ORIGINAL ARTICLE

Neurobiological correlates of PTSD chronicity: Integrating stress biomarkers and brain morphometric changes

Barbara Paraniak-Gieszczyk
COLLEGIUM MEDICUM, JAN DLUGOSZ UNIVERSITY IN CZESTOCHOWA, CZESTOCHOWA, POLAND

ABSTRACT

Aim: This study aimed to investigate how the chronicity of post-traumatic stress disorder (PTSD) shapes neurobiological functioning by integrating biochemical stress-related biomarkers (serotonin, cortisol, noradrenaline, IL-12, IGF-1, CASP-9, nNOS, IL-10) with morphometric and microstructural brain parameters assessed using magnetic resonance imaging (MRI). A further objective was to determine whether early PTSD (≤5 years) and long-term PTSD (>5 years) exhibit distinct profiles of neuroinflammatory, neurodegenerative, and neuroplastic alterations, with particular focus on brain regions involved in emotion regulation, memory, and cognitive control (hippocampus, amygdala, insular cortex, and prefrontal cortex).

Materials and Methods: The study included 92 adult male miners and mine rescue workers exposed to life-threatening events. Participants were assigned to three groups: PTSD ≤5 years (n = 33), PTSD >5 years (n = 31), and controls without PTSD symptoms (n = 28). PTSD diagnosis was confirmed using the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). MRI was performed on a 1.5 T General Electric (GE) Optima 360 scanner and included volumetric T1-weighted imaging, T2-weighted FLAIR, SWAN, and diffusion tensor imaging. Assessed brain parameters included ventricular width, amygdala dimension, corpus callosum thickness, insular cortex thickness, and lateral fissure width. Biochemical markers were quantified using standard laboratory assays.

Results: Significant differences across all groups were observed for nearly all biomarkers and structural brain measures ($p < 0.001$). Early PTSD was characterized by elevated neuroinflammatory markers, reduced anti-inflammatory and neurotrophic activity (lower IL-10 and IGF-1), early ventricular enlargement, thinning of the corpus callosum and insular cortex, and reduced amygdala dimensions. Long-term PTSD demonstrated pronounced cortical atrophy, including marked widening of the lateral fissures, significant third-ventricle enlargement, and persistent thinning of the insular cortex and callosal body. Cortisol showed the strongest positive correlation with structural degeneration. Noradrenaline exhibited a potential compensatory effect, demonstrating negative correlations with ventricular width. The control group displayed physiological, homeostatic correlation patterns.

Conclusions: The chronicity of PTSD substantially modulates both biochemical and structural brain profiles. Early PTSD reflects acute neuroinflammation and impaired neuroprotection, whereas long-term PTSD is dominated by progressive neurodegeneration associated with chronic dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis. Integrating biomarker profiles with MRI-derived measures provides a robust framework for identifying markers of disease progression and for developing phase-specific therapeutic strategies aimed at mitigating atrophy, modulating stress-response systems, and supporting neuroplasticity.

KEY WORDS: post-traumatic stress disorder, stress biomarkers, brain morphometry, Neuroinflammation, neuroplasticity

Wiad Lek. 2025;78(12):2565-2576. doi: 10.36740/WLek/214755 DOI

INTRODUCTION

Post-traumatic stress disorder (PTSD) is a complex condition characterized by persistent impairments in stress regulation, heightened activation of inflammatory pathways, increased oxidative stress, and diminished adaptive capacity. These changes affect both the central nervous system and psychological functioning, influencing emotional processing, behavior, and overall quality of life [1, 2]. PTSD is among the most frequently diagnosed trauma-related disorders, developing as a consequence of exposure to events that exceed the organism's adaptive threshold. Its pathophysiology involves multiple interacting biological processes that, over time, lead to lasting functional and structural alterations within the central nervous system.

A central mechanism underlying PTSD is the sustained activation of the hypothalamic–pituitary–adrenal (HPA) axis, which regulates the stress response. Individuals with PTSD exhibit disturbances in cortisol secretion, resulting in heightened limbic system sensitivity, impaired emotional regulation, and increased vulnerability to anxiety-related reactions [3, 4]. Chronic inflammation also plays a critical role, maintained by persistent microglial activation, elevated levels of proinflammatory cytokines, and dysregulation of anti-inflammatory pathways. These processes accelerate the loss of volume in regions essential for memory, learning, and emotional integration, including the hippocampus and prefrontal cortex. Concurrently, oxidative stress - arising from excessive production of reactive oxygen species

combined with impaired antioxidant defense - leads to neuronal damage, mitochondrial dysfunction, and reduced synaptic plasticity [5–7].

PTSD is therefore a systemic disorder involving the interaction of biological, psychological, and environmental factors. Neurobiological alterations manifest directly in emotional and behavioral functioning. Individuals with PTSD frequently experience affective dysregulation, chronic hyperarousal, irritability, sleep disturbances, and difficulties with memory retrieval and organization. Many of these symptoms stem from dysfunction and overload of limbic structures, particularly the amygdala, which plays a key role in fear responses and threat detection [8, 9].

Equally important are alterations in brain networks involved in the integration of internal and external stimuli. Dysfunction of the prefrontal cortex - especially its medial and dorsolateral subdivisions - compromises cognitive control and emotional inhibition, leading to difficulties in decision-making, anticipation of consequences, and planning. Disturbances within the insular cortex impair interoceptive processing, promoting somatization and increasing the severity of dissociative symptoms [10, 11].

The impact of chronic stress on brain function is reinforced by extensive neurobiological evidence showing that prolonged exposure to trauma and its psychological aftermath leads to microstructural changes affecting both gray and white matter. Brain regions responsible for memory consolidation, emotional integration, executive control, and interoceptive perception demonstrate increased susceptibility to degeneration and reorganization. While some of these processes may be partially reversible due to neuroplasticity, their trajectory is strongly influenced by PTSD duration, age, environmental factors, and individual cognitive reserve [12, 13].

PTSD therefore represents a multidimensional disorder in which neuroinflammatory, hormonal, metabolic, and psychological processes converge. Understanding these interrelations in the context of morphometric and biochemical changes within the brain allows for deeper insight into the underlying pathophysiological mechanisms and facilitates the identification of therapeutic targets - particularly within HPA axis modulation, attenuation of neuroinflammation, and enhancement of neuroplasticity [14, 15].

The duration of PTSD has a significant influence on the structure and function of key brain regions - including the hippocampus, amygdala, and prefrontal cortex. In the present study, brain structure was assessed using magnetic resonance imaging (MRI), including diffusion tensor imaging (DTI) [16, 17]. The length of PTSD duration is one of the primary factors differentiating the extent and nature of neurobiological alterations observed in limbic and cortical structures.

Neuroimaging studies consistently show that chronic exposure to trauma-related stress leads to progressive neuronal changes involving both volumetric parameters and the microstructure of white matter and communication pathways within the brain [18]. The hippocampus—highly sensitive to cortisol and oxidative stress - undergoes gradual volumetric reduction as PTSD persists, reflecting neurodegenerative processes and impaired neuroplasticity. Reduced hippocampal volume contributes to memory impairments, disrupted consolidation of memory traces, and diminished capacity to inhibit fear responses, thereby perpetuating PTSD symptoms [19, 20].

The amygdala, a central hub for emotional processing, fear responses, and aversive learning, exhibits more complex patterns of alteration [21, 22]. Early stages of PTSD may be associated with transient volume increases due to heightened neuronal activation and metabolic demand. However, chronic PTSD is characterized by gradual amygdala shrinkage, likely attributable to prolonged cytotoxic stress and overload of limbic pathways. These changes contribute to persistent hyperreactivity to emotional stimuli, impaired emotion regulation, and exacerbated intrusive symptoms [23].

The prefrontal cortex (PFC) - critical for executive function, impulse control, stress modulation, and integration of emotional information - also demonstrates stage-dependent alterations. Early in the disorder, functional impairments of the PFC may occur in the absence of pronounced structural changes, whereas later stages are characterized by cortical thinning, disruptions in white-matter integrity, and dysregulated connectivity with limbic regions [24, 25].

MRI-based techniques, including diffusion tensor imaging, enable measurement of fractional anisotropy (FA) and mean diffusivity (MD), which provide sensitive indices of microstructural neural integrity. These measures allow detection of subtle early-stage neuronal abnormalities that may not be apparent in standard volumetric imaging. The incorporation of advanced MRI modalities into PTSD research has been essential for elucidating how disorder duration shapes the trajectory of neurobiological alterations and which adaptive or degenerative mechanisms predominate at different stages of illness progression [26].

AIM

The aim of the study was to determine the impact of PTSD duration on selected morphometric, brain parameters assessed using magnetic resonance imaging

(MRI). A multiparametric MRI protocol was employed for this purpose.

A further objective of the study was to compare the MRI-derived parameters with biochemical markers, including serotonin, cortisol, noradrenaline, interleukin-12 (IL-12), insulin-like growth factor-1 (IGF-1), caspase-9 (CASP-9), neuronal nitric oxide synthase (nNOS), and interleukin-10 (IL-10). These biochemical markers had been previously quantified and analyzed by the author in two independent studies: *Neurobiological Correlates of Coping Strategies in PTSD: The Role of IGF-1, CASP-9, nNOS, and IL-10 Based on Brief-COPE Assessment* (doi: 10.3390/cimb47100868) and *Neurobiological and Existential Profiles in Posttraumatic Stress Disorder: The Role of Serotonin, Cortisol, Noradrenaline, and IL-12 Across Chronicity and Age* (doi: 10.3390/ijms26199636) [27, 28].

MATERIALS AND METHODS

SUBJECTS

The study sample consisted of 92 adult males aged 18–50 years who had been exposed to life-threatening events, including occupational hazards associated with mine rescue operations and mining-related work. Participants were stratified into three groups: (1) PTSD duration ≤5 years (early phase; n = 33), (2) PTSD duration >5 years (late/chronic phase; n = 31), and (3) a trauma-exposed control group without PTSD symptoms (n = 28).

Diagnostic evaluation was conducted by a board-certified psychiatrist through a structured clinical interview, review of medical records, and administration of the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). Individuals were eligible for inclusion if they met DSM-5 diagnostic criteria for PTSD and had a documented Criterion A traumatic exposure. Exclusion criteria included the presence of any other psychiatric disorders (e.g., major depressive disorder, bipolar disorder, substance abuse), significant somatic illnesses, and current use of psychotropic or hormonal medications. Additional exclusion criteria encompassed employment in uniformed services and a history of substance dependence.

The control group was matched to the PTSD groups with respect to age, educational attainment, and occupational characteristics. All participants provided written informed consent prior to participation.

ETHICAL APPROVAL

The study procedures were conducted in accordance with the ethical standards outlined in the Declaration of Helsinki. The study protocol was approved by the Bioethics Committee of the Silesian Medical Chamber in Katowice, Poland (Decision No. 39/2018 of 10 October 2018, Annex No. 1 of 28 October 2019, Annex No. 2 of 19 June 2023, Annex No. 3 of 31 March 2025).

MRI

Brain structural assessments were acquired on a 1.5 T General Electric (GE) Optima 360 MRI system using a standardized neuroimaging protocol. The protocol included high-resolution T1-weighted volumetric imaging (3D T1 BRAVO; fast spoiled gradient-recalled echo [SPGR], isotropic slice thickness 2 mm); volumetric FLAIR imaging (3D CUBE FLAIR; 3D fast spin echo [FSE], 1.6-mm slices); susceptibility-weighted angiography (SWAN; 3D gradient-echo T2*-weighted sequence, 3-mm slices); and diffusion tensor imaging (DTI; 32 noncollinear directions, b = 1000 s/mm^2, 4-mm slice thickness). Additionally, axial T2-weighted turbo spin echo (TSE) images (5-mm slices) were obtained. The total acquisition time was approximately 40 minutes.

All datasets were reviewed and post-processed on a GE AW workstation using the Brain View platform. Quantitative morphometric analyses included: the width of the third ventricle (WTV), defined as the maximal transverse diameter in the axial plane at the level of the thalami; the thickness of the left amygdala (TLA) and the right amygdala (TRA), quantified as the maximal mediolateral extent in the coronal plane at the level of the infundibular recess of the third ventricle; the thickness of the corpus callosum body (TBCC), measured in the craniocaudal axis in the mid-sagittal plane halfway between the genu and the splenium; the thickness of the left insular cortex (TLIC) and the right insular cortex (TRIC), assessed as the mean cortical thickness in the axial plane at the level of the basal ganglia, the width of the left lateral cerebral fissure (WLLCF) and the width of the right lateral cerebral fissure (WRLCF), defined as the maximal separation between the insular cortex and the temporal lobe in the axial plane; and the width of the interhemispheric fissure in the frontal region (WIFFR), calculated as the maximal distance between the frontal lobes in the coronal plane anterior to the genu of the corpus callosum. measurements of third-ventricle width, corpus callosum thickness (body), and the width of the lateral fissures. All measurements represent the mean of two independent raters [29].

STATISTICAL METHODS

Analyses were conducted using the R Statistical language (version 4.3.3; [30]) on Windows 11 Pro 64 bit

(build 26100), using the packages *report* (version 0.5.8; [31]), *GGally* (version 2.2.1; [32, 33]), *gtsummary* (version 1.7.2; [34]), *corrplot* (version 0.94; [35]), *reshape2* (version 1.4.4; [36]), *ggplot2* (version 3.5.0; [37]), *dplyr* (version 1.1.4; [38]) and *tidyr* (version 1.3.1;[39]). [30-39].

RESULTS

To provide a comprehensive comparison of the neurobiological profile across individuals with different durations of PTSD, we analyzed a range of stress-related, neurodegenerative, and immunological biomarkers, along with morphometric measurements of key brain structures. Table 1 presents a summary of these biochemical and structural indicators in three study groups: early PTSD (≤5 years), chronic PTSD (>5 years), and controls without PTSD symptoms. The data reveal distinct and statistically significant differences among groups, reflecting both altered biomarker patterns and structural brain changes associated with the chronicity of PTSD. This comparison highlights characteristic biological signatures that may differentiate the stages and progression of post-traumatic stress disorder (Table1).

NEUROSTRUCTURAL ALTERATIONS ACROSS PTSD GROUPS

Statistical analyses of brain morphometry revealed significant group differences across the majority of structural parameters ($p < 0.001$), providing robust evidence for the impact of PTSD on neural architecture. The neurostructural consequences of PTSD manifested as measurable alterations in brain morphology, with distinct patterns corresponding to the chronicity of the disorder. PTSD exerted widespread effects on structures implicated in emotional regulation, cognitive processing, and stress responsivity (Fig. 1) depicts the distribution of brain measurements across groups).

The third ventricle was significantly wider in individuals with recent PTSD than in controls, with a median difference of 2.3 mm ($p < 0.001$; CLD: A > B > C). This enlargement is consistent with atrophy of surrounding periventricular tissue, and may reflect prolonged activation of the hypothalamic–pituitary–adrenal (HPA) axis and glucocorticoid-induced neurotoxicity in stress-sensitive regions. The amygdala, essential for threat detection and fear processing, displayed reduced left and right transverse diameters in the recent PTSD group relative to controls (median differences: 3.8 mm and 4.0 mm; $p < 0.001$; CLD: C > B > A). Such reductions may reflect excitotoxic damage associated with sustained hyperarousal, contributing to heightened emotional reactivity and impaired fear extinction - core PTSD features.

Similarly, the corpus callosum, critical for interhemispheric information integration, was significantly thinner in the recent PTSD group compared with controls (median difference 1.7 mm; $p < 0.001$; CLD: C > B > A), suggesting reduced white-matter integrity and potentially underlying impairments in attention, memory, and cognitive flexibility. The insular cortex, a region central to interoception, emotional salience, and autonomic integration, was also thinner bilaterally by approximately 0.5 mm in recent PTSD relative to controls ($p < 0.001$; CLD: B > A), which may exacerbate dissociative experiences and emotional dysregulation. Marked widening of the lateral cerebral fissures (median difference 3.5 mm between recent PTSD and controls; $p < 0.001$; CLD: A > B > C) further supports the presence of cortical atrophy consistent with stress-induced neurotoxicity. Collectively, these statistically significant deviations demonstrate PTSD's broad and clinically meaningful impact on limbic, cortical, and white-matter structures (Table 1).

IMPACT OF PTSD DURATION ON STRUCTURAL BRAIN CHANGES

The chronicity of PTSD significantly modulated these structural abnormalities. Across several measurements, the long-term PTSD group (>5 years) displayed intermediate values between the recent PTSD group (≤5 years) and controls, suggesting partial yet incomplete recovery over time.

For the third ventricle, the long-term PTSD group displayed a median width 1.0 mm smaller than the recent group ($p < 0.001$), suggesting attenuation of periventricular atrophy, potentially reflecting reduced HPA axis instability or adaptive neuroplastic modifications. Amygdala measurements in the long-term group approached control values, with median differences of 1.3 mm (left) and 1.0 mm (right), compared with 3.8 mm and 4.0 mm in recent PTSD ($p < 0.001$), implying partial restoration of limbic integrity. The corpus callosum was 0.7 mm thicker in long-term PTSD compared with recent PTSD ($p < 0.001$), indicating improvement in white-matter coherence. Likewise, insular cortex thickness in the long-term group closely approximated that of controls ($p < 0.001$), in contrast to pronounced thinning in early PTSD. Although the lateral fissures remained wider in long-term PTSD relative to controls, they were 1.8–2.0 mm narrower than in recent PTSD ($p < 0.001$), indicating partial mitigation of cortical atrophy. No significant differences were observed in interhemispheric fissure width ($p = 0.955$), suggesting relative resilience of this region to PTSD-related changes.

Taken together, these patterns support a model in which early PTSD is associated with acute stress-driven structural disruption, whereas long-term PTSD reflects a mixed profile of persistent neurodegeneration and partial compensatory adaptation.

Table 1. Comparison of selected biochemical biomarkers and morphometric measurements of key brain structures in the study cohort (N = 92), stratified by PTSD duration (≤5 years – early PTSD; >5 years – late/chronic PTSD) and a trauma-exposed control group without PTSD symptoms

Characteristic	N	Overall (N = 92)	Past PTSD (≤5y) (N = 33)	Past PTSD (>5y) (N = 31)	No PTSD (Control) (N = 28)	p-value	CLD Relations
Age (years)	92	34.0 (28.8, 41.0)	34.0 (31.0, 41.0)	36.0 (29.5, 41.0)	33.5 (24.2, 41.5)	0.524	-
Biomarkers							
IGF-1 (nmol/ml)	92	10.8 (5.2, 32.3)	4.9^{A} (4.0, 5.8)	13.6^{B} (7.6, 19.7)	37.1^{C} (32.5, 44.6)	**< 0.001**	C > B > A
CASP9 (ng/ml)	92	10.2 (3.0, 22.9)	23.8^{A} (20.8, 26.5)	6.8^{B} (3.7, 16.6)	2.7^{C} (1.8, 3.3)	**< 0.001**	A > B > C
nNOS (ng/ml)	92	25.7 (7.0, 57.9)	62.3^{A} (46.6, 82.1)	19.1^{B} (9.5, 35.7)	5.7^{C} (4.8, 7.1)	**< 0.001**	A > B > C
IL10 (ng/l)	92	806.9 (319.2, 2411.8)	279.0^{A} (231.0, 345.3)	833.7^{B} (523.0, 1448.5)	3159.0^{C} (2814.0, 3516.3)	**< 0.001**	C > B > A
Serotonin (ng/ml)	92	144.8 (120.2, 203.4)	109.9^{A} (96.6, 122.2)	147.4^{B} (139.6, 153.2)	225.2^{C} (209.6, 296.7)	**< 0.001**	C > B > A
Cortisol (ug/dl)	92	14.0 (10.9, 36.2)	9.8^{A} (6.8, 11.6)	47.5^{B} (36.4, 57.6)	13.5^{C} (12.0, 15.4)	**< 0.001**	B > C > A
Noradrenaline (pg/ml)	92	371.3 (220.3, 544.8)	271.7^{A} (210.7, 406.3)	271.7^{A} (189.0, 399.7)	580.2^{B} (449.1, 830.2)	**< 0.001**	B > A
IL-12 (pg/ml)	92	21.6 (8.5, 54.7)	62.4^{A} (51.8, 69.1)	17.0^{B} (11.2, 33.9)	7.7^{C} (6.3, 8.6)	**< 0.001**	A > B > C
Brain Measurements							
Width of the Third Ventricle (WTV)	92	6.6 (5.5, 7.7)	7.7^{A} (7.1, 8.4)	6.7^{B} (5.8, 7.6)	5.4^{C} (4.4, 6.0)	**< 0.001**	A > B > C
Width of the Left Amygdala (TLA)	92	17.5 (16.0, 18.1)	15.0^{A} (14.0, 18.0)	17.5^{B} (16.5, 18.0)	18.8C (18.0, 20.0)	**< 0.001**	C > B > A
Width of the Right Amygdala (TRA)	91	18.0 (15.0, 19.0)	15.0^{A} (13.8, 15.0)	18.0^{B} (17.0, 19.0)	19.0C (19.0, 20.0)	**< 0.001**	C > B > A
Thickness of the Body of the Corpus Callosum (TBCC)	91	5.4 (4.5, 6.2)	4.6^{A} (4.2, 5.4)	5.3^{B} (4.7, 5.8)	6.3C (5.9, 7.0)	**< 0.001**	C > B > A
Thickness of the Left Insular Cortex (TLIC)	91	2.5 (2.2, 2.9)	2.3^{A} (2.0, 2.5)	2.6^{B} (2.4, 3.0)	2.8^{B} (2.5, 3.0)	**< 0.001**	B > A
Thickness of the Right Insular Cortex (TRIC)	91	2.5 (2.1, 2.9)	2.2^{A} (1.9, 2.5)	2.7^{B} (2.2, 3.0)	2.7^{B} (2.4, 3.0)	**< 0.001**	B > A
Width of the Left Lateral Cerebral Fissure (WLLCF)	91	4.7 (3.1, 5.8)	6.0^{A} (5.4, 6.3)	4.2^{B} (3.3, 5.2)	2.5^{C} (2.1, 3.2)	**< 0.001**	A > B > C
Width of the Right Lateral Cerebral Fissure (WRLCF)	91	4.9 (3.0, 5.8)	6.0^{A} (5.5, 6.4)	4.0^{B} (3.4, 5.0)	2.5C (2.0, 3.1)	**< 0.001**	A > B > C
Width of the Interhemispheric Fissure in the Frontal Region (WIFFR)	91	2.4 (2.0, 3.0)	2.4 (2.0, 3.0)	2.5 (2.0, 3.0)	2.6 (2.0, 2.9)	0.955	-

Notes: Continuous variables are presented as median (interquartile range, IQR); categorical variables as n (%). Values were rounded to one decimal place. p-values were calculated using the Kruskal–Wallis test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. A p-value < 0.05 indicates statistical significance. Groups labeled with different letters (A, B, C) differ significantly (p < 0.05) according to compact letter display (CLD) notation following significant Kruskal–Wallis or chi-square tests. Groups sharing the same letter do not differ significantly. The letter order corresponds to PTSD ≤5 years, PTSD >5 years, and No PTSD (Control).
Source: Own material

BIOMARKER – MORPHOMETRY CORRELATION PROFILES

Correlation analyses (Fig. 2) integrating eight biochemical markers (IGF-1, CASP-9, nNOS, IL-10, serotonin, cortisol, noradrenaline, IL-12) with nine brain morphometric variables (WTV, TLA, TRA, TBCC, TLIC, TRIC, WLLCF, WRLCF, WIFFR) revealed distinct neurobiological profiles across recent PTSD, long-term PTSD, and controls.

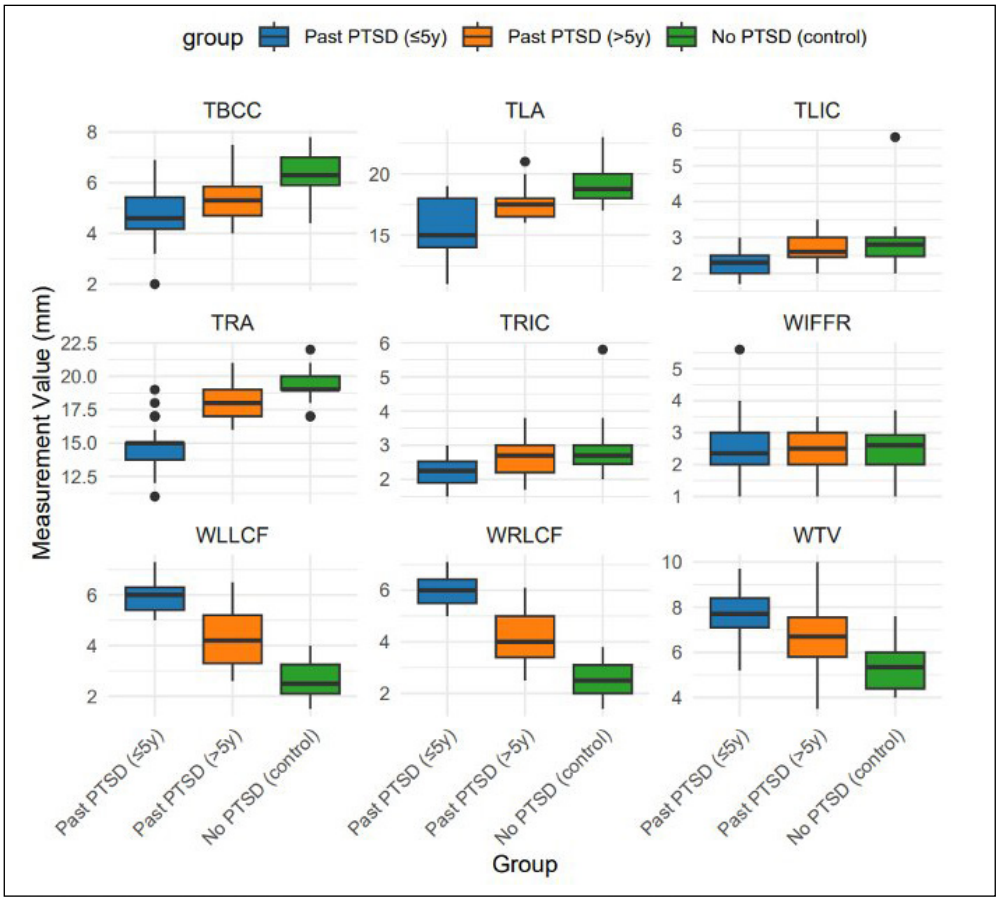

Fig. 1. Distribution of the brain measurements across PTSD groups
Notes: Distribution of morphometric brain parameters across the three study groups: PTSD ≤5 years, PTSD >5 years, and the trauma-exposed control group without PTSD symptoms. The presented measurements include: WTV (width of third ventricle), TLA and TRA (width of left/right amygdala), TBCC (thickness of body of the corpus callosum), TLIC and TRIC (thickness of the left/right insular cortex), WLLCF and WRLCF (width of the left/right lateral cerebral fissure), and WIFFR (width of the interhemispheric fissure in the frontal region). All values are expressed in millimeters.
Source: Own material

RECENT PTSD (≤5 YEARS)

Recent PTSD was characterized by correlations indicative of acute neuroinflammatory and neurodegenerative processes:

IGF-1 negatively correlated with WRLCF (rho = –0.42, p = 0.017), linking lower neurotrophic activity with frontotemporal cortical atrophy.

IL-10 negatively correlated with WTV (rho = –0.44, p = 0.011), suggesting that diminished anti-inflammatory signaling contributes to ventricular enlargement.

CASP-9 negatively correlated with WTV (rho = –0.36, p = 0.037), consistent with regulated apoptotic activity exerting a potentially protective effect during early pathology.

Cortisol positively correlated with TLA (rho = 0.35, p = 0.045), indicating that elevated glucocorticoids may transiently preserve amygdala structure, thereby maintaining heightened emotional reactivity and hyperarousal.

LONG-TERM PTSD (>5 YEARS)

Correlation patterns shifted toward markers of chronic neurodegeneration and compensatory neurobiological responses:

Cortisol exhibited strong positive correlations with WRLCF (rho = 0.78, p < 0.001) and WLLCF (rho = 0.74, p < 0.001), underscoring its role in sustaining frontotemporal atrophy through chronic HPA axis dysregulation.

Noradrenaline correlated with WTV (rho = 0.51, p = 0.006), suggesting activation of compensatory mechanisms that may preserve neural perfusion and suppress proinflammatory microglial activity.

CONTROL GROUP

Patterns in controls reflected physiological homeostasis:

CASP-9 negatively correlated with WTV (rho = –0.39, p = 0.042), consistent with regulated apoptosis supporting healthy neuronal turnover.

Serotonin positively correlated with TRIC (rho = 0.51, p = 0.006) and TLIC (rho = 0.38, p = 0.044), indicating preserved insular integrity essential for emotional and interoceptive stability.

Cortisol correlated with WIFFR (rho = 0.39, p = 0.042), reflecting normative stress responsivity.

Noradrenaline correlated with WRLCF (rho = 0.41, p = 0.039), indicating physiological variability rather than pathological change.

CLINICAL AND NEUROBIOLOGICAL INTERPRETATION

PTSD significantly disrupts normal biomarker–brain coupling, with distinct clinical implications. In recent

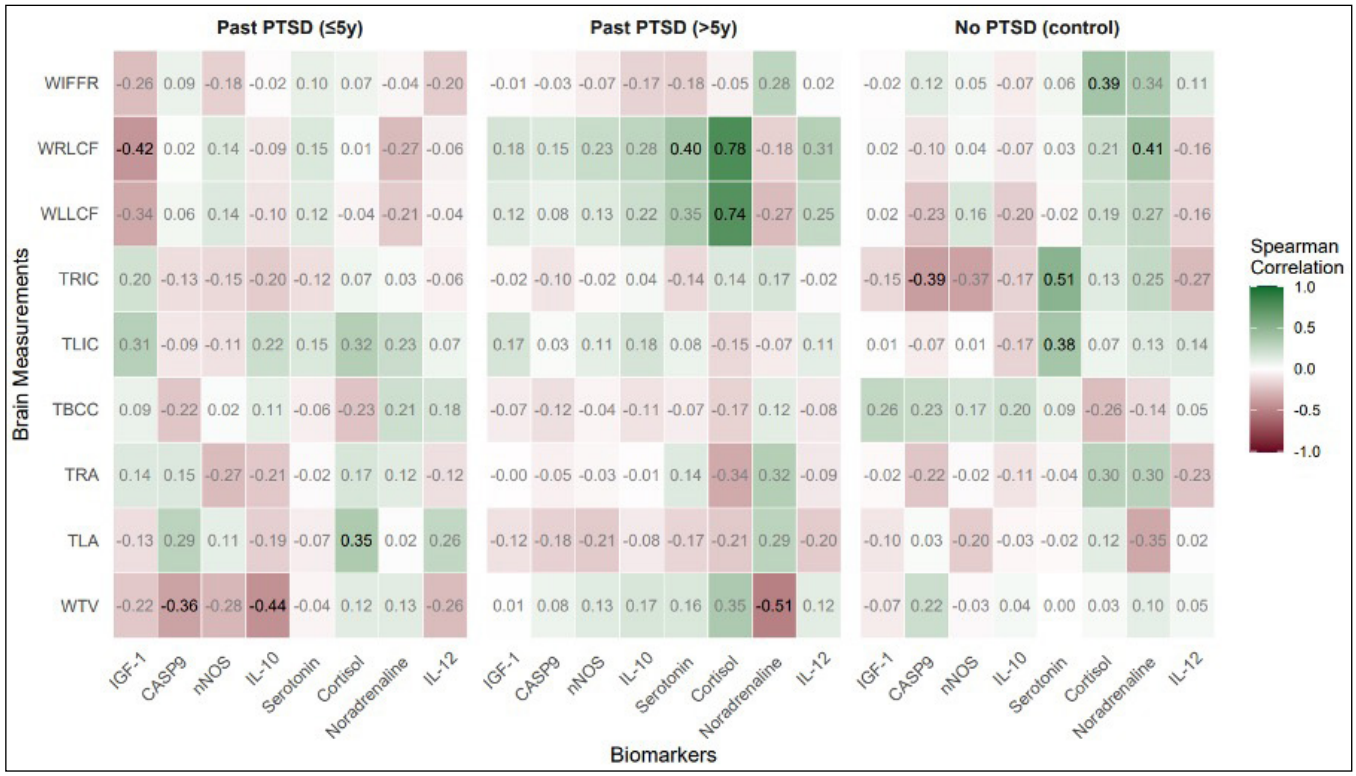

Fig. 2. Spearman Correlations: Biomarkers *vs*. Brain Measurements by PTSD Group
Notes: Correlation coefficients represent Spearman's rank correlations between biomarkers (x-axis) and brain measurements (y-axis) across three groups: Past PTSD (≤5 years), Past PTSD (>5 years), and No PTSD (Control). Values range from -1 (red, strong negative correlation) to 1 (green, strong positive correlation), with white indicating no correlation. Significant correlations ($p < 0.05$) are shown in black, while non-significant correlations are in grey. Brain measurements (all in mm) include WTV (width of the third ventricle), TLA/TRA (width of left/right amygdala), TBCC (thickness of the body of the corpus callosum), TLIC/TRIC (thickness of left/right insular cortex), WLLCF/WRLCF (width of left/right lateral cerebral fissure), and WIFFR (width of the interhemispheric fissure in the frontal region). Biomarkers include IGF-1 (nmol/ml), CASP9 (ng/ml), nNOS (ng/ml), IL-10 (ng/l), Serotonin (ng/ml), Cortisol (ug/dl), Noradrenaline (pg/ml) and IL-12 (pg/ml)
Source: Own material

PTSD, reduced IGF-1 and IL-10 levels correspond with cortical atrophy and ventricular enlargement, respectively, suggesting heightened vulnerability to cognitive impairment and accelerated neuronal loss. CASP-9 patterns imply partial neuroprotection, while cortisol-related amygdala preservation contributes to hyperarousal and emotional dysregulation.

In long-term PTSD, strong cortisol-morphometry correlations reveal persistent neurodegeneration driven by chronic stress hormone exposure, consistent with progressive cognitive decline, impaired decision-making, visuospatial deficits, and increased susceptibility to mood disorders. Noradrenaline's protective correlations suggest compensatory neurobiological mechanisms that may slow structural deterioration.

In healthy controls, correlations predominantly reflect homeostatic regulation of apoptosis, serotonergic support of insular integrity, and normative stress responsivity. However, baseline cortisol- and noradrenaline-related patterns indicate subtle predispositions that, under pathological stress, may increase vulnerability.

OVERALL SUMMARY

The duration of PTSD acts as a critical risk factor that amplifies structural and biochemical dysregulation over time. Recent PTSD is marked by acute inflammatory and stress-driven neurobiological disruption, whereas long-term PTSD exhibits persistent cortical atrophy and maladaptive stabilization of chronic stress pathways. Compared with the predominantly protective patterns seen in controls, prolonged PTSD is associated with accelerating structural deterioration, emphasizing the need for early, targeted interventions to prevent long-term clinical consequences such as cognitive decline, emotional instability, and diminished treatment responsiveness.

DISCUSSION

Previous publications by the author [27, 28] have described neurobiological disturbances and associations among stress-related biomarkers as a function of PTSD duration and patient age, providing an interpretive framework for the present findings. The current study

extends these analyses by demonstrating that biochemical alterations not only reflect underlying pathophysiological processes but are also directly linked to quantifiable morphometric changes in the brain. This integration advances the understanding of PTSD neurobiology by bridging molecular markers with structural imaging indicators [40].

Correlation analyses between biochemical markers and brain morphometric parameters revealed a heterogeneous pattern of neurobiological alterations depending on PTSD chronicity, supporting the hypothesis that the disorder's pathophysiology evolves over time. Early PTSD (≤5 years) was characterized predominantly by disruptions in neuroinflammatory balance, whereas chronic PTSD (>5 years) exhibited structural brain changes consistent with progressive cortical atrophy. In the control group, the observed associations were physiologically normative and reflected intact neurotransmitter modulation and homeostatic regulation of neuronal plasticity.

In individuals with early PTSD, diminished anti-inflammatory activity played a key role, exemplified by the strong negative correlation between IL-10 levels and third-ventricle width. Reduced IL-10 - an essential cytokine inhibiting proinflammatory M1 microglial activation—was associated with enlargement of periventricular structures, suggesting neurodegenerative processes [41]. The negative correlation between IGF-1 and the width of the lateral fissures (WRLCF, WLLCF) indicates that lower IGF-1 levels are linked to greater tissue loss in frontotemporal regions, consistent with reduced neuroprotective capacity.

The negative correlation between caspase-9 and third-ventricle width in early PTSD suggests that early-stage apoptotic activation may serve a protective role by containing excessive degradation of neural tissue. Conversely, the positive correlation between cortisol and amygdala dimensions reflects heightened limbic reactivity, which clinically manifests as hyperarousal, intrusive symptoms, and deficits in emotional regulation [42, 43].

Morphometric findings further corroborated these biochemical associations. In early PTSD, the most pronounced atrophic tendencies were observed in third-ventricle width (WTV), lateral fissure width (WLLCF, WRLCF), and reductions in corpus callosum thickness (TBCC) and insular cortex thickness (TLIC, TRIC). These patterns suggest that neuroinflammatory processes during the initial years of PTSD contribute to early atrophic changes. Alterations in the amygdala - relatively mild in this phase - may reflect a state of emotional overload rather than advanced structural deterioration [44].

In chronic PTSD (>5 years), a distinct profile emerged, indicating progressive structural damage, particularly in the frontotemporal cortex. The strongest correlations involved cortisol, which exhibited a robust positive association with lateral fissure width. This finding is consistent with extensive evidence demonstrating the neurotoxic effects of prolonged HPA axis activation, leading to loss of gray matter volume and reduced neuronal connectivity [45, 56]. The magnitude of this correlation - the largest among all observed associations - underscores cortisol's central role in the pathomechanisms of late-stage PTSD and supports its utility as a biomarker of neurodegenerative progression [45, 46].

Morphometric data reinforce this interpretation: individuals with chronic PTSD exhibited widening of the lateral fissures and third ventricle, significant thinning of the corpus callosum and insular cortex, and moderate reductions in amygdala volume. The negative correlation between noradrenaline and third-ventricle width may indicate activation of compensatory mechanisms. Noradrenaline, by suppressing proinflammatory microglia and supporting cerebral perfusion, may mitigate the progression of atrophy, suggesting its potential as a neuroprotective biomarker in chronic PTSD. The positive association between IGF-1 and morphometric variables in this group may reflect attempts to re-engage regenerative processes [47].

The control group exhibited associations characteristic of physiological neurotransmitter regulation and homeostatic neuronal plasticity. The positive correlation between serotonin and insular cortex thickness supports its role in modulating interoception, affective processing, and autonomic regulation. Noradrenaline showed moderate correlations with lateral fissure width, reflecting normative anatomical variability in healthy individuals. The negative correlation between CASP-9 and insular thickness suggests regulated, homeostatic apoptosis typical of healthy neuronal remodeling.

Taken together, these findings indicate that PTSD duration is a crucial factor shaping both the direction and magnitude of associations between biochemical and morphometric brain parameters. The early phase of the disorder is dominated by neuroinflammation and dysregulated neuroendocrine function, whereas the chronic phase is characterized by progressive neurodegeneration, particularly within frontotemporal networks. The integration of biochemical and structural data underscores the complexity of PTSD pathophysiology and highlights the need to tailor therapeutic strategies to specific disease stages. Neuroinflammatory and neuroprotective mechanisms appear to be promising targets for early interventions, while in chronic PTSD, therapeutic priorities shift toward slowing atrophy and supporting residual compensatory mechanisms. Understanding these associations may inform the development of prognostic biomarkers and personalized

therapeutic approaches aimed at modulating HPA axis activity, noradrenergic signaling, and neuroinflammatory pathways [48, 49].

LIMITATIONS

This study has several limitations that should be considered when interpreting the findings. First, the study population consisted exclusively of male participants employed in the mining industry, which restricts the generalizability of the results to women and to individuals who have experienced trauma from other sources. Second, both the MRI assessments and the biochemical measurements were conducted at a single time point, which precludes evaluation of the temporal dynamics or longitudinal progression of the observed changes.

FUTURE DIRECTIONS

Future research should aim to address several important gaps identified in the present study. Longitudinal designs, incorporating repeated MRI measurements and serial biomarker assessments, are essential to clarify the temporal dynamics of neuroinflammatory, neuroendocrine, and structural changes across the trajectory of PTSD. Such approaches would enable the identification of early markers predictive of transition to chronicity as well as mechanisms underlying potential recovery.

Expanding the study population to include women and individuals exposed to diverse forms of trauma would increase generalizability and allow examination of potential sex-specific or trauma-type–specific neurobiological pathways. Given the known influence of sex hormones on stress reactivity, neuroinflammation, and neuroplasticity, exploring sex differences may yield critical insights into personalized treatment strategies.

Future studies would also benefit from integrating multimodal neuroimaging approaches - including functional MRI, resting-state connectivity, MR spectroscopy, and advanced diffusion models - to obtain a more comprehensive characterization of neuronal integrity, microglial activation, and network dysfunction. Combining imaging data with detailed neuropsychological assessments could further elucidate the clinical significance of structural and biochemical abnormalities, particularly in domains such as memory, interoception, emotional regulation, and executive functioning.

Another promising direction involves investigating therapeutic modulation of the biomarkers identified in this study, such as cortisol, IGF-1, noradrenaline, IL-10, and CASP-9. Interventional studies - pharmacological, psychotherapeutic, behavioral, or neuromodulatory (e.g., tDCS, TMS, neurofeedback) - could determine whether targeted modulation of neuroinflammatory and neuroendocrine pathways translates into measurable neuroprotective or restorative effects on brain structure.

CONCLUSIONS

The findings of this study demonstrate that the duration of PTSD is a key determinant of both biochemical and structural alterations within the brain. Early PTSD is characterized primarily by neuroinflammatory imbalance and disturbances in neuroendocrine homeostasis, which manifest as early morphometric deviations - particularly reduced hippocampal and amygdalar volumes, thinning of the insular cortex and corpus callosum, and enlargement of periventricular and frontotemporal spaces. These changes are consistent with emerging neurodegenerative processes during the initial phase of the disorder.

In contrast, chronic PTSD (>5 years) is associated with more pronounced and progressive structural abnormalities, including widening of the lateral fissures and third ventricle, consistent with advancing cortical atrophy. These structural changes strongly correlated with elevated cortisol levels, supporting the role of sustained HPA axis activation as a major contributor to long-term neurotoxicity. At the same time, partial microstructural reorganization was observed, suggesting engagement of adaptive neuroplastic responses. Compensatory mechanisms - reflected in increased IGF-1 levels and the neuroprotective influence of noradrenaline - may represent endogenous attempts to counteract ongoing neuronal injury.

The control group exhibited patterns characteristic of physiological neuronal homeostasis, further emphasizing the pathological nature of the biochemical and morphometric alterations identified in PTSD.

Altogether, these results indicate that PTSD is not a static disorder but rather a dynamic condition with evolving neurobiological mechanisms. Early phases are dominated by neuroinflammation and dysregulated neuroendocrine signaling, whereas chronic stages are marked by progressive neurodegeneration alongside limited compensatory plasticity. Integrating biochemical profiling with MRI-derived parameters provides strong evidence that PTSD involves complex interactions between neuroinflammatory, neuroendocrine, and neuroplastic pathways.

These findings highlight the importance of stage-specific therapeutic strategies: interventions targeting neuroinflammation and promoting neuroprotection may be most

effective in early PTSD, while approaches aimed at slowing cortical atrophy and supporting residual compensatory mechanisms may be essential in chronic stages. Understanding these dynamic relationships may contribute to the development of prognostic biomarkers and guide the implementation of personalized, mechanism-based treatments focused on modulating the HPA axis, noradrenergic signaling, and neuroinflammatory processes.

REFERENCES

1. Yang L, Meng M, Tian M, et al. Aberrations in peripheral blood interleukin-6 levels in post-traumatic stress disorder: A systematic review and meta-analysis. Behav Brain Res. 2026;497:115881. doi: 10.1016/j.bbr.2025.115881. DOI
2. Larsen SE, Chavin RS, Flores J, et al. Comparing probable subthreshold and full PTSD prevalence in older versus younger veterans. J Affect Disord. 2026;394(Pt A):120549. doi: 10.1016/j.jad.2025.120549. DOI
3. Czernin NS, Seuling PD, Zillich L, et al. Serotonin transporter gene methylation and cortisol reactivity to acute stress: modeling the pathogenetic and therapeutic effects of stress-related disorders? J Neural Transm (Vienna). 2025;132(9):1399-1410. doi: 10.1007/s00702-025-03009-8. DOI
4. Gerber L, Müller MM, Oender A, et al. Psychological, neuroendocrine and inflammatory stress responses in women after miscarriage or stillbirth: investigating early psychobiological adaptations to potential traumatic events. J Neural Transm (Vienna). 2025;132(9):1263-1274. doi: 10.1007/s00702-025-02927-x. DOI
5. Dow CT, Obaid L. Proposing Bromo-Epi-Androsterone (BEA) for Post-Traumatic Stress Disorder (PTSD). Cells. 2025;14(14):1120. doi: 10.3390/cells14141120. DOI
6. Sah A, Singewald N. The (neuro)inflammatory system in anxiety disorders and PTSD: Potential treatment targets. Pharmacol Ther. 2025;269:108825. doi: 10.1016/j.pharmthera.2025.108825. DOI
7. Li K, Luo G, Fu M, et al. Potential Mitochondria-Related Key Genes in Post-Traumatic Stress Disorder Analyzed by Machine Learning Methods. Neuropsychiatr Dis Treat. 2025;21:2109-2124. doi: 10.2147/NDT.S535798. DOI
8. Candela SM, Ramiro CM, Melisa RG, et al. A hyperexcited basolateral amygdala complex state determines the hippocampal structural plasticity associated with the reconsolidation of a fear memory. Neuroscience. 2025;0306-4522(25)01115-7. doi: 10.1016/j.neuroscience.2025.11.023. DOI
9. Liu J, Totty MS, Bayer H, et al. Integrating Aversive Memories in the Basolateral Amygdala. Biol Psychiatry. 2025;98:746-755. doi: 10.1016/j.biopsych.2025.03.019. DOI
10. Wang Q, Guo L, Luo L.et al. Shared and distinct neural signatures in major depressive disorder and comorbid post-traumatic stress disorder: Insights from structural and functional imaging. J Affect Disord. 2026;393(Pt B):120414. doi: 10.1016/j.jad.2025.120414. DOI
11. Li X, Sun L, Zeng Z, et al. Regional homogeneity differences between the brains of young men and young women: A resting-state functional magnetic resonance imaging study. IBRO Neurosci Rep. 2025;19:417-425. doi: 10.1016/j.ibneur.2025.08.006. DOI
12. Denis D, Bottary R, Cunningham TJ, et al. Slow Oscillation-Sleep Spindle Coupling Is Associated With Expectancy Measures of Fear Extinction Retention in Trauma-Exposed Individuals. Biol Psychiatry Cogn Neurosci Neuroimaging. 2025;2451-9022(25)00257-5. doi: 10.1016/j.bpsc.2025.08.009. DOI
13. Recher D, Rohde J, Da Poian G, et al. Targeted memory reactivation during sleep improves emotional memory modulation following imagery rescripting. Transl Psychiatry. 2024;14(1):490. doi: 10.1038/s41398-024-03192-4. DOI
14. Ma M, Fan H, Zhang H, et al. Epitranscriptomic Analysis of the Ventral Hippocampus in a Mouse Model of Post-Traumatic Stress Disorder Following Deep Brain Stimulation Treatment of the Basolateral Amygdala. Brain Sci. 2025;15(5):473. doi: 10.3390/brainsci15050473. DOI
15. Dimitrova LI, Chalavi S, Vissia EM, et al. Brain white matter structural connectivity of trauma and trauma-related dissociation disorders and symptoms. Psychiatry Res. 2025 Apr;346:116383. doi: 10.1016/j.psychres.2025.116383 DOI
16. Vicario CM, Martino G, Lucifora C, et al. Preliminary evidence on the neural correlates of timing deficit in post-traumatic stress disorder. Eur J Psychotraumatol. 2022;13:2008151. doi: 10.1080/20008198.2021.2008151. DOI
17. Knaust T, Tarnogorski D, Siebler MBD, et al. Investigating amygdala nuclei volumes in military personnel with post-traumatic stress disorder, major depressive disorder, and adjustment disorder: A retrospective cross-sectional study using clinical routine data.PLoS One. 2025;20(1):e0317573. doi: 10.1371/journal.pone.0317573. DOI
18. Sisk LM, Keding TJ, Cohodes EM, et al. Multivariate Links Between the Developmental Timing of Adversity Exposure and White Matter Tract Connectivity in Adulthood. Biol Psychiatry Cogn Neurosci Neuroimaging. 2025;10:964-977. doi: 10.1016/j.bpsc.2025.02.003. DOI
19. Harrington DL, Shen Q, Angeles-Quinto A, et al. Linking intrinsic brain dysfunction to behavioral outcomes in combat-exposed males with PTSD symptoms. Front Psychiatry. 2025;16:1591938. doi: 10.3389/fpsyt.2025.1591938. DOI
20. See CRZ, Si S, Baird CL, et al. A whole-brain voxel-based analysis of structural abnormalities in PTSD: An ENIGMA-PGC study. Eur Psychiatry. 2025;68(1):e97. doi: 10.1192/j.eurpsy.2025.10062. DOI

21. Chmiel J, Kurpas D. Burnout and the Brain-A Mechanistic Review of Magnetic Resonance Imaging (MRI) Studies. Int J Mol Sci. 2025;26:8379. doi: 10.3390/ijms26178379. DOI
22. de Voogd LD, Hashemi MM, Zhang W, et al. Amygdala Hyperactivity in Posttraumatic Stress Disorder: Disentangling Predisposing From Consequential Factors Using a Prospective Longitudinal Design. Biol Psychiatry. 2025;98:427-435. doi: 10.1016/j.biopsych.2025.02.894. DOI
23. Krenz V, Alink A, Roozendaal B, et al. Memory Boost for Recurring Emotional Events Is Driven by Initial Amygdala Response Promoting Stable Neocortical Patterns across Repetitions. J Neurosci. 2025;45:e2406232025. doi: 10.1523/JNEUROSCI.2406-23.2025. DOI
24. Bauer EA, Cooper SE, Keller NE, et al. Encoding-Retrieval Similarity Reveals Distinct Neural Reinstatement of Safety Memories Following Counterconditioning in Posttraumatic Stress Disorder. Biol Psychiatry Cogn Neurosci Neuroimaging. 2025;10:1125-1133. doi: 10.1016/j.bpsc.2025.07.007. DOI
25. Gharios C, van Leent MMT, Chang HL, et al. Cortico-limbic interactions and carotid atherosclerotic burden during chronic stress exposure. Eur Heart J. 2024;45:1753-1764. doi: 10.1093/eurheartj/ehae149. DOI
26. Sydnor VJ, Cieslak M, Duprat R, et al. Cortical-subcortical structural connections support transcranial magnetic stimulation engagement of the amygdala. Sci Adv. 2022;8:eabn5803. doi: 10.1126/sciadv.abn5803. DOI
27. Paraniak-Gieszczyk B, Ogłodek EA. Neurobiological Correlates of Coping Strategies in PTSD: The Role of IGF-1, CASP-9, nNOS, and IL-10 Based on Brief-COPE Assessment. Curr Issues Mol Biol. 2025;47:868. doi: 10.3390/cimb47100868. DOI
28. Paraniak-Gieszczyk B, Ogłodek EA. Neurobiological and Existential Profiles in Posttraumatic Stress Disorder: The Role of Serotonin, Cortisol, Noradrenaline, and IL-12 Across Chronicity and Age. Int J Mol Sci. 2025;26:9636. doi: 10.3390/ijms26199636. DOI
29. Cwik JC, Vahle N, Woud ML, et al. Reduced gray matter volume in the left prefrontal, occipital, and temporal regions as predictors for posttraumatic stress disorder: a voxel-based morphometric study. Eur Arch Psychiatry Clin Neurosci. 2020;270:577-588. doi: 10.1007/s00406-019-01011-2. DOI
30. R Core Team: A Language and Environment for Statistical Computing; R Foundation for Statistical Computing: Vienna, Austria, 2024. Available online: https://www.R-project.org/ (Access: 18 April 2025).
31. Makowski D., Lüdecke D, et al. Automated Results Reporting as a Practical Tool to Improve Reproducibility and Methodological Best Practices Adoption. CRAN 2023. Available online: https://easystats. github.io/report/ (Access: 18 April 2025).
32. Patil I. Visualizations with statistical details: The 'ggstatsplot' approach. J Open Source Softw. 2021;6:3167. doi:10.21105/joss.03167 DOI
33. Schloerke B, Cook D, Larmarange J, et al. GGally: Extension to 'ggplot2'. R package, version 2.2.1. 2024. Available online: https://CRAN.R-project.org/package=GGally (Access: 15 July 2025).
34. Sjoberg, D, Whiting, K, Curry, M, et al. Reproducible Summary Tables with the gtsummary Package. R J. 2021, 13, 570–580.
35. Wei, T, Simko, V. R package 'corrplot': Visualization of a Correlation Matrix. GitHub, version 0.94. 2024. Available online: https://github.com/taiyun/corrplot (Access: 15 July 2025).
36. Wickham, H. Reshaping Data with the reshape Package. J Stat Softw. 2007;21:1-20. doi:10.18637/jss.v021.i12. DOI
37. Wickham, H. ggplot2: Elegant Graphics for Data Analysis; Springer-Verlag, New York, 2016. doi:10.1007/978-3-319-24277-4_9. DOI
38. Wickham, H., Francois, R., Henry, L, et al. dplyr: A Grammar of Data Manipulation. R package, version 1.1.4. 2023. https://CRAN.R-project.org/package=dplyr (Access: 15 July 2025).
39. Wickham, H., Vaughan, D., Girlich, M. tidyr: Tidy Messy Data. R package, version 1.3.1. 2024. https://CRAN.R-project.org/package=tidyr (Accessed: July 2025).
40. Segal A, Charquero-Ballester M, Vaisvasser S, et al. Brain network dynamics following induced acute stress: a neural marker of psychological vulnerability to real-life chronic stress. Psychol Med. 2025;55:e187. doi: 10.1017/S0033291725100913. DOI
41. Speakman S, White K, LaPorta AJ, et al. Cytokine fluctuation during acute stress is correlated to life trauma. J Trauma Acute Care Surg. 2023;95:535-541. doi: 10.1097/TA.0000000000004006. DOI
42. Eales K, Lipp OV, Anderson J, et al. Fear extinction using a conditioned stimulus that was temporally proximal to the unconditioned stimulus reduces physiological and subjective return of fear. Behav Res Ther. 2025;193:104828. doi: 10.1016/j.brat.2025.104828. E DOI
43. Hardi FA, Ye J, Zhou I, et al. Trauma-predictive brain network connectivity adaptively responds to mild acute stress. Proc Natl Acad Sci USA. 2025;122:e2505965122. doi: 10.1073/pnas.2505965122. DOI
44. Awasthi S, Pan H, LeDoux JE, et al. The bed nucleus of the stria terminalis and functionally linked neurocircuitry modulate emotion processing and HPA axis dysfunction in posttraumatic stress disorder. Neuroimage Clin. 2020;28:102442. doi: 10.1016/j.nicl.2020.102442. DOI
45. Li X, Qin L, Sun Y, et al. Qingyu Yangjing formula ameliorates cyclophosphamide-induced oligoasthenospermia by regulating the hypothalamic-pituitary-gonadal axis and inhibiting testicular oxidative stress and apoptosis in rats. J Ethnopharmacol. 2026;356:120842. doi: 10.1016/j.jep.2025.120842. DOI
46. Mirjalili R, Shokouh E, Dehkordi NS, et al. Prior short-term exercise prevents behavioral and biochemical abnormalities induced by single prolonged stress in a rat model of posttraumatic stress disorder. Behav Brain Res. 2022;428:113864. doi: 10.1016/j.bbr.2022.113864. DOI

47. Mishra V, Rosenthal K, Hillaker E, et al. IGF-1 as a biomarker for symptom severity in adolescents with traumatic brain injury. Brain Inj. 2025;39:1268-1273. doi: 10.1080/02699052.2025.2552336. DOI
48. Steardo L Jr, D'Angelo M, Di Stefano V, et al. Targeting PTSD with ultramicronized palmitoylethanolamide: Results from a randomized trial integrating pharmacotherapy and cognitive behavioral therapy. J Psychiatr Res. 2026;192:439-450. doi: 10.1016/j.jpsychires.2025.10.071. DOI
49. Gu Z, Song R, Liu G, et al. Esketamine attenuates post-traumatic stress disorder via suppressing neuroinflammation and abnormal myelination. Neurochem Int. 2025, 191:106089. doi: 10.1016/j.neuint.2025.106089. DOI

CONFLICT OF INTEREST

The Author declare no conflict of interest

CORRESPONDING AUTHOR

Barbara Paraniak-Gieszczyk
Collegium Medicum,
Jan Dlugosz University in Czestochowa,
Częstochowa, Poland
e-mail: b.paraniak-gieszczyk@ujd.edu.pl

ORCID AND CONTRIBUTIONSHIP

Barbara Paraniak-Gieszczyk: 0009-0002-5518-9931 A B C D E F

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 05.08.2025
ACCEPTED: 26.11.2025