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Hippocampus and amygdalar volumes in patients with refractory obsessive–compulsive disorder

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ABSTRACT

Functional and structural neuroimaging studies have implicated the hippocampus–amygdala complex in the pathophysiology of obsessive–compulsive disorder (OCD), although no consensus has been established. These brain regions have not been investigated in refractory OCD patients. Volumes of the hippocampus, and amygdala were measured by magnetic resonance imaging (MRI) in a sample of 14 refractory OCD patients and 14 healthy comparison subjects. The mean left and right hippocampal and amygdala volumes of the patients were smaller than those of the healthy controls. OCD severity was not correlated with amygdala volumes but was related to the left hippocampus. Duration of illness was correlated with both hippocampus and left amygdala. Our findings suggest that hippocampus and amygdalar abnormalities can be considered in refractoriness to OCD.

1. Introduction

Based on functional and structural neuroimaging findings, current findings regarding the pathophysiology of obsessive–compulsive disorder (OCD) have emphasized abnormalities in fronto-striatal-thalamic-cortical circuits and orbitofronto-striato-thalamic circuits (Cummings, 1993; Saxena et al., 1998; Saxena et al., 2001; Graybiel and Rauch, 2000). However, other candidate structures include hippocampus–amygdala complex. More recently, investigators included the hippocampus, anterior cingulate and basolateral amygdala to this circuit because of the fact that these structures have connections with the orbitofrontal cortex which may have in the pathophysiology of OCD (Lawrence et al., 1998; Phillips et al., 2003). On the other hand, a loss of the normal hemispheric asymmetry of the hippocampal–amygdalar complex (Szeszko et al., 1999) and other amygdala volumetric differences (Szeszko et al., 1999, 2004) wasere reported. Hippocampal and amygdalar abnormalities were emphasized in the studies involving positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) and authors commented that the region might have an important role in the pathophysiology of OCD, with neglected discussion (McGuire et al., 1994; Adler et al., 2000). On the other hand, structurally, it has been suggested that hippocampal structural alteration may play a role in the pathophysiology of OCD (Hong et al., 2007). Furthermore, the agents which are efficacious in the management of OCD (e.g., serotonergic reuptake inhibitors, and anti-anxiety drugs) have been shown to exert their effects on receptors in the amygdaloid (Nagy et al., 1979; Gonzalez et al., 1996; Zangrossi et al., 1999). In addition, the cybernetic models proposed by Gray (1982) and Pitman (1987) both emphasized that the hippocampus could be play an important role in compulsive behavior. On the other hand, in their study, Van Laere et al. (2006) performed high-frequency anterior capsular stimulation and obtained PET imagings preoperatively and after stimulation in 6 refractory OCD patients. They found that there were positive correlations between clinical improvement and the metabolic activity changes in the left ventral striatum, left amygdala, and left hippocampus. Despite the knowledge aforementioned regarding the importance of the hippocampus–amygdalar complex, its role has not been extensively investigated in OCD. The purpose of this study was to compare hippocampal and amygdalar volumes in patients with refractory OCD with those in healthy subjects with no psychopathology.

Abbreviations: MRI, magnetic resonance imaging; OCD, obsessive–compulsive disorder; SCID, Structured Clinical Interview for the Diagnostic Schedule for Mental Disorders; Y-BOCS, Yale–Brown Obsessive–Compulsive Scale; ANCOVA, analyses of covariance.

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2. Methods

2.1. Participants

Fourteen patients with OCD (9 females and 5 males), with a mean age of mean age = 29.1 years, SD = 5.7 from the Firat University School of Medicine Department of Psychiatry were compared to the same number of healthy subjects without psychiatric disorder (9 females and 5 males), with a mean age of mean age = 31.8 years, SD = 6.9. The duration of illness of the patients is 5.5 years, SD = 2.4. All participants gave written informed consent before participation in the study and were right-handed. The study was prepared in accordance with the ethical standards laid down in the Declaration of Helsinki. Diagnoses were made according to the Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV) and the Structured Clinical Interview for the Diagnostic Schedule for Mental Disorders—Fourth Edition (SCID) (Corapcioglu et al., 1999). Current comorbid psychiatric disorders were also assessed by SCID. Severity of OCD symptoms was assessed with the Y-BOCS (Goodman et al., 1989a,b). Each treatment refractory patient was required to have had adequate trials (at least 10 weeks at the maximally tolerated dose) of at least three of the serotonin reuptake inhibitors (clomipramine, fluoxetine, sertraline, paroxetine, fluvoxamine, or citalopram) and augmentation of at least one of the previous drugs for 1 month with at least two of the following medications: lithium, clonazepam, buspirone, or a neuroleptic. In addition, they included (a) less than 35% decrease on the Yale–Brown Obsessive–Compulsive Scale (Y-BOCS) total score at final evaluation as compared to baseline or a final score of >18 on the Y-BOCS, (b) no better than "minimally improved" on the Clinical Global Impression improvement item, (c) the agreement of two of the authors (M.A. and S.O.) that the patient was not enough improved (Goodman et al., 1989a,b; Atmaca et al., 2002). The most frequent obsession was dirty and contamination (n = 9) and the most frequent compulsion was washing (n = 9).

Patients and comparison subjects were excluded if they had any comorbid psychiatric disorder including tic disorder and Tourette's disorder, current or lifetime neurologic, current medical problems, history of head trauma, and alcohol/substance abuse within the 6 months preceding the study. Healthy control subjects had no DSM-IV Axis I disorders in self or in a first-degree relative, as determined by the SCID nonpatient version, no current medical problems, neurologic or psychiatric histories.

2.2. MRI procedure

Magnetic resonance imaging scans were acquired with a 1.5 T General Electric scanner. Spiral pulse sequences were employed because of insensitivity to subject motion. A high-resolution structural image of the entire brain was obtained using sagittally acquired 2D spiral fast spin echo high-resolution images (TR = 2000 ms, TE = 15.6 ms, TI = 700 ms, FOV = 240 mm, echo SPACING = 15.6 ms, 8 echoes, RESOLUTION = 0.9375 × 0.9375 × 1.328 mm, 128 contiguous slices, 8 min 36 s). The tracing and measurements were done by raters (HY, HO) who were blind to identity and diagnoses of the subjects. The intra-class correlation coefficients for all anatomical structures measured were above r = 0.89.

The hippocampal and amygdalar regions were drawn with reference to standard anatomic atlases (Duvernoy and Cabanis, 1991; Bertolino et al., 1996; Talairach and Tournoux, 1998) and adapted from Caetano et al. (2004) and Brambilla et al. (2003): For the hippocampus, tracing was started on the coronal slice where the superior colliculus completely connected with the thalamus and finished one slice before the mammillary bodies appeared. The corona radiata and ambient cistern were indicated as the superior border. The inferior border was selected as the white matter. Finally, the lateral border was the inferior horn of the lateral ventricle. For amygdala, tracing started when the mammillary body can be seen. The superior and lateral limits were temporal lobe white matter. The white matter of parahippocampal gyrus was selected as inferior border. When the amygdala could not be seen, this limit was accepted as anterior border. Sample imagings are presented in Fig. 1.

2.3. Statistical analysis

Repeated-measures analyses of covariance (ANCOVA) as the repeated measure were used to analyze group differences in total volumes. Whole brain volume was used as covariate. t tests for nonpaired samples were used to compare group differences in left and right hippocampal and amygdalar volumes. Significance was defined as $p < 0.05$.

3. Results

As presented in Table 1, there were no significant differences in demographic variables of age, gender composition, educational level, and intracranial volume (ICV), whole brain volume, gray and white matter volumes between refractory OCD patients and healthy controls ($p > 0.05$).

The mean left and right hippocampal volumes of the patients were smaller than those of the healthy controls (for left hippocampus, for

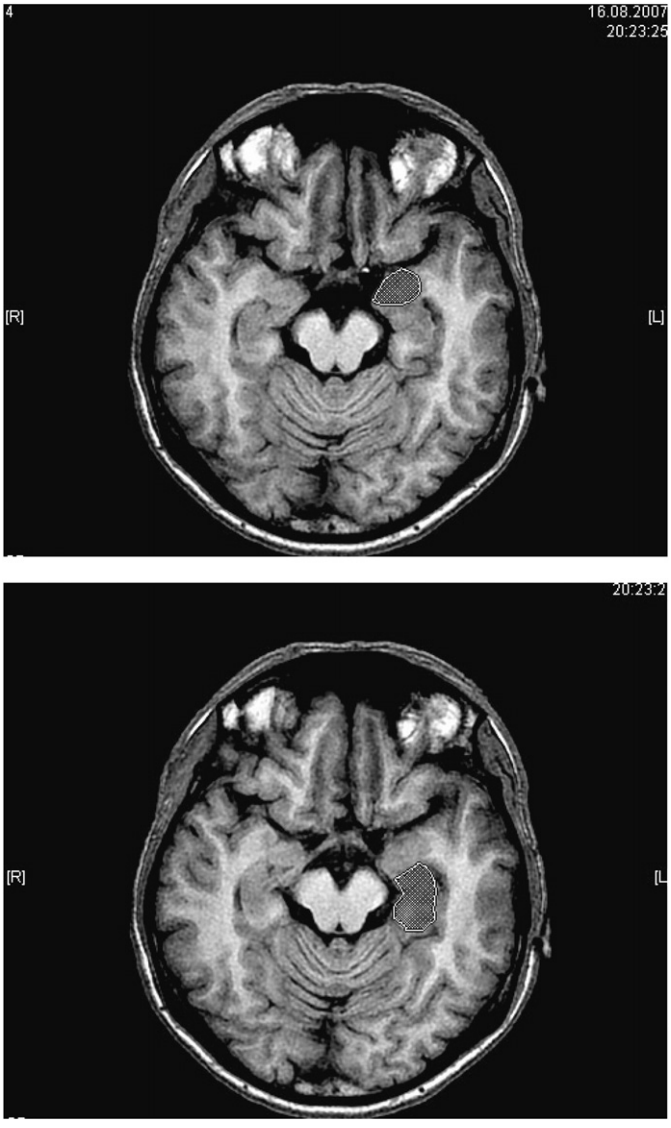

Fig. 1. Sample imagings of the hippocampus and amygdala.

Table 1
Clinical and demographic characteristics of normal control subjects and patients with refractory OCD

	Patients with OCD (n=14)	Controls (n=14)
Age	29.1±5.7	31.8±6.9
Gender (F/M)	9/5	9/5
Age at onset (years)	20.6±4.9	–
Handedness (right)	14	14
Graduated from high school	8	10
Number of subjects who had family history	4	–
Y-BOCS score	24.7±3.6	–
ICV	1561.3±162.7	1487.5±128.1
Whole brain volume	1229.8±90.2	1118.7±107.9
Gray matter volume	891.3±107.4	827.5±84.3
White matter volume	338.5±41.4	291.2±32.1
Hippocampus		
Left	2551.1±272.2	2953.4±462.4**
Right	2468.3±218.4	2762.7±372.8*
Amygdala		
Left	1738.5±204.9	2242.4±290.8**
Right	1884.6±190.1	2211.2±302.5*

No significant differences exist between groups in age, handedness and gender composition. ICV, Intracranial volume; Y-BOCS, Yale–Brown Obsessive–Compulsive Scale. All volumes are in cubic millimeters (mm^3).
* $p<0.05$.
** $p<0.01$.

patients: mean=2551.12 mm^3, SD=272.24; comparison subjects: mean=2953.35 mm^3, SD=462.41; t=3.14, df=27, p=0.0082; for right hippocampus, for patients: mean=2468.28 mm^3, SD=218.35; comparison subjects: mean=2762.70 mm^3, SD=372.83; t=2.29, df=27, p=0.032). With repeated-measures ANCOVA with side as the repeated measure and whole brain volume as covariate, this difference maintained as significant (for left, F=4.45, df=1,26; p=0.039; for right, F=4.04, df=1,26, p=0.044).

The mean left and right amygdalar volumes of the patients were smaller than those of the healthy controls (for left amygdala, for patients: mean=1738.45 mm^3, SD=204.91; comparison subjects: mean=2242.37 mm^3, SD=290.78, t=3.37, df=27, p=0.0071; for right amygdala, for patients: mean=1884.55 mm^3, SD=190.12; comparison subjects: mean=2211.23 mm^3, SD=302.48, t=2.39, df=27, p=0.027). As seen in hippocampal volumes, when controlled whole brain volume was covariate, repeated-measures ANCOVA showed that the difference continued (for left, F=5.23, df=1,26; p=0.033; for right, F=4.78, df=1,26; $p<0.041$).

OCD severity was not correlated with amygdala volumes (r's<0.18, p's>0.8) but was negatively related to left hippocampus ($r<-0.53$, $p<0.05$). Duration of illness was negatively correlated with both hippocampus (for left, $r<-0.46$, $p<0.05$ and for right, $r<-0.55$, $p<0.05$) and left amygdala ($r<-0.58$, $p<0.05$). No other significant correlation was detected.

4. Discussion

This is the first investigation to demonstrate smaller hippocampal and amygdalar volumes in patients with refractory OCD compared to healthy subjects. The patients with refractory OCD in the present study showed a 12% smaller hippocampal volume and a 23% smaller amygdalar volume compared with the healthy subjects.

It has been suggested that OCD may involve abnormalities of the hippocampus and amygdala. However, to date, functional neuroimaging studies failed to achieve a consensus with regard to this issue (McGuire et al., 1994; Adler et al., 2000). On the other hand, there have been totally four volumetric studies involving hippocampus and/or amygdala and they reported mixed results, away from accessing a clear conclusion (Jenike et al., 1996; Szeszko et al., 1999; Kwon et al., 2003; Hong et al., 2007). Kwon et al. (2003) found that while hippocampal volume was bilaterally reduced in OCD patients versus the normal controls, left amygdala volume was significantly enlarged in patients with OCD, contrary to our findings. Szeszko et al. (1999) and Hong et al. (2007) reported that the patients with OCD had significantly reduced bilateral amygdala volumes and hippocampal volumes, as in our study. Partial contradictory in these results can be attributed to different study methods, heterogeneous samples and differences in the definition of the studied regions. In addition, we included only refractory OCD patients in the present study, differently than the other studies, so both reduced hippocampus and amygdala volumes may be contributing to the refractoriness to OCD. Consequently, as supported by our findings, hippocampus and amygdala abnormalities seem to be associated with the pathophysiology of OCD. Some important notions support this result: (1) especially also taking into consideration the potential role of hippocampus in the best-established neuroanatomical model of OCD, called the fronto-striatal circuitry model, as hippocampal projections direct into the orbitofrontal cortex (OFC) with topographical specificity in both the hippocampus and the OFC (Barbas and Blatt, 1995; Cavada et al., 2000). (2) Serotonergic input to the amygdala specifically stimulates fear-associated behavioral suppression mediated by this structure. In their animal model of anxiety, Zangrossi et al. (1999) implicated gamma-aminobutyric acid (GABA)/benzodiazepine and serotonergic systems within the basolateral/lateral amygdala in the modulation of conditioned anxiety responses. These are also clinical characteristics of OCD. (3) On the other hand, amygdalar nuclei have been proposed as an important corner in which serotonin reuptake inhibitors, agents treating OCD effectively, bind the receptors on those (Nagy et al., 1979; Gonzalez et al., 1996). In regard to refractoriness, recently, in their study, Van Laere et al. (2006) performed high-frequency anterior capsular stimulation and obtained PET imagings preoperatively and after stimulation in 6 refractory OCD patients. They found that there were positive correlations between clinical improvement and the metabolic activity changes in the left ventral striatum, left amygdala, and left hippocampus. The knowledge aforementioned suggests that reduced hippocampal–amygdalar complex in patients with OCD might also be an epiphenomenon of the underlying psychopathology of the illness, moreover, it is worth noting here the fact that correlations were found between the volumes and both Y-BOCS (in left hippocampus) and duration of illness may further support the association between refractoriness to OCD and hippocampus and amygdalar abnormalities. However, these preliminary results should be cautiously approached until new investigations support these findings adequately.

Our study has a number of limitations that should be considered. First of all, the small sample size might have limited our power to detect differences, actually a common shortcoming in the field of neuroimaging. A potential solution for this shortcoming may be multi-centered investigations. The statistical thresholds applied were modest, thereby accentuating these risks and underscoring the importance of replication. In addition, we only used refractory OCD patients, taking also pure OCD patients would be more useful. Finally, we should note our manual tracing technique, comparing potential other alternatives such as computational morphometry and multivariate approaches.

Finally, our results suggest that hippocampal and amygdalar structural abnormalities may be associated with the pathophysiology of OCD. However, this conclusion merits to be supported by new investigations with larger sample size.

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