between the amygdala dorsally and the hippocampus ventrally. The delineation continues below the fimbria until it disappears (Figure.1).

Mapping of the Amygdala (Bergstrom, 2020)

In coronal slices, we started below the level of the mammillary bodies, tubera, and optic tracts; we cut out uncal tissue by cutting straight up from the uncal notch. Also, if the grey matter has been marked as the amygdala but is not connected to hippocampus (each of two directly or via the gyrus uncinatus/gyrus ambiens), we erased it when we went back through coronal slices (Figure 2).

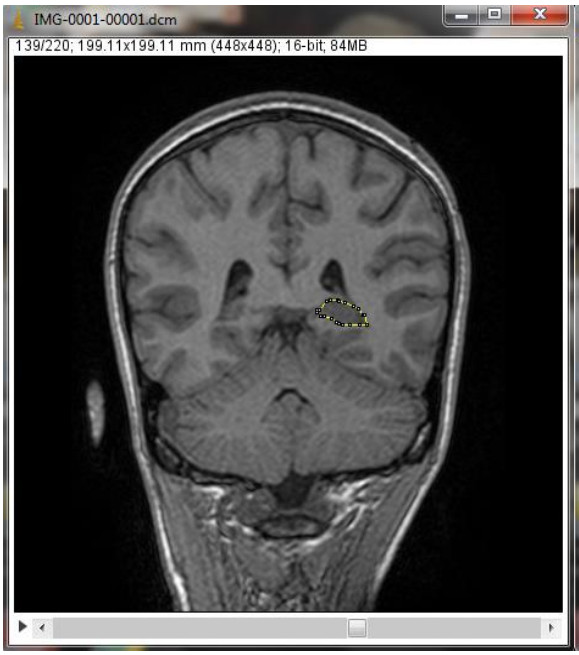

Figure 1 Delineation of Hippocampus

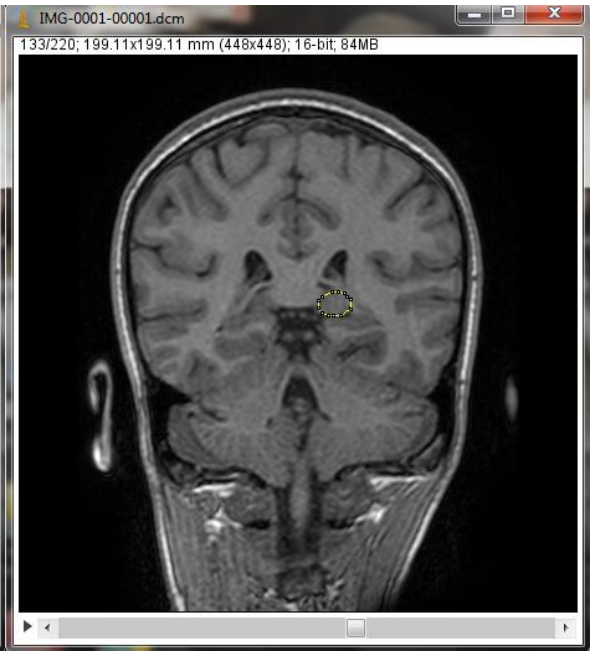

Figure 2 Delineation of Amygdala

Statistical Analysis

Data examination and analysis were implemented on a personal computer (specification: HP pavilion 620 Intel dual cores Processor 3.4 GHz, Memory 4). SPSS version 18 was employed for all different statistical analyses. Tables were used to produce the findings; differences between the control and diseased groups were tested using independent T-test, tests for the categorical variable (gender) and volumes. P. Value equal to or lower than 0.05 was defined as accepted as statistical significance.

3. RESULTS

The volumes mean of the right and left hippocampus in patients with depression were (2.9056 cm3 and 2.7778 cm^3) (SD ± 0.47061 and ±0.41959) respectively. They showed higher values in healthy control group (2.9746 cm3 and 2.9244 cm^3) (SD ± 0.36617 and ±0.43798) respectively. On contrary, the volume means of the amygdala appeared to be increased for both right and left sides of the depression group (2.3690 cm^3 and 2.2762 cm^3) (SD ± 0.49640 and 0.44885) respectively in compared with the healthy control group (2.2442 cm^3 and 2.1808 cm^3) (SD± 0.40968 and 0.35663) for the right and left side respectively table (1).

Table 1 shows the volumes' mean (±SD) of the hippocampus and amygdala in control and depression group

	N	Control group Mean cm^3 (±SD)	depression group Mean cm^3 (±SD)	P. Value
Right hippocampus	50	2.9746 (SD ± 0.36617)	2.9056 (SD ± 0.47061)	0.415
Left hippocampus	50	2.9244 (SD ± 0.43798)	2.7778 (SD ± 0.41959)	0.091
Right amygdala	50	2.2442 (SD ± 0.40968)	2.369 (SD ± 0.4964)	0.173
Left amygdala	50	2.1808 (SD ± 0.35663)	2.2762 (SD ± 0.44885)	0.242

Hippocampus volumes' means (3.0904 cm3 and 2.9392 cm3) (±SD 0.39577 and 0.45004) respectively, are reduced in male patients with depression in comparison with the right in addition to left hippocampus mean volumes (3.0920 cm3 and 3.0392 cm3) (±SD 0.36637and 0.38768), respectively in healthy control. Amygdala mean volumes (2.3732 cm3 and 2.3104 cm3) (±SD 0.54238 and 0.48329), respectively, are increased in patients with depression in comparison with amygdala mean volumes (2.3532 cm3 and 2.2892 cm3) (±SD 0.44267 and 0.36460), respectively in healthy control.

Our findings indicate that there was volume reduction of hippocampus in male patients with depression compared with male control. However, the mean volume of the amygdala was increased in male patients with depression more than in control table (2).

Table 2 shows the volumes' mean (±SD) of the hippocampus and amygdala in male control and depression group

	N	Control group Mean cm^3 (±SD)	depression group Mean cm^3 (±SD)	P. Value
Right hippocampus	25	3.092 (SD ± 0.36637)	3.0904 (SD ± 0.39577)	0.988
Left hippocampus	25	3.0392 (SD ± 0.38768)	2.9392 (SD ± 0.45004)	0.404
Right amygdala	25	2.3532 (SD ± 0.44267)	2.3732 (SD ± 0.54238)	0.887
Left amygdala	25	2.2892 (SD ± 0.3646)	2.3104 (SD ± 0.48329)	0.862

The hippocampus in both sides means volumes (2.7208 cm3 and 2.6164 cm3) (±SD 0.47370 and 0.32039), respectively, are reduced in female patients with depression in association with the mean volumes of hippocampus in both sides (2.8572 cm3 and 2.8096 cm3) (±SD 0.33289 and 0.46248), respectively in healthy control. There were no statistical variances between the groups and across the groups. The right in addition to left amygdala mean volumes (2.3648 cm3 and 2.2420 cm3) (±SD 0.45704 and 0.41871), respectively, are increased in patients with depression in contrast with the amygdala in both sides mean volumes (2.1352 cm3 and 2.0724 cm3) (±SD 0.34923 and 0.31978), respectively in healthy control. There were statistical differences, the P value <0.05.

The current study finds that there was volume reduction of hippocampus in female patients suffering from depression compared with control females. Regarding of amygdala mean volume it was increased in female patients with depression more than in female control table (3).

Table 3 shows the volumes' mean (±SD) of the hippocampus and amygdala in female control and depression group

	N	Control group Means cm^3 (±SD)	depression group Means cm^3 (±SD)	P. Value
Right hippocampus	25	2.8572 (SD ± 0.33289)	2.7208 (SD ± 0.4737)	.245
Left hippocampus	25	2.8096 (SD ± 0.46248)	2.6164 (SD ± 0.32039)	.092
Right amygdala	25	2.1352 (SD ± 0.34923)	2.3648 (SD ± 0.45704)	.052*
Left amygdala	25	2.0724 (SD ± 0.31978)	2.242 (SD ± 0.41871)	.114

*P. value is significant at the level of 0.05 or less

4. DISCUSSION

This study's findings clearly demonstrated that there was a variance between the control and depression patients in concern with volume of the hippocampus and amygdala but nevertheless, the difference didn't reach the significant level regardless of gender. The hippocampus volumes in patients who suffer from depression are less than control; these findings which aligns with previous histological studies (Bremner et al., 2000) in conjunction with MRI findings (Sheline et al., 1999). In the first occurrence of disease, the glucocorticoid levels will increase, leading to neurotoxicity, will increase and release excitatory amino acids, and the latter may inhibit neurogenesis, plasticity losing in hippocampus leading to an initial decrease in volume (Pinder, 2004; Pagliaccio et al., 2014; Lupien et al., 1998)

Test of memory function revealed the alteration differences of performance between the healthy and depression affected group; such memory deficits clearly related to the function of hippocampus (Vedhara et al., 2000; Thompson et al., 2004; Von Gunten et al., 2000). Therefore, the hippocampus might be considered as a key structure in the production of schizophrenia as well as depression (Aleman et al., 1999; Gradin & Pomi, 2008). In this investigation, the right and left amygdala was shown to be significantly smaller in individuals with depression. In addition, the left volume amygdala, not the right one, in the female patients was significantly smaller than in female controls, and no differences were reported between male patients and male controls.

Female patients with depression and hormonal fluctuation exhibit a decrease in density of the glial cells (Altshuler et al., 2010), which decreases the volume of amygdala in females. However, volume reduction in female patients, particularly the left amygdala appears to be consistent with neuropsychological observations to some extent, that the amygdala is involved in maintaining the emotional memory (von Gunten et al., 2000). Huge strong emotional memories are an increased susceptibility to depression (Hamann, 2005); while our results were contradictory to some findings has been described previously in the literature, for example; the study of Romanczuk-Seiferth et al., (2014) for whole-brain analysis exhibited significant increase in the volume of bilateral amygdala. This disagreement can be clearly explained by using a completely different methodology than abstracts and parameterized individuals. They studied the amygdala-hippocampal complex rather than the hippocampus and amygdala independently.

We used a handed skill delineation approach rather than automatic segmentation. Different methodologies used probably increased the controversy of findings. For example, (1) many studies depend totally on the thickness of MRI sections are used to measure temporal lobe size, hippocampus and amygdala volume (Caetano et al., 2007); (2) Other studies rely on thin MRI sections to determine the volume of temporal lobe regions (Hsu et al., 2002); (3) Since separating the amygdala besides hippocampus on coronal slices is difficult, amygdala besides hippocampus were combined into the amygdala-hippocampal complex in the most of MRI findings (Giedd et al., 1996); (4) In the meanwhile, a slight number of recent investigations have individually evaluated these two cerebral areas (Caetano et al., 2004). We measured the amygdala and hippocampal volume manually and separately as much as we could by delineation using ImageJ software.

Limitation of the study

There are several potential limitations of our study. First, our analysis only involved cross-sectional studies of individuals complain from depression as well as healthy controls and only examined the amygdala and hippocampus. Second, we have not examined the hippocampal subfields

5. CONCLUSION

In our conclusion, the current study's findings revealed abnormalities in amygdala as well as hippocampus volume in a patient suffering from depression associated to healthy people. In addition, female patients' amygdala volume is decreased on the left side. Volume reduction was clearly noted in hippocampus. The findings specify that the amygdala size shows side and gender variances in the patients with depression. This will motivate the researcher to link brain structure with gender differences.

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Conflict of interests

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

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