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Bilateral MR Volumetry of the Amygdala in Chronic PTSD Patients

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A B S T R A C T

Posttraumatic stress disorder (PTSD) patients experience symptoms which implicate dysfunction of emotional memory circuits, and possible damage of the amygdala. Laterality differences in activity of the amygdala have been reported in PTSD patients, with presumed adaptive plasticity in the hippocampus and the amygdala. The aim of this study was to investigate possible interhemispheric differences of amygdalar volume in chronic PTSD patients, with calculation of right-to-left volume ratios. Bilateral magnetic resonance (MR) volumetry was applied in 11 chronic PTSD patients. The mean right amygdalar volume of our patients was significantly smaller than the left one (p=0.031), with the right-to-left volume ratio of 0.96±0.06. This tendency towards smaller right amygdala may be an acquired effect as a result of stress-induced plasticity, however we can not exclude the possibility of a predisposing condition.

***Key words**: MR volumetry, amygdala, PTSD*

Introduction

Patients suffering from posttraumatic stress disorder (PTSD) experience distortion and fragmentation of memory, declarative and non-declarative memory deficits and dissociative amnesia[1]. Such symptoms are commonly referred to as psychological problems, although they may be related to physical effects of extreme stress on specific brain structures. The amygdala, especially the amygdalar basolateral nucleus, is a prominent structure in emotional memory circuits and stress-induced aversive learning. Possible dysfunction of the amygdala can influence pathophysiology of PTSD at multiple levels[2,3]. It modulates the effect of emotional stimuli and stress hormones on encoding and/or consolidation of declarative memory, through direct and indirect influence on the hippocampus[4–6]. There are reports of laterality differences in activity of the amygdala in patients with PTSD[4,7,8]. Since chronic stress may cause adaptive plasticity, as well as dendritic remodeling in the amygdala in animal models[9–12], the purpose of this study was to explore possible asymmetry in the amygdalar volume in chronic PTSD patients, with calculation of right-to-left volume ratios. The volumes and the volume ratios were compared with healthy subjects used as control groups in studies of Szabo et al.[13] and Bower et al.[14].

Materials and Methods

The patients included in the study were 11 Croatian War veterans. They were diagnosed as chronic PTSD patients meeting the criteria stated in Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV), without other Axis-I and/or Axis-II diagnosis[15]. Their symptoms lasted for more than 5 years. They were receiving no psychotropic medication for at least six months preceding the study. Neurological examination excluded possible comorbid conditions, head trauma or loss of consciousness the year preceding the study. Unfortunately, at the time of inclusion of the patients in the study, there was no Croatian standardized version of Clinician Administered PTSD Scale (CAPS score) for PTSD severity. Patients with depressive symptoms were excluded from the study based on a psychiatric clinical interview, at the time and in our circumstances it was not

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possible to control these aspects in more details. All the patients were male, right-handed, with no history of alcohol or drug abuse. The age of the participants ranged from 32 to 52 (the average of 40). Comparison groups were healthy subjects matched for sex, handedness, and without history of alcohol abuse[13,14]. The control group, used for comparison from a study by Szabo et al., consisted of 9 healthy male participants, all right-handed, with a mean age of 27 years. The study by Bower et al. used the control group consisting of 31 male subjects without past head injury, medical or psychiatric history.

Magnetic resonance (MR) examinations were performed on a »Prestige Gyrex» General Electric/Elscint scanner with 2.0 Tesla field-strength. The imaging sequence used for volumetric analysis was a coronal three-dimensional (3D) T1 spoiled gradient-echo (SPGR) acquisition of the whole brain (repetition time 540 msec, echo time 20 msec, field of view 240 x 240 mm, Matrix 256 x 192). 1.1 mm thick slices were measured, without an interleave gap, with 1.0 x 1.0 mm in plane resolution. Both compared studies also used a coronal 3D T1 SPGR sequence without an interleave gap, Bower et al. used a 1.5 mm slice thickness, while Szabo et al. used a slice thickness of 1 mm. MR acquisition parameters have been comparable since minor differences in slice thickness do not lead to false estimation of volume[16].

The boundaries of the amygdala on individual slices were demarcated manually by an experienced neuroradiologist unfamiliar with the patients' diagnosis or the purpose of the measurement. The volume was measured using DicomWorks v 1.3.5 software (2000–2001. Philippe Puech, Loic Boussel). Both amygdalae in each subject were measured in three separate cycles. During each cycle both amygdala were measured in each subject once. The cycles were separated by one-week period. Mean values and standard deviation for each amygdala were calculated, and in such form used in statistical analysis. Amygdalar volume segmentation was performed in accordance with compared studies and previous studies on the subject of volumetry[13,14,17–19]. The posterior border of the amygdala was the slice where it first became visible as gray matter superior to the alveus and laterally to the hippocampus, overlying the temporal horn of the lateral ventricle. The anterior border of the amygdala was not clear in all patients, and for the purpose of consistency it was defined at the level of the opening of the endorhinal sulcus forming the lateral fissure. Superiorly, a straight line was drawn from the superolateral aspect of the optic tract to the fundus of the circular sulcus of insula, excluding parts of basal ganglia. Superomedially, the endorhinal sulcus separated the cortical amygdaloid nucleus from the substantia innominata. Inferolaterally, it was separated from the hippocampal head by the alveus and temporal horn of the lateral ventricle. Inferomedially, tentorial indentation served as a demarcation line between the amygdala and entorhinal cortex. Posteromedial border was delineated by the crural cistern and anteromedial by the angular bundle from entorhinal cortex. Amygdalar volumes were calculated by summing cross sectional areas and multiplying by slice thickness (Cavalieri's principle)[14].

For the purpose of statistical analysis, results were analyzed using Stat View software v. 5.0.1. Right-to-left amygdalar volume ratios were calculated for each patient. We used a paired t test for the assessment of any significant asymmetry in the volumes between right and left amygdala. The correlation between the patients' age and volume ratios was analyzed by simple regression. Volumes and right-to-left volume ratios were presented as arithmetic means ±SD. We compared our mean volume ratio (±SD) to the mean volume ratios (±SD) of healthy male subjects used as control groups in studies of Szabo et al.[13] and Bower et al.[14]. For the comparison of two means, unpaired t test was used.

Results

The mean right and left amygdalar volume of the patients in our study is presented in Table 1. The mean right and left volumes were significantly different ($p=0.031$). 8 of 11 patients had smaller right amygdalar volumes than left, the difference ranging from 0.14 to 14.51%. The mean right-to-left difference in these 8 patients was 7.8%. The right amygdala was larger in remaining 3 patients, in a range from 0.3% to 7%, with a mean difference of 2.9%. The right-to-left amygdalar ratio was 0.96±0.06. There was no correlation between the age of the patients and the inter-amygdalar ratios ($p=0.339$). The mean volume ratio (±SD) of our patients was directly compared to the mean volume ratio (±SD) of control groups in studies of Szabo et al.[13] and Bower et al.[14]. In a study by Szabo et al. a control group had a mean volume ratio of 1.07±0.06. The control group in a study of Bower et al. had the amygdala volume ratio of 1.04±0.06. The comparison of the mean volume ratio in our study with the ones from Szabo et al. and Bower et al. produced $t=4.88$ and $p<0.0001$ (degrees of freedom=29); and $t=3.80$ and $p=0.0005$, (degrees of freedom=40), respectively.

Discussion

Individuals with PTSD show hypothalamo-pituitary-adrenal (HPA) axis alterations[20] with attenuated feedback inhibition and release of epinephrine from the locus coeruleus to the amygdala. This is in line with reported hyper reactivity of the amygdala in these patients[21–23]. It modulates the effect of stress hormones on memory consolidation involving long-term potentiation (LTP) in hippocampus[5,24,25]. Prolonged stress with cortisol exposure impairs LTP in the hippocampus, while the same stress facilitates LTP in the amygdala[9–12]. Animal studies have shown dendritic growth in the amygdala during fear conditioning[26,27], as opposed to the effect in hippocampus where stress induced dendritic atrophy[12]. These data suggest volume alterations of the amygdala in PTSD, not necessarily in the same direction as hippocampal changes.

TABLE 1
CHARACTERISTICS OF THE PATIENTS AND AMYGDALAR VOLUMES

Subjects	Age (years)	Amygdalar volumes (cm^3)		Right-to-left volume ratios
		Right	Left	
1	32	2.33	2.53	0.918
2	41	2.35	2.35	0.999
3	42	2.28	2.37	0.962
4	36	2.74	3.03	0.906
5	33	1.91	2.09	0.915
6	52	2.23	2.37	0.941
7	43	2.13	2.12	1.003
8	41	2.60	2.84	0.915
9	40	2.43	2.26	1.075
10	42	1.74	1.72	1.014
11	38	2.50	2.87	0.873
X±SD	40±5.44	2.30±0.29	2.41±0.39	0.957

There are reports of asymmetric amygdalar activity in PTSD, in terms of greater relative cerebral blood flow (rCBF) and functional MR imaging (fMRI) activity in right amygdala[7,8], and in terms of correlation of affectively influenced memory with the activity of the right amygdala [4]. Therefore, there is reason to believe that the right amygdala may exhibit more pronounced volume changes compared to the left side in PTSD patients.

Most studies on amygdalar volume in healthy right-handed participants found larger right-than-left amygdalar volumes, while some found no interhemispheric differences[28]. Studies concerning brain volume changes in PTSD patients have primarily been focused on hippocampal volumetry, with little data on laterality differences of amygdalar volume. These studies also reported higher mean values of right amygdalar volumes compared to left[29–32]. Therefore, volume of the amygdala in PTSD patients in afore-mentioned studies did not differ significantly from the results in healthy subjects. However, Teicher et al.[33] found reduced size of the left amygdala related to stress, though it was in patients with history of sex abuse, accompanied by fear and terror, and not in PTSD patients. Bilaterally symmetric reduction of amygdalar volume in relation to stress was reported in patients with childhood maltreatment and borderline personality disorder[34].

The mean right amygdalar volume of the patients in our study was significantly smaller than left, with a right-to-left volume ratio of 0.96±0.06. This finding was interesting, and not easily explained, considering stress induced LTP and possible dendritic growth in right amygdala, which is hyper reactive in PTSD patients. When discussing the connection between hippocampal or amygdalar volume changes and effects of extreme stress, there are two confronted theories.

One is the possibility of stress-induced plasticity, with hippocampal volume reduction attributed to glucocorticoid toxicity[35,36]. The reduction of cortison level in patients with Cushing syndrome resulted in improved memory and increased hippocampal volume[37], which is in favor of this possibility. The same assumption may be applicable to amygdalar volume changes. However, one would expect stress-induced growth with an increase in volume of the right amygdala, which is not found in our patients. The patients in our study had a long duration of symptoms, more than five years, as opposed to one of the studies, where symptoms lasted 6 months[30]. The difference between our results and other, mostly Anglo-American studies in PTSD patients could possibly be caused by longer duty duration at battle field, in a homeland defensive war including multiple extreme stressor events, with lower rate of early trauma debriefing and professional psychological support. Therefore, it is likely that stress has a very gradual impact on amygdalar volume, so after a longer period of time hyper reactivity of the right amygdala could lead to noticeable cell loss. Alternatively, dendritic growth in amygdala, which would be responsible for stress-induced greater right amygdalar volume, has only been hypothesized according to studies in animal models, and may not be equivalent in human subjects.

The second possibility is that smaller volume of right-than-left amygdala represents predisposing factor which enlarges the risk of PTSD development after traumatic experience. This would be in line with hypothesized PTSD pathophysiology, which suggested that smaller hippocampal volumes may also be a preexisting condition in PTSD patients, since not all victims of trauma develop PTSD, and continued combat stress combined with already developed PTSD does not seem to produce further reduction of hippocampal volume[31]. However, smaller amygdala in the right hemisphere as a preexisting condition could hardly explain the higher risk of PTSD development, since it is the very side that is hyper reactive in these patients.

The role of amygdala in the pathophysiology of PTSD is substantial. Whether laterality differences reflect the vulnerability to PTSD development, or they represent a secondary event to traumatic experience, remains unclear. These volume changes may be, to a certain degree, related to the duration of PTSD. The limitations of our study were small sample size and the lack of PTSD symptom severity score. Unfortunately, there is no data on inter-rater reliability between morphometric raters in studies used for comparison groups and our study.

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OBOSTRANA VOLUMETRIJA AMIGDALA MAGNETSKOM REZONANCOM U BOLESNIKA S KRONIČNIM PTSP-OM

SAŽETAK

Bolesnici s posttraumatskim stresnim poremećajem (PTSP) imaju simptome koji upućuju na disfunkciju neuronskih krugova emocionalne memorije i na moguće oštećenje amigdala. Različita lateralizacija aktivnosti amigdala opisana je u bolesnika s PTSP-om, s pretpostavkom adaptivnog plasticiteta u hipokampusu i amigdalima. Cilj ove studije bio je istražiti moguće interhemisferične razlike volumena amigdala u bolesnika koji boluju od kroničnog PTSP-a, s izračunavanjem omjera volumena desnih i lijevih amigdala. Obostrana volumetrija magnetskom rezonancom (MR) provedena je u 11 bolesnika s kroničnim PTSP-om. Srednja vrijednost volumena desnih amigdala u naših bolesnika bila je značajno manja nego lijeve strane ($p=0.031$), s omjerom volumena desnih i lijevih amigdala 0.96 ± 0.06. Ta tendencija prema manjim desnim amigdalima može biti stečena kao rezultat plasticiteta induciranog stresom, međutim ne možemo isključiti mogućnost da se radi o predisponirajućem stanju.