



TO WHAT EXTENT ARE GENETIC AND ENVIRONMENTAL FACTORS LINKED WITH THE DEVELOPMENT OF POSTTRAUMATIC STRESS DISORDER?

UDZIAŁ CZYNNIKÓW GENETYCZNYCH I ŚRODOWISKOWYCH W ROZWOJU ZESPOŁU STRESU POURAZOWEGO

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Abstract

Purpose: PTSD is a disorder that may develop in people who have been exposed to traumatic events or stressors. Four main types of symptoms of PTSD can be distinguished: affective, cognitive, behavioural and somatic. Although much research has been done, the exact cause of the development of PTSD is still unknown. The risk of susceptibility to PTSD is probably increased by environmental and genetic factors.

Review: According to the meta-analysis Broekman *et al.* there are certain genes which may promote PTSD. It seems that specific polymorphisms in the serotonin transporter gene (5-HTT), GABA receptor, dopamine receptor (DRD2) and dopamine transporter (DAT) might be involved in the development of PTSD. On the other hand, environmental factors have also been investigated. There is a diversified group of these, including among others manmade catastrophes, natural disasters, SOT transplantations and experiences of migration. Vulnerability to PTSD increases with the duration of exposure, the power of the stress and individual sensitivity.

Conclusions: Our results indicate that there must be a relationship among a number of factors in the development of PTSD. It is possible when strong environmental factors affect a vulnerable organism with predisposing genes that the disorder is going to develop considerably. However, despite a lot of research which has already been done, the exact cause of PTSD is still unknown and requires further study.

Key words: stress, PTSD development, genetic and environmental factors.

Streszczenie

Cel: Zespół stresu pourazowego (*posttraumatic stress disorder* – PTSD) rozwija się u ludzi, którzy doświadczyli traumatycznych wydarzeń. Wyróżniono cztery rodzaje stresu pourazowego: afektywny, kognitywny, somatyczny i behawioralny. Pomimo wielu badań dokładna przyczyna powstawania zespołu stresu pourazowego jest nieznana. Skłonność do rozwoju zespołu stresu pourazowego prawdopodobnie wzrasta na skutek oddziaływania czynników genetycznych i środowiskowych.

Poglądy: Metaanaliza wykonana przez Broekman i wsp. wskazuje na istnienie genów, które usposabiają do rozwoju choroby. Wydaje się, że w rozwoju choroby mogą mieć udział polimorfizmy transportera dla serotoniny (5-HTT), GABA receptorów, receptorów dopaminy (DRD2), transporterów dopaminy (DAT). Z drugiej strony, przebadano wiele czynników środowiskowych zaangażowanych w rozwój choroby, m.in. katastrofy spowodowane przez człowieka, klęski żywiołowe, przeszczepy narządów i migracje ludności. Podatność na stres wzrasta wraz z czasem ekspozycji, siłą stresora i zależy od indywidualnej wrażliwości.

Wnioski: Dane z literatury wskazują, że wiele czynników bierze udział w rozwoju stresu pourazowego. Wydaje się, że zespół stresu pourazowego rozwinię się znacznie częściej u osób wrażliwych z istniejącą predyspozycją genetyczną. Pomimo wielu badań dokładna przyczyna zespołu stresu pourazowego nie została poznana i wymaga dalszych badań.

Słowa kluczowe: stres, zespół stresu pourazowego, czynniki genetyczne i środowiskowe.

INTRODUCTION

One of the psychiatric disorders that is prevalent in people who have experienced long-lasting and devastating life events is posttraumatic stress disorder (PTSD) [1]. Analysis of the literature on the subject shows that there are three distinct areas of research into the identification of risk and the protective factors which influence the development of PTSD. These factors include: pre-trauma factors (genetics and personality- and temperament-related characteristics, as well as those pertaining to demographic data such as age and sex), factors directly related to the traumatic experience (the type of experienced trauma, its severity and duration) and post-trauma factors (i.e. social support) [2].

To date, there are no obvious and known reasons that cause the development of the disease. According to research to date, there are some presumable genetic and environmental factors that might promote PTSD [1, 3-8]. Therefore, due to complicated aetiology of the disorder, the human sciences do not have one favourable and effective method of treatment at their disposal. Recently, huge progress has been made in the field of psychotherapy, however, there are still many inquiries that should be dealt with.

Posttraumatic stress disorder is a condition characterised by a permanent feeling of fear, horror and helplessness because of having experienced, witnessed or been confronted by a traumatic experience that involved a threat to the physical integrity of self or others, a serious injury or even actual or threatened death [9]. The condition is classified in the Diagnostic and Statistical Manual of Mental Disorders V (DSM-V) according to the specific criteria of the American Psychiatric Association DSM-5 Development [10]. A person who suffers from the disorder re-experiences obtrusive recollections of the event, including perceptions, images or thoughts.

A sufferer may also possess a sense of reliving the trauma, have hallucinations, illusions and dissociative flashback episodes. The person feels detached from others and avoids stimuli that remind them of the traumatic event, for example, places, people, thoughts and feelings. Commonly, the afflicted are unable to remember an important part of the experience. PTSD is followed, as well, by persistent symptoms of anxiety and arousal such as difficulty falling or staying asleep and concentrating, constant fear or outbursts of anger. The disturbance has to last more than one month to be categorized as PTSD [11].

SYMPTOMS OF PTSD

Posttraumatic stress disorder is unique among anxiety disorders, because according to recent research, conducted by Stein *et al.*, it can manifest itself differently across individuals. However, there are some basic symptoms

that allow for a disorder to be diagnosed [4]. These can be divided into four types: Affective, Cognitive, Behavioural and Somatic [9]. Emotions play an enormous role when it comes to anxiety disorders. Patients suffering from PTSD may exhibit, as far as affective symptoms are concerned, an inability to feel positive emotions i.e. anhedonia, experiences emotional numbing, have negative feelings about themselves and others, lack interest in activities that they once enjoyed, have difficulty in maintaining close relationships and feelings of hopelessness about the future. Cognitive symptoms might be very intrusive and may prevent an individual from having a normal and peaceful life. They are accompanied by frightening thoughts, an inability to concentrate and hyperarousal. In addition, if a person was exposed to a sufficiently traumatic event, striking changes in his or her behaviour may be observed. Mainly, the sufferer feels continually "on guard" and fears that danger is lurking around every corner, a state referred to as hypervigilance. What is more, as far as behavioural symptoms are concerned, it is common for the afflicted to be susceptible to passivity, flashbacks and nightmares. Frequently, it also happens that on account of an unexpected, sudden stimulus, such as a loud sound or a blinding flash of light, a person expresses an exaggerated startle response [12]. PTSD can also be characterised by somatic symptoms such as a loss of already-acquired developmental skills, such as speech or toilet training, regression in some children, insomnia, headaches, lower back pain, stomach ache and digestion or heart problems [9]. The aetiology of the disorder, then, is not entirely explained and depends on various factors. As Stein *et al.* report, PTSD can be triggered not only by environmental influences, but also by some genetic factors and, intriguingly, personality traits [4]. Numerous studies emphasize the significant role of personality traits in reacting to traumatic experiences [13, 14]. Neuroticism is one trait that has been proven to be linked to the disorder [15-18]. People with high neuroticism indexes tend to experience higher levels of stress, irrespective of the circumstances [19]. Epidemiological research also indicates an exacerbation of PTSD symptoms in persons who have personally experienced victimization (sexual abuse, torture), compared with road traffic accident casualties, people suffering from life-threatening conditions, or those affected by natural disasters [20].

AETIOLOGY OF PTSD – GENETIC FACTORS

Broekman *et al.* argue that not everyone exposed to a traumatic event develops the mental disorder [3]. Even though the lifetime prevalence of exposure to a frightening experience is said to be between 40% and 90%, statistics show that in the general population the prevalence

of PTSD is only between 7% and 12%, with women suffering from PTSD twice as much as men. The more frequent occurrence of PTSD among women indicates the possible sex-linked inheritance [21, 22]. As a result of women's exposure to traumatic events, not only increases the risk of disclosure of the phenotype of PTSD, but also of other anxiety disorders such as panic and agoraphobia [23]. Moreover, experiments on animals have shown that the influence of trauma in early childhood, among females, is modulated by a polymorphism of the 5-HTT transporter gene, whereas no such connection was determined among males. Female vulnerability to stress is said to increase with the s (short) allele of 5-HTT transporter gene, which is connected with smaller activity in terms of transcriptional regulation. However, there are a few studies whose results imply an equal susceptibility to the appearance of PTSD in both women and men [24]. Kessler *et al.* suggest that the genetic predisposition among men is often connected with addiction to alcohol [25]. Overall, the data presented indicate that females are more vulnerable to experiencing PTSD than males. Furthermore, a study designed by Tian *et al.* analysed the correlation between genes and environment after the 2008 Wenchuan earthquake in China [26]. The high earthquake-exposure group who participated in the study involved 183 adolescents. The researchers examined their genotypes using polymerase chain reaction-based restriction fragment length polymorphism. The results showed a statistically significant correlation between exposure to the earthquake and the 5-HTTLPR and 5-HTTVNTR polymorphisms, having a positive effect on PTSD development. Thus, PTSD is not only caused by genetic effect and environmental factors, but also of the interactive effect of the two.

Transgenerational studies performed by Yehuda *et al.* and Koenen *et al.* have shown that PTSD is more likely to develop in particular families [27, 28]. Twin studies have found that monozygotic twins are more susceptible to the development of PTSD than dizygotic twins [4]. Other research on twins, conducted by Gilbertson *et al.*, has reported that PTSD may also be related to structural brain abnormalities [29]. The smaller the volume of the hippocampus in the septum pellucidum, the greater the susceptibility to PTSD. Studies have determined that the hippocampus may become affected by a high level of stress. Too much stress leads to an increase in the activity of the HPA-axis, which causes the release of cortisol – the stress hormone – which might permanently damage the hippocampus, the area of long-term memory [1]. Additionally, some specific genetic mutations cause the hippocampus to decrease in size and during research on twins it was observed that this is a favourable condition for provoking PTSD. The connection between the genetic basis and the development of PTSD may also be explained in terms of the involvement of individual genes

in the regulation of such areas as the amygdala, hippocampus, prefrontal cortex, HPA axis, and locus coeruleus, which is responsible for the production of noradrenaline. All of the above mentioned areas are crucial in triggering the anxiety reaction in the body, including in the course of PTSD [30-32]. To summarize the above analysis, there is some strong evidence which points out that monozygotic twins are likely to suffer from PTSD more often than dizygotic twins. Moreover, hippocampus abnormalities may contribute to susceptibility to PTSD.

The complexity of PTSD makes it multifactorial [33]. Taking into consideration the majority of mental disorders, the heritable part of PTSD can be regarded as polygenic. This means that various genes are considered to interact or to play an additional role in the disorder's onset. Broekman *et al.* have precisely reviewed molecular genetic studies relating to PTSD that were found in the literature such as Web of Science, Medline and Embase [3]. The authors took 8 major genotypes under investigation in connection with PTSD, which were the key candidate genes: the glucocorticoid receptor expression (GR), brain derived neurotrophic factor (BDNF), neuropeptide Y (NPY), serotonin transporter (also called 5-HTT and SERT), dopamine D2 receptor expression (DRD2, DAT), GABA receptors (which respond to neurotransmitter gamma-aminobutyric acid) and the apolipoprotein system (APOE2). Throughout the 10 years of research, the obtained results were inconsistent because many of them can be closely associated with the shortcomings of methodology and insufficient statistical power. One limitation that was present in the majority of the research is that the control group had never experienced the trauma. Admittedly, it is unknown if some might develop the disorder after being exposed to traumatic events. Certainly, the sample of the subjects and the control group in these studies were too small and could be affected by population bias.

The complicated aetiology of PTSD, includes the experiencing of a traumatic event itself, and makes it challenging to identify the substantial genes that may trigger the disorder. Specific interactions between various genes and between them and the environment seemingly make certain people more vulnerable to the development of PTSD. Stahl speculates that there is evidence that the genes regulating serotonin are involved in susceptibility to PTSD in response to various stressors [34]. Serotonin is a significant mediator of emotional disturbance which takes part in regulating HPA-axis. Even though the participation of serotonergic transmission in the pathophysiology of PTSD is still unknown, serotonin is considered to be engaged in the onset of PTSD symptoms relating to sleep, arousal and mood [3]. Evidence was found that changes in the gene cause higher sensitivity of individuals to stressful factors. According to Gross *et al.* the polymorphism of the 5-HTT transporter gene,

among humans and anthropoid apes, causes an increase in anxiety in the adulthood of patients who have already experienced a traumatic event before [35]. Additionally, promising results were obtained by Lee *et al.*, who investigated 100 patients from 11 collaborating centres, having a control group of 197 randomly selected individuals. This work showed that the short allele (ss genotype) was correlated with vulnerability to PTSD [36]. This causes a lower expression of a gene responsible for serotonin transport (5-HTT), leading to the lower cellular uptake of serotonin. It might be assumed that the higher frequency of the ss genotype is related to a decreased expression of serotonin transporter in the brain. This investigation, however, had some limitations. Firstly, the control and subject groups were only Korean individuals, so the general outcome should not be applied to other nations. On the other hand, females and males were examined in approximate proportion and the results thus refer to both genders. Moreover, all aspects of participation were explained to each person and participants' written consent was obtained. As far as the methodology is concerned, an interview was conducted, which on the one hand has the advantage that there is less risk of interview bias, as the interviewer is more likely to be objective, but on the other the validity might be threatened by the formality of the situation.

Other possible genes that may play a role in developing PTSD are the dopamine receptor (DRD2) and the dopamine transporter (DAT). According to Puglisi-Allegra and Cabib, genetically modified changes in dopamine release and dopamine receptor expression in mice were involved in behavioural abnormalities induced by chronic stress [37]. Other research involving humans showed that there was a certain correlation between the urinary excretion of dopamine, plasma dopamine and symptoms of PTSD [38]. This may indicate a substantial role of dopamine in the pathogenesis of PTSD. In the first study performed by Comings *et al.* the relationship between the DRD2 A1 allele and PTSD was found [39]. Nevertheless, Gelernter *et al.* did not confirm this correlation in a later study [40]. These discrepancies could have been due to selection bias, small size of the examined group and comorbidity (e.g. alcohol abuse). Young *et al.* reported that there is an association between the DRD2 A1 allele, however, only among those individuals who drank excessive amounts of alcohol daily [41]. To summarize, despite many studies that have already been done in reference to the dopamine receptor, dopamine transporter and the developing of PTSD, the results are still incompatible and require further studies.

It is assumed that GABA is involved in the pathogenesis of insomnia and anxiety, phenomena that also appear in PTSD. Weizman *et al.* argue, on the basis of the studies made on animals, that stress and anxiety may alter the GABA receptor. Moreover, clinical studies of human

subjects also support a correlation between changes in the GABA receptor function and anxiety [42]. Medicines active for the GABA receptor are effective in the treatment of anxiety disorder, which is present in patients with PTSD. The only study on this, conducted by Feusner *et al.*, displayed the potential links between GABA and PTSD. The study examined 86 veterans of the Vietnam War who met the criteria of PTSD [43]. However, there was a limitation to the study that the differences with regard to the symptom scores and any associations with a genotype might have been less prominent than if a more random group were studied, both with and without prior psychiatric diagnoses. Admittedly, the study could also compare the control group with the PTSD subjects. On the other hand, one of the strengths of this research is that the individuals with PTSD were not excluded even if they had a comorbid psychiatric disorder. This greatly reinforces the generality of the findings, as investigation of only 'pure' cases might not lead to a complete insight into the aetiology of a disorder. In conclusion, however, the research carried out so far does not provide specific evidence of a certain relationship between GABA and PTSD.

Mutations in genes which might lead to possible alterations in the developing brain may intensify sensitivity to environmental factors and initiate anxiety disorders. Nothing but stress in the early prenatal and perinatal stages of life may modify the expression of genes [44, 45]. Some studies have investigated mothers who were pregnant during the World Trade Center attack and who later developed PTSD. Yehuda *et al.* (2005) examined thirty-eight women and their infants as far as the level of salivary cortisol is concerned [45]. The findings showed a negative correlation between the maternal severity of PTSD and the level of salivary cortisol among infants. The babies of the mothers were found to have, just like their mothers, low levels of salivary cortisol. Thus it was suggested that during pregnancy some alterations caused by the stress-induced elevations may affect foetal brain development and, therefore, trigger permanent changes. According to Yehuda *et al.* the final results of the investigation were remarkably similar to the studies on Holocaust survivors [27]. This means that there was also a negative correlation between parental PTSD and urinary cortisol levels in adult offspring. All in all, the extent to which any risk factor for PTSD is connected with parental exposure, taking into account prenatal factors, is still unknown.

Interestingly, some authors suggest that temperament is a factor which modulates the connection between genes and PTSD development [46]. The research demonstrates temperamental differences between individuals battling against PTSD symptoms [47, 48]. Temperament-related traits such as perseverance or emotional reactivity play an important role in human behaviour, especially in situ-

ations which trigger intense excitement [49]. This stems from the fact that both nervous and hormonal mechanisms of those traits participate in regulating the level of excitement (activity) in an individual. They influence both its duration and the intensity of the changes. If this leads to the development of excessive excitement (stress) lasting for extended periods of time and if it remains unreduced either due to the lack of possibility or failure on the part of an individual, the course of this process may be of considerable significance to the pathogenesis of various psychological disorders [46]. It is worth noting that analyses which employ molecular techniques have revealed an association between temperament-related traits and polymorphisms in the genes of the dopaminergic (DAT1, DRD2, DRD3, DRD4, COMT) and serotonergic (5-HTT, 5-HTTLPR) systems [50-53].

AETIOLOGY OF PTSD – ENVIRONMENTAL FACTORS

Since time immemorial man has been exposed to various types of danger and stressors both environmental and those caused by human beings. The reaction of a person to the effect of a traumatic event is dependent on the power of the stress, the duration of the exposure to it and the individual's level of vulnerability. Undoubtedly, there are plenty of environmental factors that may contribute to the prevalence of PTSD. They consist of a diversified group of factors which may act separately or together, threatening not only human health but also life. For instance: natural disasters (tornados, tsunamis, earthquakes, hurricanes, floods and fires), manmade catastrophes (wars, terrorist attacks, kidnapping, rapes, plane crashes, car accidents), loss of the next of kin, solid-organ transplantation and even experiences of migration [7, 8, 54, 55].

During the last century there were many military conflicts, notably in Vietnam, Iraq, Afghanistan and Syria. Thousands of soldiers died, but also many became physically and mentally disabled. The stress that they had to face, in many cases, triggered PTSD [56]. There are over 2.3 million US veterans of the Afghanistan and Iraq wars, 20% of whom have been diagnosed with the disorder. Similarly, among Vietnam veterans (2.6 million) the prevalence of PTSD reached 18%. According to Lawson, the hallmark symptoms of PTSD were social withdrawal, combative behaviour and flashbacks [8]. Both these pieces of research involved thousands of people who were examined and their results are very similar, thus it can be said that the final findings are reliable.

Natural disasters result mainly from natural processes of the Earth. They are often unpredictable and have enormous economic, social, cultural and health conse-

quences. A report made by the International Red Cross and Red Crescent Movement estimated that between 1967 and 1991 7766 natural disasters were noted, which caused the death of more than 7 million people and were the reason for the occurrence of PTSD, which could persist for many years after [57]. For example, a study made by Flores *et al.* included 1012 adult survivors of the earthquake in 2007 in Pisco, Peru [7]. Patients who were investigated lived in the city's main 5 districts which, which were devastated. The overall prevalence of chronic PTSD was 15.9%, which was much higher than anticipated. Furthermore, Matsumoto *et al.* described the prevalence of PTSD among workers in earthquake- and tsunami-affected areas [58]. The Great East Japan Earthquake was the largest earthquake ever recorded in that country, and caused the tsunami and the Fukushima Daiichi nuclear disaster. 21,000 people died or went missing, but also 400,000 households were entirely destroyed. As a result, 5 months after the GEJE scientists evaluated PTSD symptoms among employees of small and medium enterprises in affected areas. The prevalence of likely PTSD in men and women employees was 14.3% and 24.4% respectively. The study was repeated after 14 months among people living in affected coastal areas, mainly local workers and hospital medical workers. The prevalence of probable PTSD among this group was 9.0% and 9.3% respectively. In general, the prevalence of PTSD 1-2 years after the natural disaster has been estimated as ranging between 3.7% and 60%. Another piece of research, conducted by Rubens *et al.*, examined internalizing disorders among young people exposed to Hurricane Georges who were somehow connected with peer violence [59]. The researchers concluded that exposure to hurricane and peer violence may be related to DSM-IV criteria. As a result, an interaction was found between exposure to the hurricane and peer violence that was significantly in accordance with the symptoms of PTSD.

Furthermore, Baranyi *et al.* intriguingly found some interactions between solid-organ transplantation (SOT) and PTSD [60]. Transplantations are usually high-tech medical procedures. However, as the study shows, operations themselves and intensive care units (ICUs) could be stressors which could arouse posttraumatic stress symptoms (PTSS). Taking statistics into account, 126 SOT patients were involved in the study, 15.1% of whom, after investigation, were found to have PTSS. There is speculation that PTSS after SOT can trigger compliance problems and decrease long-term survival. Nowadays, many people undergo solid-organ transplantations, thus SOT can be considered as one of many environmental factors which may provoke PTSD. The relatively large sample size (126 patients) improves the general ability of the findings. Moreover, two methods were used to carry out the investigation, i.e. an interview and questionnaires. This gives greater reliability to the final findings. The study was also

approved by the Institutional Review Board of the Ludwig-Maximilians-University of Munich and written consent was obtained from each participant.

Another research project investigated 281 Latino adolescent immigrants and their primary caregivers. Pre-migration poverty combined with illegal entry to the US increases the risk of trauma. According to a study conducted by Perreira and Ornelas, 29% of Latino adolescents and 34% of their primary caregivers experienced trauma during the migration process [61]. Among those exposed to trauma 9% of Latino adolescents and 21% of their primary caregivers were at risk for PTSD. What is more, as the study reports, post-migration discrimination and lack of approval from the neighbourhood intensified the risk for PTSD.

Last but by no means least, an environmental factor that may contribute to the development of PTSD is the type of job that people do. Goodwin noted in his study that some employees, such as police and fire officers, drivers, journalists, hospital and military personnel are exposed to intense traumas, and hence are at high risk for PTSD [62]. According to Saberi *et al.* in 2002 Iran had a higher rate of death related to road traffic collisions than any country in the world [55]. As a result, a study was performed which investigated 385 commercial motor vehicle drivers. 19.2% of the questioned met the PTSD criteria. The older the person was, and the longer their job experience, the higher the prevalence of PTSD was – and a familiar history of psychiatric problems also correlated here. The results of the study seem to be reliable; however, there are some significant limitations that make it less trustworthy. First of all, the research did not embrace any control group and this limits the final findings substantially. Secondly, the researchers had a limited possibility of applying psychiatric or psychological consultations so as to make a definite diagnosis of PTSD among all the patients they investigated.

Additionally, it is worth mentioning that many authors emphasize that the stressors resulting from human activities (aggression, violence, rape, terrorism, war) are likely to have a more traumatic impact than natural disasters [63]. On the other hand, post-trauma factors play a role in modulating PTSD symptoms. The research suggests that social support is a protective factor which contributes to the recovery from PTSD as well as to dealing with the trauma experienced.

CONCLUSIONS

In conclusion, it seems that PTSD has a complicated aetiology and pathogenesis. On the basis of the examined data, some genes, such as GABA, the serotonin 5-HTT transporter and the dopamine receptor (DRD2), were discovered to be possibly connected to susceptibility to PTSD. The acknowledgement of the influence of genetic factors on the development of PTSD is shown in many cases of monozygotic veteran twins. Interestingly, a positive correlation between females and vulnerability to PTSD has been found. It also has to be stated that environmental factors affecting pregnancy may trigger PTSD within infants, due to changes in the HPA-axis. Admittedly, experience of natural disasters, manmade catastrophes, stress connected with migration and some jobs might predispose people to the anxiety disorder. The majority of researchers, however, emphasize that environmental factors have a substantially greater impact on the susceptibility to PTSD. If a strong outside stressor is active for a genetically susceptible individual, it may, to a greater extent, trigger PTSD. Thus, the PTSD might be the result of both factors.

Owing to the plenty amount of research that has been done throughout many decades, much is already known about the aetiology and pathogenesis of PTSD. It is worth noting that the issue of determinants in the development of PTSD is often presented as multifaceted. The results of various studies pertaining to this subject (cross-sectional studies, longitudinal studies carried out before and/or after the occurrence of trauma) are limited and inconsistent, in that they employ different methodological frameworks. Nevertheless, it should be stressed that over recent years significant progress has been made in accounting for the aetiology of PTSD within a psychobiological model.

Despite this, there are still unresolved questions which require further studies. What is more, certain former ambiguities in this respect have found their reflection in the changes made in the categorization and conceptualization of this disorder, which were introduced in the latest versions of international diagnostic classifications (ICD-11 and DSM-V).

Conflict of interest/Konflikt interesu

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