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ORIGINAL PAPER

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# Alterations in brain activation in posttraumatic stress disorder patients with severe hyperarousal symptoms and impulsive aggressiveness

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**Abstract** *Objective* We wanted to assess possible alterations in brain activation in PTSD patients with severe hyperarousal symptoms and impulsive aggressiveness. *Method* 25 Croatian War (1991–1995) veterans with combat-related PTSD with severe hyperarousal symptoms and impulsive aggressiveness were assessed for possible alterations in cerebral blood flow in single photon emission computed tomography brain scans. *Results* Increased regional cerebral blood flow in projection area of nucleus accumbens was found in 13 of 25 subjects, and for all in the dominant brain hemisphere. *Discussion* We believe that at least some of PTSD symptoms, and especially the impulsive aggression, can be associated with increased regional cerebral blood flow in the projection area of nucleus accumbens.

**Key words** PTSP · SPECT · brain · aggressiveness · nucleus · accumbens

## Introduction

The essential feature of posttraumatic stress disorder (PTSD) is development of characteristic symptoms commonly divided into three symptom-clusters: persistent re-experiencing symptoms, avoidance and numbing symptoms and increased arousal (hyperarousal) symptoms [1–3]. The hyperarousal symptoms and persistent re-experiencing of the traumatic event suggest abnormalities in emotion and memory regulation, thus implicating limbic brain regions as being possibly associated with the disorder. Recent brain neuroimaging studies have described several brain regions as possibly associated with PTSD symptoms. The most commonly described regions are limbic brain structures, prefrontal cortex and temporal cortex [4–16].

Our clinical experience has shown that hyperarousal symptoms and especially those associated with impulsive aggressiveness, such as hyperirritability, hyperexcitability, hypersensitivity, aggressive acting outs, outbursts of anger, present some of the dominant disturbances for chronic PTSD patients. These kinds of symptoms can be understood in the perspective of loss of the affective modulation, which can explain the PTSD patient's lack of capacity to use affect states as cues to attend to incoming information. The elevated – arousal – state is likely to precipitate flight-or-fight reactions in these patients, so they often go immediately from stimulus to response without psychologically assessing the meaning of the event. This makes them prone to freeze or, alternatively, to overreact in response to minor provocations [15].

## Method

Participants in our study were selected from all PTSD patients treated at the Clinic for Psychological Medicine, University of Zagreb Medical School, during the period from April to July 2001. We selected 25 participants from the total of 82 patients treated in the day-hospital unit at the clinic over the period. All the participants in the study were Croatian War [1991–1995] veterans who actively participated in the combat and were exposed to multiple traumatic experiences such as witnessing the death of fellow soldiers and sudden air-rides or artillery attacks. The patients who experienced other kinds of traumatic experiences such as prisoners of war, concentration camp detainees, refugees, etc. were not included in this study. They all signed informed consent to participate in the study.

All the participants were engaged in the standard psychiatric and psychotherapeutic day-hospital treatment, which is organized as a one-month intensive individual and group psychotherapeutic program. Group psychotherapy was organized into median groups (12 to 15 members), held twice-a-week with 90-minute sessions, making eight group sessions all together. These groups are specially designed homogenous groups (only war veterans with PTSD) using psychodynamic and cognitive-behavioral techniques to enable ventilating and self-modulation of impulsive aggressive behavior in our patients. The groups are conducted by a co-therapist pair.

Due to the high financial costs of the investigation procedure, par-

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ticipants were carefully selected on the basis of specially designed inclusion procedure. The inclusion procedure consisted of evaluation in a group and individual psychiatric evaluation.

The group evaluation was performed over a two-week group psychotherapy, as described above, encompassing four group sessions, and consisted of monitoring of the patient's symptom manifestation. The same co-therapist pair performed the selection for all the participants in the study. Individual evaluation was organized in the form of the Structured Clinical Interview for DSM-IV (SCID-CV) [17]. The interview was held during the first week of the patient's treatment at the clinic, and was conducted by the same therapist for all the participants. All therapists conducting the selection were clinicians with at least a three year experience in working with psychotraumatized patients. Group therapists were not informed of the evaluation performed by the individual therapist and conversely.

All patients selected for the investigation had chronic, combat-related PTSD with severe hyperarousal symptoms and impulsive aggressiveness and no other Axis-I and/or Axis-II diagnosis in accordance with DSM-IV criteria [18]. Severity of hyperarousal symptoms was assessed on the basis of anamnesis and heteroanamnesis and also on the basis of symptoms they manifested in group therapy and the individual psychiatric interview. Only the patients who continuously presented all hyperarousal symptoms over the two-week observation as defined in the DSM-IV and impulsive aggressiveness symptoms were selected for the study. Impulsive aggressiveness symptoms were defined as: hyperirritability, aggressive acting outs, outbursts of anger. Only patients who manifested these symptoms in both individual interviews and all four group sessions over the observation period, and who had positive anamnesis and heteroanamnesis for hyperarousal symptoms in the month preceding the hospitalization were included in the study. This selection design had to be implemented because no psychometric instrument for assessing hyperarousal and/or impulsive aggressiveness symptoms as such, qualitatively or preferably quantitatively was available in Croatia.

The patients selected for the study received no pharmacotherapy other than benzodiazepine for at least six months preceding the study, and 4 weeks before the study entry the patients had received no psychotropic medication at all. After the psychiatric evaluation, neurological examination was conducted for all participants to exclude those with possible neurological comorbid conditions, head trauma or loss of consciousness in the year preceding the study. The Annett Handedness Questionnaire was performed by a neurologist to determine hand preference and indirectly dominant brain hemisphere [19]. All patients included in the study were male, right-handed, of similar age (mean = 52 years, SD = 2), and had no history of alcohol or drug abuse or dependence.

Single photon emission computed tomography (SPECT) using $Tc^{99}$-ECD functional brain imaging was organized in the week after the two-week observation period immediately after the first group session in that week to establish possible alterations in regional cerebral blood flow (rCBF). The procedure was organized in the following way. Patients who manifested at least one and no more than three aggressive acting outs during the pre-SPECT session were asked to remember the specific situation in the group that provoked the last aggressive acting out. The ultimate of no more than three aggressive acting outs during the designated session was a pre-set criterion to enable remembering of the specific situation that provoked the last acting-out, but was not used because none of our subjects actually manifested more than three aggressive acting outs during the pre-SPECT session. The subjects were asked to try to remember the exact situation in the group that provoked their aggressive acting out and to describe it. Only the subjects who were able to do this and who manifested aggression and anger while remembering and also who felt distressed by that were included in the further procedure. Once again all of our subjects fulfilled these criteria and all declared being very distressed when remembering the situation. Following this, subjects were introduced into the SPECT procedure, and the scans were obtained in 50 to 60 minutes after the end of the session. Once again immediately before the SPECT brain scan was made, each subject was asked to remember the situation that provoked his last aggressive acting out in the pre-SPECT session.

SPECT scans were started 20 minutes after administration of 740 MBq of 99mTc-ECD in resting state ("white noise" environment, without any auditory or visual combat stimuli provocation). Measurements were made with IRIX triple-headed rotating scintillation gamma camera fitted with high-resolution collimators, using a 360° circular orbit and step and shoot mode (20-s image each 3°) so that the acquisition lasted 40 minutes. Within-subject correlated slices were obtained. Images were acquired in a 128x128 matrix, with an acquisition zoom of 1.5. The final pixel size was 2.96 mm. The full-width at half-maximum (FWHM) in the transaxial plane was 9 mm. Filtered back-projection was used for reconstruction by applying a Metz filter. Attenuation correction of the reconstructed data was applied using Chang's method, with a coefficient factor of 0.075. Two-pixel-thick slices were obtained in the coronal, sagittal and oblique (fronto-occipital) planes.

SPECT data were quantitatively analyzed using an Odyssey FX820 workstation by means of a region-of-interest (ROI) based method and calculation of asymmetry percentages. The following ROIs were considered: temporal, frontal, orbitofrontal and occipital cortices, cingulate gyrus, amygdala, thalamus, basal ganglia (caudate, putamen, ventral basal ganglia) and cerebellum. The irregular ROIs were outlined in the right hemisphere and mirrored in the left. The same investigator, blinded to all clinical data, placed ROIs. For each ROI, mean counts per pixel in two consecutive slices were averaged to minimize partial volume effects. In each patient, studies were normalized to the mean whole-brain uptake; so relative hypo/hyperperfusion was established for each ROI. The percentage of asymmetry between two homologous regions was calculated as 200x(right–left/right + left), where right and left indicate mean average counts per pixel in the ROIs of the respective hemisphere. The negative values indicate, thus, lower perfusion in the right hemisphere. Percentages of interhemispheric asymmetry between homologous brain regions were used to identify abnormalities.

Based on studies of normal subjects, it is well documented that the normal cerebral blood distribution is bilaterally symmetric, with percentages of interhemispheric asymmetry never exceeding 12% for any brain region [20–27]. In our study we therefore considered only findings with interhemispheric asymmetry exceeding 20% as significant. Also due to the well-documented normal brain perfusion patterns in SPECT studies, paralleled with our own 10-year experience, and due to the radioactive properties of the method coupled with high financial costs of the procedure, it was ethically and financially impossible for us to include a control group of normal subjects.

## Results

We found interhemispheric differences in regional blood flow (rCBF) in projection areas of four brain regions: ventral basal ganglia (VBG), thalamus, temporal cortex and occipital cortex.

In 13 of 25 subjects, we found interhemispheric asymmetry in the projection area of the VBG, exceeding 20%. For all 13 subjects, the finding was caused by an increased perfusion rate in the VBG in the left (dominant) brain hemisphere, as normalized against the mean whole-brain perfusion rate. One subject of the 13 also had increased rCBF in the projection areas of the left thalamus and left occipital cortex, another two in the projection area of the left thalamus and an additional one in the projection area of right temporal cortex. The remaining 12 subjects had symmetrical brain SPECT findings.

## Discussion

In our study we found unilaterally increased perfusion in the projection area of ventral basal ganglia (VBG) in

the dominant brain hemisphere in 52% (13/25) of our PTSD subjects with severe hyperarousal symptoms and impulsive aggressiveness. One subject of the 13 had also increased rCBF in the projection areas of the left (dominant) thalamus and the left (dominant) occipital cortex, another two in the projection area of the left (dominant) thalamus and an additional one in the projection area of right (non-dominant) temporal cortex.

We believe our findings correspond with those in similar studies, which found increases and rarely decreases of rCBF in regions such as the anterior and posterior cingulate regions bilaterally; temporal, parietal, frontal, and orbitofrontal cortices; also in the thalamus, basal ganglia, and hippocampus [4–16]. Nevertheless, the only consistent finding was activation in the right and also left amygdala and in the sensorimotor cortices. One study found activation in the region of the left amygdala and nucleus accumbens after exposure to combat sounds [8].

Most of the similar studies used combat or non-combat stress-related auditory or visual stimuli to provoke changes in rCBF in PTSD subjects [4–16]. With such a design, we believe, it should be expected to find activation of different sensory and sensorimotor regions in the brain responsible for stimuli processing, along with areas possibly related to PTSD symptoms as such. For this reason we did not use any external provocation stimuli, but rather induced our subjects to remember an exact situation that provoked their aggressive acting during the group session that took place shortly before SPECT examination. In this respect, we believe our study significantly differs from any other similar, so far published study.

VBG, which corresponds to the anatomical location of nucleus accumbens, is functionally and spatially closely related to amygdala [28–35]. Both structures together have been implicated in adaptive responding and non-declarative emotional memory [28–35]. Adaptive responding is a process by which an organism, having extracted information from its external environment and internal milieu, interprets and utilizes those cues in creating appropriate emotional response to incoming stimuli. Nucleus accumbens receives inputs primarily from the highest order of integrative, polymodal cortical and cortical-like structures, such as the prefrontal cortex, basal amygdala and subiculum. It also projects mainly to the basal forebrain, diencephalon and rostral brainstem. In this way, the nucleus accumbens appears to be a sensitive recipient of information about the hedonic/aversive valences of incoming stimuli and appropriately stimulates or inhibits activity in brain structures with more direct capacities to effect the decision-making, initiation and motor control aspects of adaptive responding. The way it fashions these functions is nevertheless still largely vague.

Hyperarousal symptoms within PTSD can, at least to some extent, be explained by malfunction of the nucleus accumbens and related limbic brain structures and the psychological processes they mediate [1, 15, 35–37]. Hyperirritability, hyperexcitability, hypersensitivity in the respect that they present inadequate, exaggerated responses ("emergency" fight-or-flight reactions) to information that would normally produce reaction of a considerably modest extent can be associated with malfunction of adaptive responding process.

For these reasons we believe that increased rCBF in the projection area of the nucleus accumbens that we found in our subjects might substantiate disturbed neuronal activity in this region, thus, allowing for the disturbances in the psychological processes it mediates. Unfortunately, it was impossible for us to quantitatively measure hyperarousal symptoms and/or impulsive aggressiveness in our subjects and to correlate these with the alterations in rCBF. This was due to the lack of adequate psychometric instruments in Croatia. Perhaps subjects with changed rCBF pattern had more severe symptoms in this respect. Also for the same reasons, it was not possible for us to more specifically define and quantify the symptom profile in each subject, regarding different hyperarousal/impulsive aggressiveness symptoms. This, if possible, would, we believe, yield some additional information and possibly explain normal findings in almost half of our subjects.

Apart from these problems, the main handicap of our study was the lack of a normal-subject control group. But it was impossible for us to include one for ethical and financial reasons, as previously explained. Nevertheless, with respect to the well-documented normal SPECT brain findings and other investigations similar to ours, we believe that our findings are far from spurious, and yield important information for the further understanding of neurophysiology of PTSD. If anything, our results strongly suggest the necessity of further investigation and set some important clues to follow.

## References


1. Yehuda R (2002) Post-traumatic Stress Disorder. N Engl J Med 436(2):108–114
2. Maes M, Mylle J, Delmeire L, Altamura C (2000) Psychiatric morbidity and comorbidity following accidental man-made traumatic events: incidence and risk factors. Eur Arch Psychiatry Clin Neurosci 250(3):156–162
3. Frommberger UH, Stieglitz RD, Nyberg E, Schlickewei W, Kuner E, Berger M (1998) Prediction of posttraumatic stress disorder by immediate reactions to trauma: a prospective study in road traffic accident victims. Eur Arch Psychiatry Clin Neurosci 248(6):316–321
4. Liberzon I, Taylor SF, Fig LM, Koeppe RA (1996–1997) Alteration of corticothalamic perfusion ratios during a PTSD flashback. Depress Anxiety 4(3):146–150
5. Zubieta JK, Chinitz JA, Lombardi U, Fig LM, Cameron OG, Liberzon I (1999) Medial frontal cortex involvement in PTSD symptoms: a SPECT study. J Psychiatr Res 33(3):259–264
6. Mirzaei S, Knoll P, Keck A, Preitler B, Gutierrez E, Umek H, Kohn H, Pecherstorfer M (2001) Regional cerebral blood flow in patients suffering from post-traumatic stress disorder. Neuropsychobiology 43(4):260–264
7. Bremner JD, Innis RB, Southwick SM, Staib L, Zoghbi S, Charney DS (2000) Decreased benzodiazepine receptor binding in prefrontal cortex in combat-related posttraumatic stress disorder. Am J Psychiatry 157(7):1120–1126

8. Liberzon I, Taylor SF, Amdur R, Jung TD, Chamberlain KR, Minoshima S, Koeppe RA, Fig LM (1999) Brain activation in PTSD in response to trauma-related stimuli. Biol Psychiatry 45(7): 817–826
9. Lucey JV, Costa DC, Adshead G, Deahl M, Busatto G, Gacinovic S, Travis M, Pilowsky L, Ell PJ, Marks IM, Kerwin RW (1997) Brain blood flow in anxiety disorders. OCD, panic disorder with agoraphobia, and post-traumatic stress disorder on 99mTcHMPAO single photon emission tomography (SPET). Br J Psychiatry 171: 346–350
10. Rauch SL, Shin LM (1997) Functional neuroimaging studies in posttraumatic stress disorder. Ann N Y Acad Sci 21(821):83–98
11. Bremner JD, Staib LH, Kaloupek D, Southwick SM, Soufer R, Charney DS (1999) Neural correlates of exposure to traumatic pictures and sound in Vietnam combat veterans with and without posttraumatic stress disorder: a positron emission tomography study. Biol Psychiatry 45(7):806–816
12. Shin LM, Kosslyn SM, McNally RJ, Alpert NM, Thompson WL, Rauch SL, Macklin ML, Pitman RK (1997) Visual imagery and perception in posttraumatic stress disorder. A positron emission tomographic investigation. Arch Gen Psychiatry 54(3):233–241
13. Rauch SL, van der Kolk BA, Fisler RE, Alpert NM, Orr SP, Savage CR, Fischman AJ, Jenike MA, Pitman RK (1996) A symptom provocation study of posttraumatic stress disorder using positron emission tomography and script-driven imagery. Arch Gen Psychiatry 53(5):380–387
14. Sachinvala N, Kling A, Suffin S, Lake R, Cohen M (2000) Increased regional cerebral perfusion by 99mTc hexamethyl propylene amine oxime single photon emission computed tomography in post-traumatic stress disorder. Mil Med 165(6): 473–479
15. van der Kolk (1999) The body keeps the score. In: Horowitz MJ (ed) Essential Papers on Posttraumatic Stress Disorder. New York – London: New York University Press, pp 55–120
16. Pissiota A, Frans O, Fernandez M, Von Knorring L, Fischer H, Fredrikson M (2002) Neurofunctional correlates of posttraumatic stress disorder: a PET symptom provocation study. Eur Arch Psychiatry Clin Neurosci 252(2):68–75
17. First, Michael B, Spitzer, Robert L, Gibbon Miriam, Williams, Janet BW (1996) Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV). Washington, DC.: American Psychiatric Press, Inc.
18. American Psychiatric Association (1994) Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Revised. Washington, DC: American Psychiatric Association
19. Annett M (1994) Assessment of laterality. In: Crawford JR, Parker DM, McKinlay WW (eds) A Handbook of Neuropsychological Assessment. Hove: Lawrence Erlbaum Associates, pp 54–70
20. Juni JE, Waxman AD, Devous MD Sr, Tikofsky RS, Ichise M, Van Heertum RL, Holman BL, Carretta RF, Chen CC (1998) Procedure guideline for brain perfusion SPECT using technetium-99m radiopharmaceuticals. Society of Nuclear Medicine. J Nucl Med 39(5):923–926
21. Denays R, Ham H, Tondeur M, Piepsz A, Noel P (1992) Detection of bilateral and symmetrical anomalies in technetium-99m-HMPAO brain SPECT studies. J Nucl Med 33(4):485–490
22. Houston AS, Kemp PM, Macleod MA (1994) A method for assessing the significance of abnormalities in HMPO brain SPECT images. J Nucl Med 35(2):239–244
23. Hooper HR, McEwan AJ, Lentle BC, Kotchon TL, Hooper PM (1990) Interactive three-dimensional region of interest analysis of HMPAO SPECT brain studies. J Nucl Med 31(12):2046–2051
24. Barber DC, Tindale WB, Hunt E, Mayes A, Sagar HJ (1995) Automatic registration of SPECT images as an alternative to immobilization in neuroactivation studies. Phys Med Biol 40(3):449–463
25. Koyama M, Kawashima R, Ito H, Ono S, Sato K, Goto R, Kinomura S, Yoshioka S, Sato T, Fukuda H (1997) SPECT imaging of normal subjects with technetium-99m-HMPAO and technetium-99m-ECD. J Nucl Med 38(4):587–592
26. Catafau AM, Lomena FJ, Pavia J, Parellada E, Bernardo M, Seatoain J, Tolosa E (1996) Regional cerebral blood flow pattern in normal young and aged volunteers: a $^{99m}$Tc-HMPAO SPECT study. Eur J Nucl Med 23:1329–1337
27. Camarago EE (2001) Brain SPECT in Neurology and Psychiatry. J Nucl Med 42(4):611–623
28. Lang PJ, Bradley MM, Cuthbert BN (1998) Emotion, motivation, and anxiety: brain mechanisms and psychophysiology. Biological Psychiatry 44:1248–1263
29. Davis M, Whalen PJ (2001) The amygdala: vigilance and emotion. Molecular Psychiatry 6:13–34
30. Davis M (1992) The role of the amygdala in fear and anxiety. Annu Rev Neurosci 15:353–375
31. Zahm DS (2000) An integrative neuroanatomical perspective on some subcortical substrates of adaptive responding with emphasis on the nucleus accumbens. Neurosci Biobehav Rev 24(1): 85–105
32. Zahm DS (1999) Functional-anatomical implications of the nucleus accumbens core and shell subterritories. Ann N Y Acad Sci 29(877):113–128
33. de Olmos JS, Heimer L (1999) The concepts of the ventral striatopallidal system and extended amygdala. Ann N Y Acad Sci 29(877):1–32
34. Adamec RE (1991) Partial kindling of the ventral hippocampus: identification of changes in limbic physiology which accompany changes in feline aggression and defense. Psychobiol Behav 49: 443–454
35. Le Doux J (1986) Mind and Brain: Dialogues in Cognitive Neuroscience. New York: Cambridge University Press
36. Yehuda R, Davidson J (2000) Clinician's Manual on Posttraumatic Stress Disorder. London: Science Press
37. Bremner JD, Scott TM, Delaney RC, Southwick SM, Manson JW (1993) Deficits in short-term memory in posttraumatic stress disorder. Am J Psychiatry 150:1015–1019