

BRAIN CHANGES IN PATIENTS WITH POSTTRAUMATIC STRESS DISORDER AND ASSOCIATED ALCOHOLISM: MRI BASED STUDY

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received: 18.8.2014;

revised: 17.11.2014;

accepted: 16.12.2014

SUMMARY

Background: Studies imposing rigorous control over lifetime alcohol intake usually have not found smaller hippocampal volumes in persons with posttraumatic stress disorder (PTSD). Since the majority of negative studies have used adolescent samples, it has been suggested that chronicity is a necessary condition for such findings. We have hypothesized that the volumes of hippocampus, amygdala, prefrontal cortex and the intracranial volume are reduced in the patients with PTSD and excessive alcohol intake.

Subjects and methods: Study has been carried out on 54 therapy naive PTSD suffering subjects and healthy controls, divided in two groups: 29 with PTSD and consequent alcoholism, 25 with PTSD but without problems of excessive alcohol intake, and 25 healthy volunteers. All of the patients underwent same magnetic resonance imaging (MRI) protocol and volumetric evaluation of the region of interest.

Results: Only hippocampal volume appeared to be significantly reduced in patients with PTSD and alcoholism. Other differences in the volumes obtained remained to be insignificant.

Conclusion: Alcohol intake definitely worsens the deterioration of the hippocampal formation in PTSD suffering patients. Nevertheless, other structures of interest for this study did not manifest any kind of statistical differences in volumetric analysis.

Key words: posttraumatic stress disorder – PTSD - hippocampus – MRI – brain – anatomy

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INTRODUCTION

Posttraumatic stress disorder (PTSD) is a chronic mental state that possibly emerges after life or body integrity threatening events. On the neuronal level, the deterioration of hippocampus, medial prefrontal and medial temporal structures, amygdaloid complex and anterior cingulate cortices have been reported (Brewin 2001, Elbert & Schauer 2002, Yamasue et al. 2003, Corbo et al. 2005, Karl et al. 2006, Woodward et al. 2006, Kolassa & Elbert 2007, Kasai et al. 2008, Eckhart et al. 2011). Regions of the brain involved in episodic memory and emotional processing, such as parietal and lateral prefrontal cortices and posterior midline structures, have been emphasized as damaged, in studies concerning PTSD performed by functional magnetic resonance imaging (Cardinal et al. 2002, Anderson et al. 2004, Wagner et al. 2005, Cabeza et al. 200, Blair et al. 2007).

Certain overlap between structures involved in PTSD and craving, a major component determining relapses in alcohol abuse is obvious: the orbitofrontal cortex, dorsal anterior cingulate cortex and amygdala are pointed out to play a distinct role in craving (Koob & Le Moal 2008). The involvement of the anterior cingulate cortices and nucleus accumbens in alcohol craving has been demonstrated by positron emission tomography (Lingford-Hughes et al. 2006) and functional magnetic resonance imaging (De Ridder et al. 2011).

Our aim was to determine whether the alcohol intake in PTSD patients worsens the damage of the neuronal structures already emphasized as deteriorated: hippocampus, amygdaloid complex, and prefrontal cortices.

SUBJECTS AND METHODS

Patients selection

All patients were recruited from the Psychiatric Center for the PTSD Treatment. We have selected 54 therapy naïve, male PTSD patients treated in the period January – November 2006, aged 32–59, who satisfied the following recruiting criteria:

- No evidence of comorbidity with other psychiatric diseases or disorders;
- No evidence of a prior head trauma;
- No previous psychotropic medication;
- No evidence of substance abuse;
- Absence of any kind of neurological, endocrine or degenerative disorders;
- No evidence of memory impairment;
- Negative familiar history about psychiatric illnesses, suicides or homicides.

The initial group was larger and comprised 97 patients, among whom four were estimated as potentially suicidal, during the psychotherapy, and were

rescheduled for medicamentous treatment; for six of them, biochemical test revealed drug positivity, three had extensive reductive brain alteration, and another five left the study on their own will two weeks later. All subjects were acquainted in detail with the study procedure and they all signed a written consent. The study was approved by the Ethic Committee of School of Medicine, in Belgrade, Serbia (Decision No 14/07, January 15, 2007).

Upon the admittance, all of the subjects underwent structured psychiatric interview, psychological examination and MRI scanning. The diagnosis of PTSD was assessed according to the guidelines in the 10th revision of the International Classification of Diseases (ICD – 10).

All patients were followed up in one – month period and were advised to undergo psychotherapy. No medication has been proscribed.

According to the PTSD symptomatology and associated alcohol abuse, all the patients were divided into three groups:

- Patients with PTSD and alcohol intake, (n=29, aged 32-57);
- Patients with PTSD, but without diagnosed alcoholism (n=25, aged 35-59);
- Healthy volunteers (n=25, aged 37-55), were used as a control group.

Detailed demographic and clinical characteristics of patients are shown in Table 1.

Magnetic resonance imaging procedures

The MRI study was performed using a 3.0 T whole body MRI scanner (Philips Medical Systems, Best, Netherlands). After the scanning, all the patients were coded in order to blind the volumetric evaluation team, and sent to the subsequent volumetric analysis.

Volume measurements of the basal nuclei, thalamus and hippocampus were performed on 3D-T1-weighted MR images (acquisition parameters were as follows: TR=9.8 ms; TE=4.6 ms; flip angle=8; section thickness =1.2 mm; number of sections =120; no section gap; whole brain coverage; FOV=224 mm; matrix=192, reconstruction matrix =256). Routine T2-weighted MRI and 3D FLAIR were performed to rule out a mass lesion as contributory factor to memory loss or cognitive decline.

The algorithm FIRST, suggested by our external co-workers from Toronto, was applied to estimate separately the structures volume in the left and right hippocampus, left and right lateral prefrontal and anterior cingulate cortices and six subcortical entities: the caudate nucleus, accumbens nucleus, putamen, globus pallidus and thalamus, and the lateral ventricle. FIRST is a part of Functional MRI of the Brain Software Library (FSL) and performs both registration and segmentation of the mentioned subcortical regions (Smith et al. 2004, de Jong et al. 2008). During registration, the input data (3D T1 images) were transformed to the Montreal

Neurological Institute (MNI) 138 standard spaces, by means of affine transformations based on 12 degrees of freedom (i.e. three translations, three rotations, three scalings and three skews). After subcortical registration, a subcortical mask was applied, to locate the different subcortical structures, followed by segmentation based on shape models and voxel intensities. The absolute volumes of subcortical structures were calculated, taking into account the transformations made in the first stage (Smith et al. 2004, de Jong et al. 2008).

Finally, a boundary correction was used to determine whether boundary voxels belonged or not to the structure examined. In this study a Z-value of 3 was used, corresponding to a 99.998% certainty that the voxels belonged to the mentioned subcortical structure. After registration and segmentation of all 158 MR scans, all segmented subcortical regions were visually checked for errors in registration and segmentation. Brain tissue volume was estimated with SIENAX, part of FSL (Smith et al. 2004). SIENAX starts by extracting brain and skull images from the single whole-head input data (de Jong et al. 2008). Tissue-type segmentation with partial volume estimation has been carried out (Zhang et al. 2001) in order to calculate the total volume of the brain tissue (including separate estimates of volumes of the grey and white matter). For this study we used the absolute volumes generated by the algorithm.

Statistical analysis

SPSS 13.0 (SPSS Inc, Chicago II, USA) has been used for data analysis. Analyzed groups have been compared according age, respect volumes of the right and, hippocampi, amygdaloid complexes, volume of the prefrontal cortices, total and on each hemisphere, and intracranial brain volume by one way analysis of variance (ANOVA), with Bonferroni post hoc correction. Pearson's correlation coefficient and linear regression line have been estimated for all the volumes and volumes of interest. ICV was added as independent variable to adjust for differences in deep grey matter and lateral ventricles volumes due to differences in head size differences among the patients.

RESULTS

The demographic data are shown on the Table 1. The level of education of the patients with PTSD and alcoholism as a comorbidity is significantly lower, compared to the control group.

The distribution of the volumes has been presented on the Table 2. The volumes of hippocampus on both hemispheres were the smallest among patients with PTSD and excessive alcohol consumption, which was outlined by the Bonferroni posthoc test: the mean difference for the left hippocampal volume for individuals who consumed alcohol and patients with PTSD

Table 1. Characteristics of the PTSD patients

History, stressors, intracranial volume, statistics	Groups of patients according to headache features			
	Group I Alcohol+PTSD (n=29)	Group II PTSD (n=25)	Group III controls (n=25)	Total (n=79)
Age	47.31±8.17	47.08±7.31	45.36±9.02	46.62±8.19
Handedness (r/l)	26/3	22/3	23/2	71/8
Education (yrs)	10.64±2.55*	12.17±3.21	13.04±2.14	11.25±3.18
PTSD causes				
War veterans	3	2		5
Car accident	9	8		17
Sudden death of family member	9	6		15
Assault/Robbery	6	7		13
Natural disaster (fire/flood)	2	2		4
Total	29	25		54

ANOVA $F_{2,76}=13.34$; $p=0.000$; Boferroni post hoc group I $p=0.024$ vs group I and $p=0.0004$ group I vs group III

Table 2. Volumes of the structures of interest among the obtained groups (in cm^3)

Structure	Group	No	Mean	SD	Statistics
Hippocampus left	PTSD	25	3.2472	0.59418	ANOVA, $F=20.468$, $DF=2.76$, $p=0.000$ Bonferroni post hoc, $p=0.000$ for Controls vs. PTSD and Alco, PTSD, Alco+ptsd vs. PTSD $p=0.046$
	Controls	25	3.8544	0.69293	
	Alco+PTSD	29	2.9593	0.13115	
	Total	79	3.3337	0.63558	
Hippocampus right	PTSD	25	3.3128	0.58707	ANOVA, $F=16.380$, $DF=2.76$, $p=0.000$ Bonferroni post hoc, $p=0.000$ for Controls vs. PTSD and Alco, PTSD, Alco+ptsd vs. PTSD $p=0.026$
	Controls	25	3.8088	0.72217	
	Alco+PTSD	29	2.9848	0.12969	
	Total	79	3.3494	0.62454	
Amygdala left	PTSD	25	1.6500	0.23130	NS
	Controls	25	1.6748	0.18063	
	Alco+PTSD	29	1.5907	0.07910	
	Total	79	1.6361	0.17336	
Amygdala right	PTSD	25	1.6728	0.23068	NS
	Controls	25	1.6753	0.21146	
	Alco+PTSD	29	1.6007	0.07319	
	Total	79	1.6471	0.18254	
Prefrontal total	PTSD	25	328.9217	49.02373	NS
	Controls	25	322.2488	36.22486	
	Alco+PTSD	29	322.6760	44.31143	
	Total	79	324.5173	43.09554	
Intracranial volume	PTSD	25	1427.5200	212.76300	NS
	Controls	25	1395.1600	160.78782	
	Alco+PTSD	29	1405.7241	174.99386	
	Total	79	1409.2785	181.80039	
Prefrontal left	PTSD	25	166.1220	24.75946	NS
	Controls	25	162.7519	18.29539	
	Alco+PTSD	29	162.9677	22.37951	
	Total	79	163.8976	21.76543	
Prefrontal right	PTSD	25	163.6426	24.38992	NS
	Controls	25	160.3228	18.02232	
	Alco+PTSD	29	160.5353	22.04549	
	Total	79	161.4514	21.44057	

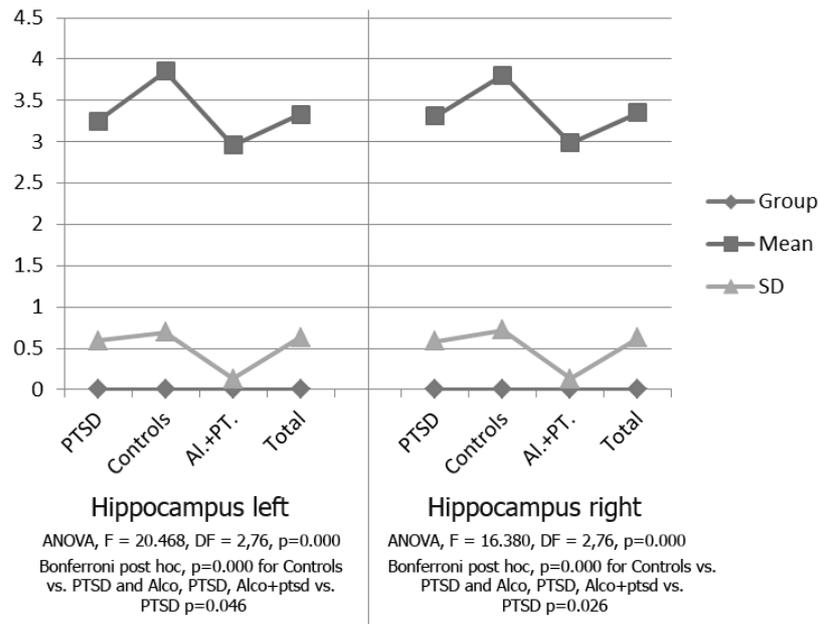


Figure 1. Volumes of hippocampus on both hemispheres were the smallest among patients with PTSD and excessive alcohol consumption

only was -0.28789 , while this difference between alcohol addicts with PTSD and normal control was -0.89509 . Mentioned differences for the right hippocampus were -0.32797 , and -0.82397 (Figure 1).

Correlation test has been performed for potential connection between drinking period and hippocampal volumes.

The drinking period varied from one to fifteen years (average \pm SD= 5.14 ± 1.29). The negative correlation has been revealed: $B = -0.016$, $p = 0.000$ for the left and $B = -0.024$, $p = 0.000$ for the right hippocampus.

For other structures no statistical differences neither any kind of correlation had been revealed.

DISCUSSION

The present study found out the diminished hippocampal volumes in patients with PTSD who had an additional drinking problem. The bilateral reduction of the hippocampal volume in PTSD suffering patients is consistent to data published in other studies (Gurvits et al. 1996, Lindauer et al. 2004, Bossini et al. 2008) or in wide meta-analysis (Karl et al. 2006). Studies performed with children with PTSD (De Bellis et al. 2001, Carrion et al. 2002, De Bellis et al. 2002), subjects with recent onset PTSD (Bonne et al. 2001), women with history of intimate partner violence (Fennema-Notestine et al. 2002), combat veterans (Yehuda et al. 2007) and witnesses of an air show crash (Jatzko et al. 2006) did not find any differences in hippocampal volume between PTSD subjects and both healthy and traumatized subjects without PTSD. The reduction of the volume of hippocampus in the individuals with drinking problems was outlined as the parameter of importance and found to be proportional with the reduction of entire gray

matter of the brain (Agartz et al. 1999). Oppositely, other studies did not delineate smaller hippocampus as alcohol consumption consequence substrate (Oscar-Berman & Song 2011) or found it to relate to the presence of lifelong anxiety suffering in chronic alcohol addicts (Sameti et al. 2011). The diminishing of the hippocampus also failed to be obtained in the study with the patients with Korsakoff syndrome (Squire et al. 1990).

A role for comorbid alcohol abuse/dependence in prior observations of smaller hippocampal volume in PTSD is tentatively supported in these data. At the same time, lifetime alcoholism was not independently associated with smaller hippocampal volume even before adjustment for total cerebral tissue volume. Deployed U.S. military veterans who do and do not meet criteria for lifetime alcoholism may have less contrastive alcohol histories than groups sampled from civilian populations. Nevertheless, the observed reversal of the aging-alcohol interaction could arise only if the effects of alcoholism on the hippocampus were accentuated in the Gulf War cohort, attenuated in the Vietnam cohort, or both. It is possible that biased attrition-attenuated selected group effects involved Vietnam-era PTSD-positive alcoholic subjects in this study (Woodward et al. 2006). Drescher et al. (2003) demonstrated that a contemporaneous Vietnam-era sample drawn from the VA Palo Alto Healthcare System PTSD inpatient population exhibited excess age-adjusted mortality in association with alcohol and substance abuse. The possibility that a smaller hippocampus participates with alcohol/substance abuse to confer a predisposition to premature mortality cannot be ruled out, particularly if a smaller hippocampus is predispositional to PTSD (Gilbertson et al. 2002), itself a consequence of exposure

to life threat. This study found modest support for an inverse relationship between hippocampal volume and exposure to potentially traumatic combat events, as reported by Gurvits et al. (1996).

In a study of monozygotic twins, (Gilbertson et al. 2002) authors obtained evidence that a smaller hippocampus represents an inherited predisposition to develop PTSD after trauma rather than being a consequence of trauma. These findings are not incompatible if the data are interpreted to indicate that a smaller hippocampus is predispositional to PTSD with comorbid alcohol abuse/dependence. Eighty two percent of the PTSD-positive subjects in the same study met criteria for comorbid alcoholism. As well, the unexposed twins of their PTSD-positive alcohol abuse/dependence-positive subjects tended to exhibit higher rates of alcohol abuse/dependence (47% vs 30%) and higher scores on the Michigan Alcoholism Screening Test than the unexposed twins of PTSD-negative subjects, both observations compatible with an elevated risk for primary alcoholism. Evidence of shared genetic vulnerability to combat exposure/PTSD and alcoholism (McLeod et al. 2001) has been obtained from other samples drawn from the Vietnam Era Twin Registry (Eisen et al. 1987).

Individual PTSD amygdale volumetric studies have typically reported null findings (e.g. Bonne et al. 2001, Fennema-Notestine et al. 2002, Gurvits et al. 1996, Wignall et al. 2004), which could be due to a combination of small effect sizes and small samples, as well as difficulty in differentiating the hippocampus and amygdala. Nonetheless, results of meta-analysis provided by Karl et al. (2006) demonstrated potential susceptibility of the left amygdaloid complex to PTSD which we cannot confirm, according to the present study.

Oppositely to our results, few investigations of pediatric subjects with PTSD revealed the diminution of the volume of the frontal lobe / prefrontal cortex (De Bellis et al. 2001, Carrion et al. 2004).

CONCLUSION

In conclusion, the reduction of the volume of hippocampus in PTSD suffering patients is worsened with the alcohol intake. According to the results obtained in this study, no significant differences have been obtained comparing the volumes of amygdale, prefrontal cortex or total intracranial volume in patients with PTSD and comorbid alcoholism with PTSD patients without comorbidities and healthy controls.

Acknowledgements

This investigation has been financed by the grant III 41020 by Serbian Ministry of Education, Science and Technological Development

Conflict of interest: None to declare.

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