REVIEW ARTICLE

Biopsychosocial approach to psychological trauma and possible health consequences

Jozef Hašto [1,2,5], Hana Vojtová [3], Radovan Hrubý [4], Peter Tavel [5]

[1] Psychiatric clinic, Pro mente sana, Trenčín/Bratislava, Slovak Republic; [2] St.Elisabeth University of Health and Social Sciences, Bratislava, Slovak Republic; [3] Psychiatric and psychotherapeutic daily clinic at the University hospital, Trenčín, Slovak Republic; [4] Psychiatric Outpatient Clinic, Martin, Slovak Republic; [5] Social Health Institute, Palacky University Olomouc, Czech Republic.

Correspondence to: Assoc. Prof. Jozef Hašto, MD., PhD., Psychiatric clinic, Pro mente sana, Pod Brezinou 84, 911 01 Trenčín, Slovak Republic. E-MAIL: j.hasto.tn@gmail.com

Reprinted from Int J Prenat Perinat Psychol Medicine 2013; **25**(3–4): 257–288.

Submitted: 2013-08-01 Accepted: 2013-09-11 Published online: 2013-12-28

Key words: **psychological trauma; trauma-related disorders; diagnostics; epidemiology; psychotherapy**

Act Nerv Super Rediviva 2013; **55**(4): 185–202 ANSR550413A06

Abstract

The diagnostic category of posttraumatic stress disorder (PTSD) has its place in the newest American diagnostic system DSM-V. The authors compare its definition with the former manual DSM-IV and the international classification ICD-10. They reflect difficulties in defining the concept of traumatic event. They summarize epidemiological findings, highlight the possible significant role of traumatogenesis in other psychiatric disorders without PTSD symptoms. The biopsychosocial model seems to be the most adequate for the study of trauma-related disorders, while in therapy the specific shaping of psychotherapy seems to be crucial. Good experiences in relationships before the trauma increase resilience and the availability of supportive empathetic relationships may favourably influence the development of the disorder and its therapy.

Introduction

Psychological trauma or repeated traumata can play an important role in the etiology of several mental illnesses. The most characteristic clinical picture resulting from a psychological trauma is described by both the international and American diagnostic systems as posttraumatic stress disorder (PTSD). According to epidemiological studies, incidence of psychological trauma in PTSD represents a serious medical and social problem.

In this short overview, we will first focus on the description of PTSD. In the second part, we describe and discuss the case of our patient. Using the bio-psycho-social model of mental illness, we will specially focus on its social aspects.

Eye Movement Desensitization and Reprocessing (EMDR) has been recognized an effective method of reprocessing the psychological consequences of traumatic experiences, especially PTSD. Since its discovery by Francine Shapiro it has been shown that not only eye movements, but also other kinds of bilateral stimulation (bilateral tactile or auditory stimuli) may be effective in trauma treatment.

In case of ongoing traumatization, EMDR as well as other exposure psychotherapeutic methods are considered contraindicated, relatively contraindicated or at least their use is considered complicated.

The Part II of this work is published: Hasto J, Vojtova H, Hruby R, Tavel P. Biopsychosocial approach to psychological trauma and possible health consequences. Part II - The case study. Int J Prenat Perinat Psychol Medicine. Vol. 25 No. 3-4, p. 289-322. (International Journal of Prenatal and Perinatal Psychology and Medicine ISSN 0943-5417).

Autogenic training (AT) is a rarely mentioned component of PTSD treatment. It is usually considered as a contraindication in acutely symptomatic patients.

In our case study, we illustrate a meaningful and effective use of both these methods in a treatment of patient with PTSD after type II trauma (repeated traumatization). EMDR was used to reduce the PTSD symptoms; AT to increase the resistance towards ongoing stressors.

The case has been closely related to recent social and political processes. Therefore, we considered it important to focus on the social level of the bio-psycho-social model of mental health and illness.

Diagnosis

PTSD diagnosis according to the International Classification of Diseases (ICD-10) (World Health Organization 2004) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association 2000/2010)

The diagnostic criteria in the ICD-10 and the DSM-IV are very similar (Smolík 2002). The ICD-10 code (World Health Organization 2004) for PTSD is F43.1. The diagnosis requires fulfilling 5 criteria, A–E:

A. The patient must have been exposed to a stressful *event* or situation (of either brief or long duration) of an exceptionally threatening or catastrophic nature, which is likely to cause pervasive distress in almost anyone.
B. There must be persistent remembering or *reliving* of the stressor in intrusive flashbacks, vivid memories or recurring dreams, or in experiencing distress when exposed to circumstances resembling the stressor.
C. The patient must exhibit an actual or preferred *avoidance* of activities and situations reminiscent of the trauma.
D. Either of the following must be present:
   1. *Inability to recall* either partially or completely some important aspects of the period of exposure to the stressor, or
   2. Persistent symptoms of *increased* psychological *sensitivity and arousal* by difficulty falling or staying asleep, irritability or outbursts of anger, difficulty concentrating, hypervigilance, and exaggerated startle response.
E. Criteria B, C and D must all arise within 6 months of the period of stress. However, a delayed onset is possible, too.

The DSM-IV-TR (APA 2000/2010) and ICD-10 criteria (WHO 2004) for diagnosis of PTSD are similar. The DSM-IV criteria are, however, more precisely formulated, and there are also some differences. For example, the DSM-IV defines a traumatic event (criterion A) as "*exposure to*, *witnessing* or *learning about* an event or events that involve actual or *threatened death* or *serious injury* or *other threat to one's physical integrity* or the physical integrity of another person. The person's response to the event must involve intense *fear*, *helplessness* or *horror*. There is a possibility of illusions, hallucinations, and dissociative flashbacks, especially after waking up or when intoxicated (criterion B). Further symptoms may include (criterion C) diminished interest or participation in significant activities, feelings of detachment or estrangement, restricted range of affect (e.g. inability to have loving feelings), and sense of foreshortened future (e.g. no expectations to have a career, marriage, children or a normal life span). The symptoms should last more than one month (criterion E). In the DSM-IV-TR, there is also criterion F: The disturbance causes

Tab. 1. PTSD criteria according to DSM-IV (APA 2000/2010) and ICD-10 (WHO 2004).

Criteria	DSM-IV	ICD-10
Criteria of a traumatic event	• A1: Event or events that involved actual or threatened death or serious injury, or a thread to the physical integrity of self or others. • A2: Person's response involving intense fear, helplessness, or horror	A stressful event or situation of exceptionally threatening nature which would likely cause pervasive distress in almost anyone
Sufficient symptoms	Symptoms from following areas: • B: Intrusions (at least one) • C: avoidance / emotional numbness (at least three) • D: autonomous hyper-arousal (at least two)	Persistent remembering or reliving of the stressor in intrusive flashbacks, vivid memories or recurring dreams
Duration of the symptoms	E: At least four weeks; acute: 1-3 months; chronic: 3 months and longer	No specifications
Onset of the symptoms	E: No specifications. Delayed onset when at least six months have passed between the stressor and the onset of the symptoms	Within six months of the period of stress
Clinical impairments	F: The disturbance causes clinically significant impairment in important areas of functioning	No specifications

clinically significant *distress* or *impairment* in social, occupational or other important areas of functioning.

After an extensive debate about trauma related disorders in the last couple of years, DSM-V has not brought a significant shift in understanding PTSD, nevertheless, there are differences worth mentioning. Moving the PTSD diagnosis from Anxiety Disorders to the chapter Trauma and Stressor-related Disoders represents a step toward more etiology-informed approach. Another important progress is in inclusion of the dissociative subtype of PTSD as proposed by Lanius *et al* (2010).

The criterion A is more precisely defined and leaves out the intense emotional reaction to the event: "Exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways:

1. Directly experiencing the traumatic event(s).
2. Witnessing, in person, the event(s) as it occurred to others.
3. Learning that the traumatic event(s) occurred to a close family member or friend, the event(s) must have been violent or accidental.
4. Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g. first responders collecting human remains; police officers repeatedly exposed to details of child abuse).

Note: Criterion A4 does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work related." (APA 2013, 271).

As a part of the intrusions criteria B, acting or feeling as if the trauma was reoccurring is named "dissociative reactions" and may be presented in a continuum up to complete loss of awareness of present surroundings.

Criterion C includes exclusively avoidance and other symptoms are transferred to criterion D "Negative alterations in cognitions and mood…" (APA 2013, 271) with additional "2. Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world… 3. Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others. 4. Persistent negative emotional state (e.g. fear, horror, anger, guilt or shame)… 7. Persistent inability to experience positive emotions…" (APA 2013, 272). In criterion E self-destructive behavior was added.

Dissociation has become an important concept in psychotraumatology, assisting the understanding of the origins and dynamics of posttraumatic reactions and it´s been a part of the discussion for the new diagnostic manual, nevertheless its definitions are ambiguous and stem from various different theoretical backgrounds. The DSM´s approach has always been descriptive and DSM-5 includes a possibility of further specification of PTSD with dissociative symptoms, either depersonalization, or derealization.

The whole subhead is dedicated to PTSD for children 6 years and younger.

Problematic definition of a traumatic event in posttraumatic stress disorder (PTSD)

According to the DSM-IV-TR, the person's response to a traumatic event must involve intense fear, helplessness or horror. These reactions can be observed in most typical cases. These criteria, however, do not allow diagnosis of PTSD in cases of dissociative amnesia, or when the predominant acute response of the person involved stupefaction, indifference or derealisation. Another problem arises when the patient displays typical symptomatology, but the traumatic event was not of an exceptionally catastrophic nature. These problems have been taken into account in the new DSM-V definition.

Mol *et al* (2005) compared the incidence of PTSD symptoms in people experiencing a traumatic event according to the DSM-IV, and those experiencing a stressful life event not fulfilling the A1 criterion according to the DSM-IV. The authors included serious illness, a chronic illness of a close person, and problems related to work and relationships. They found that PTSD symptoms were more frequent in people experiencing a stressful life event within the last 30 years, although this event did not fulfill the A1 criterion (DSM-IV).

In clinical practice, one often distinguishes between type I and type II trauma (Terr 1991). Type I trauma refers to a single traumatic event of a brief duration; type II trauma describes long-lasting and/or repeated traumatization. One possible reaction to type II trauma is the "complex PTSD" (Herman 2001) or so called disorder of extreme stress not otherwise specified (DES-NOS) (Luxenberg *et al* 2001). This disorder has not yet been included in diagnostic manuals. It can partially overlap with borderline personality disorder (F60.3) or the "enduring personality change after catastrophic experience" (F62.0) according to the ICD-10 (WHO 2004).

Psychoanalytically oriented authors have used the term trauma/psychological trauma in a broader sense, meaning, for example, *emotional overload*. This was even before traumatic event was defined in the DSM-III, IV and ICD-10. Similarly, the term neurosis was broader and did not describe only neurotic disorders as we know them today, but also syndromes like PTSD, adjustment disorders, and personality disorders, especially those in the B cluster (anxious personality disorder).

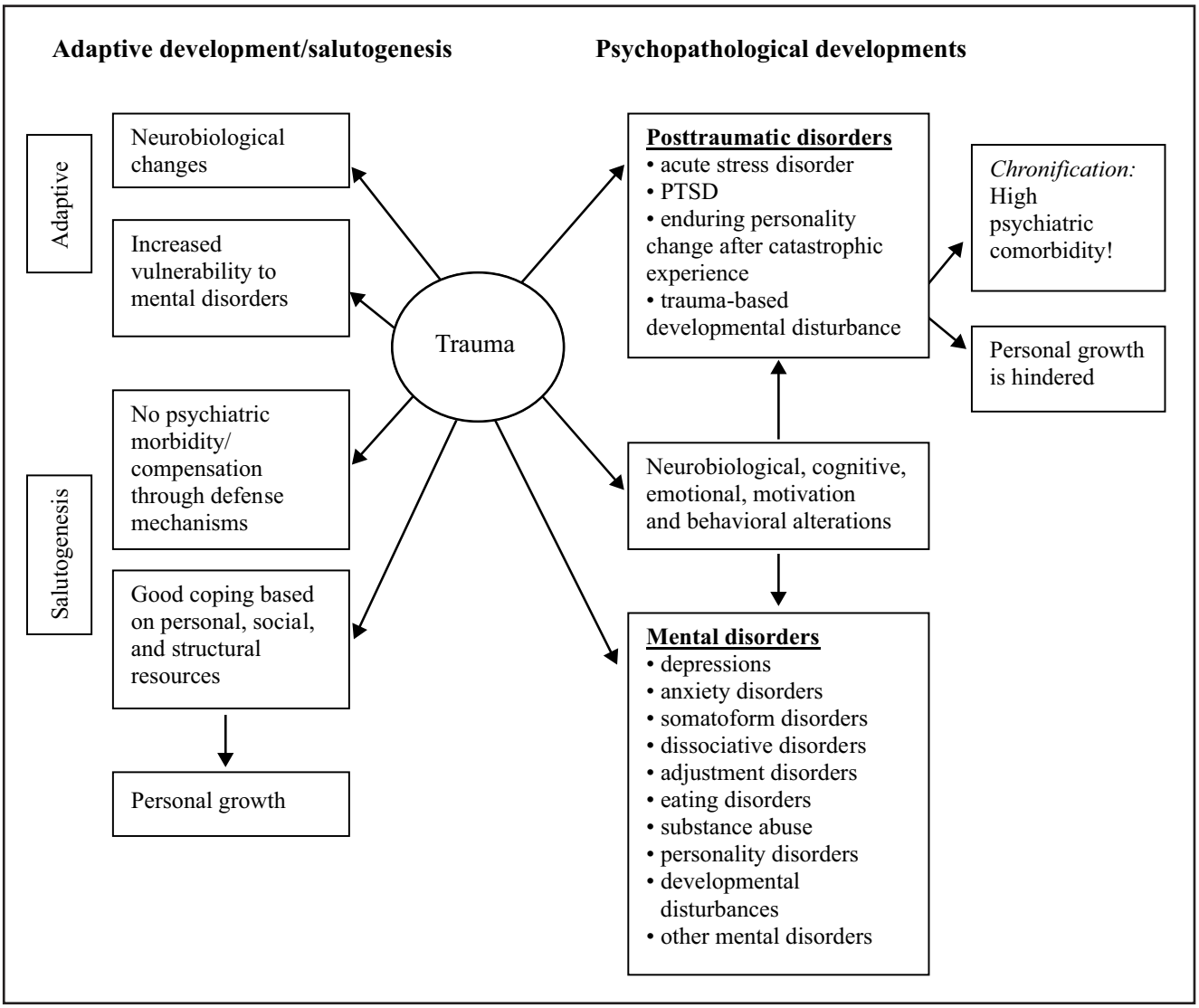
In his encyclopedic monograph mapping the development of dynamic psychological approaches, Leonhard Schlegel (2005) writes about trauma: "In dynamic psychology, trauma does not mean only an acute, shocking event. Neuroses stem, rather, from long-lasting conflict situations – a longstanding pressure of a ruthless upbringing etc. Therefore, 'chronic traumas' are of a much bigger importance. Even in situations in which single experiences appear as significant traumatic events, they can contain a symbolization of a prolonged stress. I define a psychological trauma leading to neurotic disorders as an *emotional overload* (p.30)."

In childhood, physical and emotional neglect are as harmful as sexual, physical, and emotional abuse. The long-standing effects of emotional cruelty and neglect on neurobiology and mental health might even be more significant than those of physical abuse (Teicher *et al* 2006).

Variety of posttraumatic reactions and course of PTSD

Several clinical pictures may arise as a consequence of experiencing a traumatic event. This remains true even if we define trauma according to the current diagnostic criteria. A traumatic event may lead to an acute stress reaction and consequently to PTSD. A traumatic event may also lead to a picture similar to the adjustment disorder (F43.2, F43.8). A trauma might, however, also lead to a depressive episode, an anxiety disorder, somatization disorder, substance dependency or a dissociative disorder, either directly, or through an adjustment disorder or a PTSD (Flatten *et al* 2013). The further development may contain personality alteration (aforementioned "complex PTSD"). Type II trauma in young age may play an important role in etiology of a personality disorder (borderline) (Wöller 2006). In these cases, trauma is diagnosed as one of the factors influencing health status and coded with a Z code according to the ICD-10. Comorbidity with other psychiatric disorders is common. According to various authors, the comorbidity rates are up to 80%.

Several studies have found that up to 50% of patients experiencing *acute psychosis* later show symptoms similar to PTSD as a reaction to the experience of helplessness and disintegration (Flatten *et al* 2013). We consider this finding important for clinical practice and therapy planning for psychotic patients. In his study of 208 patients suffering from schizophrenia, M. Bleuler (1978) found secondary pathogenic influence of the psychotic experience that can even lead to a personality change. In the ICD-10 (WHO 2004), this is categorized as F62.1. Furthermore, according to Bleuler (1978),



Scheme 1. Possible developmental courses after a traumatic event (copyright Tagay *et al.* 2011).

schizophrenic illness tends to have a worse course in patients coming from broken homes where serious traumatization can be assumed.

Apart from all aforementioned pathogenetic factors of trauma, in some cases, thankfully, mental health is preserved in spite of a trauma. Trauma either does not lead to a mental disorder, or a subsequent mental disorder ends with a full remission (salutogenesis). Furthermore, as our clinical experience teaches us, a psychological trauma might lead to a seemingly paradoxical personality development, deepening and broadening of the consciousness, increase in responsiveness to human suffering, improvement in the ability to protect oneself and the others from traumata, and willingness to help with their processing. A person unfolds an altruistic mode of mind and behavior and expands the ability to mentalize.

Various possibilities of coping with a trauma are shown in the following scheme (Tagay *et al* 2011).

As a result of trauma diverse life trajectories may emerge varying from resignation and mere surviving through recovery up to personal growth that is not just a way of adaptive coping with traumatic experience, but adds an extra value to the life and personality of the survivor. The concepts of posttraumatic growth provide an alternative to the prevailing problem-focused attitudes in mental health system (Mareš 2012).

Epidemiology of PTSD

Kessler *et al* (1995) studied both point and lifetime prevalence of PTSD in a representative sample of 6000 subjects. The study was conducted in the USA. The lifetime prevalence was 10.4% in women and 5% in men; the point prevalence in the last month was 2.8% (average women and men). However, approximately 51% women and 61% men in the study experienced a stressor corresponding to the DSM-IV criteria. Therefore, most people experiencing trauma do not develop PTSD; they recover spontaneously. On the other hand, 17% men had intrusive memories, but the traumatic event did not fulfil the DSM-IV criteria. In some cases, a *subliminal* PTSD arises, meaning that symptoms do not reach the diagnostic threshold. Another possibility is *partial* PTSD, when after a traumatic event, the person experiences symptoms which are not otherwise typical of PTSD. In some of these cases, the symptomatology might lead to severe impairment in important areas of functioning. In a study focusing on 185 fire and car accident victims, 22.7% fulfilled the criteria of a PTSD, but another 16.7% with partial PTSD fulfilled the F criterion referring to the impairment in everyday functioning (Mylle & Maes 2004).

In Germany and in Europe, the lifetime prevalence in people younger than 65 years is 1–3%. In German population older than 65 years, the lifetime prevalence is threefold higher. This is due to World War II experiences (Frommberger & Maercker, in Vorderholzer & Hohagen 2011).

Psychological traumatization of "children soldiers" leads to a PTSD in only about 20% of cases. The longer they participate in fighting, the smaller this percentage. "Children soldiers" are approximately eight-year-old boys kidnapped by the rebels and trained to kill, as it often happens in some African countries, but also in Asia and South America. By contrast, PTSD was found in 80% of refugees from Sudan. Apparently, "children soldiers" learn to view killing as an "exciting activity". According to Elbert (2009), they switch to a "hunter mode". They need to see blood and hear the cries of the dying. They are cutting off their ears, noses or extremities. Some of them become cannibals.

In a psychiatric and psychotherapeutic hospital in Germany, the therapists (psychiatrists, physicians with training in psychosomatics or clinical psychologists) considered trauma as a reason for mental disorder in 31.5% of patients. This group included all PTSD patients, 12% of patients with an affective disorder, 26% of anxiety disorders patients, and 19% of patients with a personality disorder. In a questionnaire assessing psychotraumatic events, these patients listed 6 and more events (Ungerer *et al* 2010).

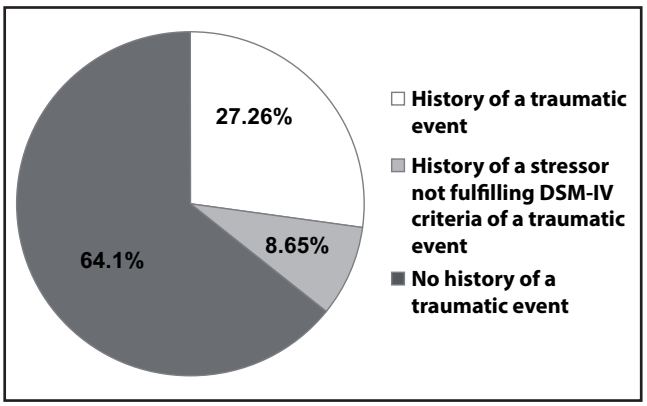


Fig. 1. Traumatic event incidence (%) in the total sample of N=532 patients.

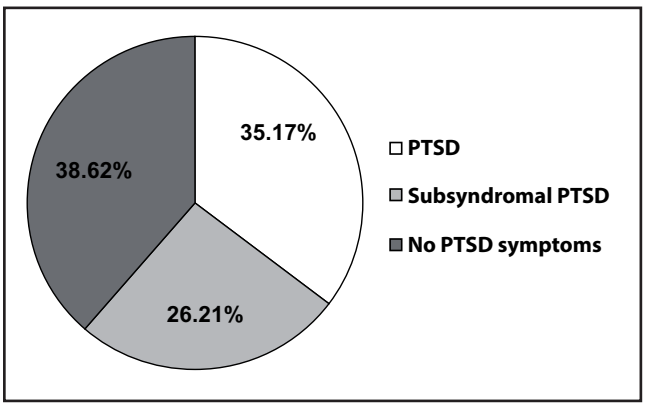


Fig. 2. Psychological traumata (N=145; 27%) and PTSD or subsyndromal PTSD in the group of patients with a history of psychological trauma.

In our hospital in Trenčín, Slovakia, we assessed all patients hospitalized in the first half of 2004. The assessment included the structured clinical DSM-IV interview focusing on psychological trauma and PTSD (Wittchen *et al* 1997). The total number of patients admitted to the ward was 577. Out of these patients, we assessed 532. Those not assessed included mostly patients with various types of dementias. A history of a traumatic event was found in 27%. In 8%, we found a serious stressor not fulfilling the DSM-IV criteria of a traumatic event. 64% of patients did not indicate a traumatic event in their history (Figure 1). PTSD was found in 35% of patients listing a traumatic event in their history, and subliminal PTSD was found in 26% of those patients. In 38.6% of patients, no symptoms of PTSD were found, although they had a history of a traumatic event (Figure 2). We did not assess possible time and content relationships between psychological traumatization and other psychiatric syndromes than PTSD. The highest comorbidity was found between PTSD and depressive disorders (Hašto *et al* 2011).

One week after psychological trauma, PTSD is found in 94% of adult patients. Three months after a traumatic event, PTSD is found only in 47%. After years, PTSD is found in 10–25% of people experiencing a psychological trauma (summarized according to Frommberger & Maercker, in Vorderholzer & Hohagen 2011). These data show that although a considerable number of people heal spontaneously, there is a relatively high risk of chronification of untreated PTSD. In some samples, a chronic PTSD was found in 25% of people with a history of a psychological trauma.

Risk and protective factors

Following factors have been identified to play a role in development of PTSD: *subjective experience of loss of control*, anticipated negative consequences on person's own health and future, event intensity and duration, physical injury or an injury or death of another person. Other risk factors include: insufficient familial and social support, female gender, experience of early separation, and former somatic illness (Frommberger & Maercker, in Vorderholzer & Hohagen 2011). Although these risk factors do statistically increase the probability of PTSD development, according to the same authors, in individual cases PTSD does not develop even when these factors are present. On the contrary, a PTSD after a serious trauma may develop even in a person with stable personality and no risk factors!

Several studies have found that up to 50% of patients experiencing *acute psychosis* later show symptoms similar to PTSD as a reaction to the experience of helplessness and disintegration (Flatten *et al* 2013). We consider this finding important for clinical practice and therapy planning for psychotic patients. In his study of 208 patients suffering from schizophrenia, M. Bleuler (1978) found secondary pathogenic influence of the psychotic experience that can even lead to a personality change. In the ICD-10 (WHO 2004), this is categorized as F62.1. Furthermore, according to Bleuler (1978), schizophrenic illness tends to have a worse course in patients coming from broken homes where serious traumatization can be assumed.

Serious dissociative symptoms are an interesting aspect of posttraumatic symptomatology. They can occasionally resemble or even equal psychotic experiences including Schneider's first rank symptoms (thought insertion, flashbacks escalating to hallucinations, voices representing dissociated parts of the personality, feelings of being influenced by external agents). They represent a real challenge for the differential diagnosis (Moskowitz *et al* 2008).

Some findings suggest that early psychological traumatization might influence manifestation, course and symptomatology of bipolar affective disorder including suicidality and functioning between the episodes (Etain *et al* 2008).

Factors indicating diminished risk of PTSD include stability prior to the trauma, ability to mobilize individual resources and problem coping strategies from the past, introspection, and "sense of coherence" according to Antonovsky. A developed sense of self-efficacy, active engagement of personal problems rather than avoidance, and an ability to share difficulties are positive prognostic factors (Flatten *et al* 2013; Frommberger & Maercker, in Vorderholzer & Hohagen 2011). The ability to share difficulties might be connected to secure attachment style (Hašto 2005).

Finally, it goes without saying that *respect for the victim and her trauma* reduces the risk of chronic PTSD (Frommberger & Maercker, in Vorderholzer & Hohagen 2011)!

There are only a limited number of ways to prevent the onset of PTSD after a traumatic event. The efficacy of psychological interventions remains questionable (Frommberger & Maercker, in Vorderholzer & Hohagen 2011); further studies might confirm the effectiveness of certain techniques elaborated by cognitive-behavioral therapists. Benzodiazepines are commonly prescribed for the acute adjustment disorder, but it is probably contra productive, as higher PTSD and depression incidence has been found in people treated with benzodiazepines in comparison with control groups (Frommberger & Maercker, in Vorderholzer & Hohagen 2011). According to our knowledge, prophylactic treatment with other psychotropic drugs has not yet been fully explored.

Biology of PTSD

In each mental disorder or predisposition to a mental disorder, the considerations of the biological aspects should include evolutionary considerations, as was suggested, for example, by Nesse and Brüne. *Evolution* created us to be social creatures, but at the same time

vulnerable. Chances of survival and reproduction are higher when we are alert to potential threats, including those inside our social group. In the course of human evolution, neuroanatomical structures involved in evaluation of potentially dangerous situations have become bigger. In normal circumstances, it is advantageous to have mechanisms enabling us to make use of previous experience to avoid present or future risks. In PTSD, this mechanism is pathologically hyperactive, and it inhibits rather than supports adaptive reactions (Brüne 2012). The more extreme the traumatic event and the more the individual was made sensitive by previous (micro?) traumata and/or the higher the genetic vulnerability, the easier it is for this mechanisms to become pathologically unbalanced.

Baldwin (2013) in his extensive synthesizing review about psychobiological base of posttraumatic symptomatology characterizes experiential and somatic-vegetative aspects of defensive states that represent primitive automatically activated reactions to various degrees of perceived threat. The knowledge of these defensive states provides a helpful background for traumatherapy. He distinguishes between freeze-alert, flight and flight, freeze-fright and collapse.

Neuroanatomical models of PTSD traditionally involve amygdothalamic pathways with hyperactivation of amygdala, which afferents to other regions (hypothalamus, brain stem nuclei), the hippocampus and frontal cortical areas (Stein & Rauch 2008). The fear conditioning model is obviously used to conceptualize the neurobiology of PTSD with the help of three primary/basic neuronal systems investigation – the hypothalamic-pituitary-adrenal axis, the locus coeruleus-noradrenegic system, and neurocircuitry interconnecting the limbic system and frontal cortex (Skelton *et al* 2012).

Neurochemical studies in subjects with PTSD consistently show increased noradrenergic function and increased norepinephrine levels, dopaminergic sensitization with increased dopamine levels, as well as functional changes in the serotonin system with decreased concentrations of serotonin in the medial and dorsal raphe (Sherin & Nemeroff 2011). Since norepinephrine (NE) is involved in many crucial autonomic system regulations, stress responses, arousal and emotional memory processing, it is hypothesized that abnormal regulation of noradrenergic brain system is markedly employed in the pathophysiology of PTSD (Krystal & Neumeister 2009). Majority of norepinephrine is produced by neurons in the locus coeruleus, which afferents to a lot of brain areas including the amygdala, hippocampus, hypothalamus, prefrontal cortex, and others. Chronic exposure to stress leads to increase of NE transporter expression in the prefrontal cortex and it is suggested this could be an adaptational mechanism to restore the neurochemical balance in the prefrontal cortex. Thereby manifestations of NE transporter abnormalities could be important markers for identifying and subtyping patients with PTSD and treatment strategies. For noradrenergic neuromodulation, an interaction between the polymorphism of gene GABRA2 and the occurrence of PTSD was described. Moreover, interaction between the number of traumatic events and Val (158) Met polymorphism of the gene coding for catecholamine-o-methyltransferase has also been found. Because of multiple effects through complex mechanisms, norepinephrine is thought to be responsible for some of the classic PTSD symptoms, including hyperarousal, heightened startle, and increased encoding of fear memories (Strawn & Geracioti 2008; Krystal & Neumeister 2009; Sherin & Nemeroff 2011; Auxéméry 2012). Despite dopaminergic system dysbalance was repeatedly found in patients with PTSD, the exact role of dopamine (DE) in pathopysiology of PTSD remains unclear. There is evidence in humans that exposure to stressors induces mesolimbic DE release, which in turn could modulate HPA axis responses. Moreover, the A1 allele coding the type 2 dopaminergic receptor is

Tab. 2. Defense states.

Safety	No threat	Relaxed, at ease; myorelaxation; HR 60-80, high HRV; VVC dominant, SNS varies; social engagement
Freeze-alert (stillness)	Threat exceeds coping capacity	Alarm, wariness, early fear; muscles stiff, tense; able to move quickly, if needed; HR above 85-90; VVC decreased, SNS activated;
Flight (active)	Threat might be manageable	Fear or panic; impulse to run; hands cold; leg movements; fast respiration, sweating; HR>100; strong SNS activation
Fight (active)	Threat might be manageable	Anger, aggression or with anxiety; impulse to hit, kick, scream; hands warm; shoulders, arms, jaws clenched, tense; adrenal activity; fast respiration, sweating; HR>100; strong SNS activation
Freeze-fright (immobile)	Inescapable threat	Fear or terror; hypervigilance; tonic paralysis, scared stiff; stomach tension; HR~100, pounding; fast, shallow intercostal breathing; both SNS and DMX strongly activated
Collapse (immobile)	Inescapable threat, no other defensive option available	Hopelessness, giving up, shame; detached, trance-like state; numbness, analgesia (endogenous opioids); flaccid immobility; HR≤60; shallow slow breathing; death feigning; sharply reduced SNS, strong DMX; syncope or death risk

(Table adapted after Baldwin, 2013, p.1560; HR=heart rate, HRV= heart rate variability, VVC=parasympathetic ventral vagal complex, SNS=sympathetic nervous system, DMX=parasympathetic dorsal vagal motor nucleus).

associated with a severe comorbidity of PTSD with the presence of somatic disorders, anxiety, social change and depression (Sherin & Nemeroff 2011; Auxéméry 2012). Serotonin (5HT) neurons originate in dorsal and medial raphe nuclei and afferent to various brain areas, including the amygdala, hippocampus, hypothalamus, and prefrontal cortex. It is hypothesized that serotonin system is markedly involved in the pathophysiology of PTSD via different mechanisms. The stress induced alterations in 5-HT activity occur in multiple brain regions, which are involved in the pathophysiology of PTSD, including the amygdala, ventral striatum and the prefrontal cortex (Krystal & Neumeister 2009). The 5HT neurons of the dorsal raphe probably mediate anxiogenic effects through $5HT_2$ receptors with projections to the amygdala and hippocampus. On the other hand, 5HT neurons from the median raphe are suggested to mediate anxiolytic effects, facilitate extinction and suppress encoding of learned associations via $5HT_{1A}$ receptors. Chronic exposure to stressors induces upregulation of $5HT_2$ and downregulation of $5HT_{1A}$ receptors in animal models. Experimental studies have also shown that 5-HT_{1B} receptors displayed role in models producing adaptive versus maladaptive responses to stress (Krystal & Neumeister 2009; Sherin & Nemeroff 2011). Activation of the 5-HT_{1A} receptor exerts a hyperpolarizing effect on cortical neurons whereas activation of the 5-HT_{2A} receptor is depolarizing. Activation of 5-HT_{2A} receptors results in glutamate release from thalamocortical afferents and increased levels of glutamate reduces neural, vascular, and glial trophic factors which, in combination with direct glucocorticoid effects, contribute to disruption of neurogenesis, and even neural death, in limbic and cortical brain regions (Hoebel *et al* 2007). The 5-HTTLPR (promoter region of SLC6A4 encoding the serotonin transporter) constitutes a genetic candidate region that may modulate emotional responses to traumatic events. The interaction between variation at the 5HTTLPR and stressful life events could predict depression and PTSD. Based on the current knowledge it is hypothesized that 5HT system dysregulation may contribute to symptoms of PTSD including hypervigilance, increased startle, impulsivity, and intrusive memories (Krystal & Neumeister 2009; Sherin & Nemeroff 2011; Auxéméry 2012). And the crosstalk between monoaminergic systems is taking the special importance. It is known that increased NE stimulates 5-HT and DE release, and 5-HT release at NE neurons reduces NE release. Moreover, blockade of the NE transporter can reduce the uptake of DE in the frontal cortex since the NE transporter has high affinity for dopamine. There is growing body of evidence showing that plastic changes in the limbic areas of monoamine neuron projections are important in the neurobiology of PTSD. It appears that the behavioral effects of NE, 5-HT, and DE have considerable overlap such that augmenting levels of any one may have treatment enhancing effects, and increasing synaptic levels of more than a single neurotransmitter may be synergistic (Krystal & Neumeister 2009). Glutamate plays a critical role in hippocampal dependent associative learning and in amygdala-dependent emotional processing in stressful conditions. Inappropriate glutamate transmission therefore could contribute to the processing distortion experienced by many patients suffering from PTSD (Martin *et al* 2009). Contrary to glutamate action, γ-Aminobutyric acid (GABA) exerts inhibitory effects in CNS. It is known to have anxiolytic effects and stress responses reducing action, in part by inhibiting the corticotropin-releasing hormone (CRH)/NE circuits involved in mediating fear and stress responses. It is suggested that GABA system dysregulation with impairment of GABA receptor´s function could participate in PTSD pathophysiology (Sherin & Nemeroff 2011). Another interesting finding is that the neuropeptide Y (NPY), polypeptide found in the locus coeruleus, hypothalamus, septum, periaqueductal grey, hippocampus, amygdala, and brainstem, is probably also employed in the pathophysiology of PTSD. NPY has been shown to be involved in fear consolidation, involving studies showing that administration of NPY impairs retention of traumatic memories, reduces anxiety during stressful actions, and enhances extinction of fear-potentiated startle (Gutman *et al* 2008; Krystal & Neumeister 2009). Human studies in combat veterans showed that combat exposed veterans without PTSD had higher NPY levels than non-combat-exposed veterans, but comparable to combat-exposed veterans with PTSD. They also reported that those veterans with past PTSD had higher plasma NPY than those without past PTSD suggesting that plasma NPY levels may represent a biologic correlate of resilience to or recovery from the adverse effects of stress exposure (Yehuda *et al* 2006). Based on this knowledge it is hypothesized that whereas NE mediates the fight and flight response to stress, NPY may have a role in dampen the impact of NE and may therefore be a system of interest for the development of novel treatment approaches in PTSD (Krystal & Neumeister 2009). Also CRH exhibits important anxiety-related effects in CNS. Stimulation of CRH_1 receptors is thought to be involved in facilitating stress response and anxiety, while activation of CRH_2 receptors appears to be responsible for reducing stress reactivity. Animal models suggest that increased CRH activity may promote certain of the cardinal features of PTSD, such as conditioned fear responses, increased startle reactivity, sensitization to stressor exposure, and hyperarousal (Sherin & Nemeroff 2011).

Other typical finding replicated in many studies in subjects with PTSD is HPA axis dysregulation with decreased plasma levels of cortisol, increased glucocorticoid receptor responsiveness and sustained increased levels of CRH. Especially decreased cortisol levels have been considered as a curious feature that is contrary to findings in other anxiety disorders or depression, and lower plasma cortisol may correspond with greater

symptom severity. It is hypothesized that decreased availability of cortisol, as a result of or in combination with abnormal regulation of the HPA axis, may promote abnormal stress reactivity and fear processing in general (Martin *et al* 2009; Sherin & Nemeroff 2011). Moreover, the crosstalk between the catecholamine system and steroids must be taken into account. It is known that NE and epinephrine by increasing the sensitivity of glucocorticoid receptors to ligand activation could alter symptoms of PTSD. There is evidence for a feed-forward circuit connecting the amygdala and hypothalamus with the locus coeruleus, in which CRH and norepinephrine interact to increase fear conditioning and encoding of emotional memories, enhance arousal and vigilance, and integrate endocrine and autonomic responses to stress. A relative lack of baseline cortisol at the time of a psychological trauma may facilitate overactivation of the central CRH-NE cascade, resulting in enhanced and prolonged stress responses (Krystal & Neumeister 2009; Sherin & Nemeroff 2011). It is hypothesized that alterations in CRH signaling and the HPA axis could result from insufficient glucocorticoid signaling caused by decreased hormone bioavailability or from decreased hormone receptor sensitivity (Raison & Miller 2003).

The persistent need of organism to maintain homeostasis and equilibrium is based on the mutual interplay of three interrelated physiological systems: the nervous, immune, and endocrine systems. This interplay is a kind of highly coordinated system of crucial regulations and integration with multi-level interactions and influences of neuromediattors, neuropeptides, cytokines, hormones, and other molecules, where each of the systems could influence other in physiological or pathophysiological way (Fedor-Freybergh 1999). Because of this persistent interplay, the neuro-endocrine-immune system is continuously modulated through the effects of various molecules. Consequently, neurotransmitters, hormones and cytokines, when occurring in unphysiological concentrations, and various toxic agents, can be effective as endogenous malorganizers and result in life-long functional disturbances and diseases or important factors modulating neuronal circuits during brain development and maturation (Fedor-Freybergh 1999; Fedor-Freybergh & Maas 2011; Fujisawa *et al* 2012; Fedor-Freybergh 2013). It is hypothesized that PTSD could represent the condition in which a considerable neuro-endocrine-immune system´s dysregulation occurs. It is clear that there are immune and endocrine alterations associated with PTSD. For most of the findings, there are some studies showing a trend in one direction with others showing no difference. Thus, trends are found for an increase in pro-inflammatory cytokines, enhanced delayed-type hypersensitivity (DTH) – reflecting cell-mediated immunity, decreased proliferation to mitogen PHA, and increased antibody titers to latent viruses. Some of these findings are consistent with enhanced immunity, whereas others are consistent with poorer immunity, such as decreased proliferation to PHA or increased antibody titers to latent viruses, suggesting poorer control of latent viruses. Alterations in enumerative immune measures have also been found, the most notable of which are increases in leukocytes, lymphocytes, and T-cells. Some of studies of linkages of immune alterations in PTSD with specific diseases have brought interesting findings. Based on this findings, it is hypothesized there is a potential link between altered cytokines and diseases that are more prevalent in PTSD, such as inflammatory and autoimmune disorders. On the other hand, glucocorticoid signaling and impaired feedback regulation, resulting in immune activation/inflammation, may in turn contribute to stress-related pathology, including alterations in behavior, insulin sensitivity, bone metabolism, and acquired immune responses. The alterations in the HPA axis and the sympathetic-adrenal-medullary (SAM) system are thought to be markedly involved in the interaction with immune system dysregulation in PTSD patients. It is suggested by findings which indicate association of PTSD with autoimmune and inflammatory diseases regulated by the immune system. For example, studies have found severe trauma/PTSD to be associated with increased rates of coronary heart disease, gastrointestinal disorders, autoimmune diseases such as rheumatoid arthritis, psoriasis, diabetes, and thyroid disease, musculoskeletal problems, asthma and other respiratory problems (reviewed by Ironson *et al* 2007).

The heritability for PTSD has an estimated range of 30% to 40%, probably resulting from a variety of genes, each with relatively small contributions to the genetic predisposition for this disorder (Martin *et al* 2009). Several genes are recognized as promising candidate genes significantly employed in the genes-environment interplay in the pathophysiolofy of PTSD. A complex-repeat polymorphism in the region of SLC6A4, the gene encoding the serotonin transporter (serotonin transporter-linked polymorphic region, 5-HTTLPR) has been studied in numerous studies, especially those related to stressful life events. The short SERT allele (serotonin transporter) has been shown to interact with stressful life events (including abuse in childhood) to increase the risk for depression later in life. This polymorphism recently has been shown to play a role in the genetic underpinnings of PTSD. Also genes interacting with early-life stress also are strong candidates for influencing susceptibility for PTSD. Preclinical studies indicate that the persistent hyperactivity of the HPA axis associated with early-life stress is mediated by a hyperactive CRH system, with chronic overactivity of CRH_1 receptors in limbic brain regions. As another important candidate gene in trauma-related HPA axis disturbances was recognized gene for FKBP5 (a co-chaperone of heat shock protein 90, which plays a role in regulating the expression of glucocorticoid-responsive genes). Single nucleotide polymorphisms of FKBP5 are hypothesized

to be involved in development of PTSD and to alter the impact of early trauma or PTSD on glucocorticoid receptors. Also gene for catechol-o-methyltransferase (COMT) was studied for functional polymorphism related to the pathophysiology of PTSD. In case that valine (Val) has been substituted by methionine (Met) at codon 158 lower enzyme activity and slower breakdown of the catecholamines was manifested. In a study of severe genocide survivors, carriers of the Val allele demonstrated the dose response relationship between higher number of lifetime traumatic events and a lifetime diagnosis of PTSD. However, homozygotes for the Met/Met genotype demonstrated a high risk for lifetime PTSD independent of the number of lifetime traumatic events experienced. Genetic studies also reported a significant main effect of the D2A1 allele of the D2 dopamine receptor (DRD2) gene in association with a diagnosis of PTSD. Another study reported a significant interaction between three single nucleotide polymorphisms in the GABA alpha-2 receptor gene and severity of childhood trauma in predicting adult PTSD in those homozygous for the risk alleles (reviewed by Martin *et al* 2009; Auxéméry 2012; Skelton *et al* 2012). Also the brain-derived neurotrophic factor (BDNF) is intensely studied within PTSD pathophysiology because of its importance for the synaptic plasticity processes that are required for long-term learning and memory. Specifically, BDNF gene expression and activation of its TrkB receptor are necessary in the amygdala, hippocampus and prefrontal cortex for the formation of emotional memories, including fear memories. PTSD is characterized by an inability to extinguish fear memories. On the other hand, the BDNF appears to enhance extinction of fear, which supports the special importance of BDNF research. For example, a single-nucleotide polymorphism that has also been suggested to be relevant for PTSD is the Val66Met polymorphism which consists in the substitution of Met for Val at position 66 in the pro-region of BDNF. The Val66Met SNP causes decreased hippocampal volume, deficits in declarative memory and impaired fear extinction. Concordantly, studies in transgenic mice containing a knock-in allele of the human Val66Met allele and cell cultures show reduced neuronal BDNF availability, neuronal survival, hippocampal dendritic arborization, hippocampal volume (reviewed by Andero & Ressler 2012).

Epigenetic mechanisms are also hypothesized to be an important factor related to events increasing the risk for PTSD development, however the direct interconnection has not been yet proved. It is suggested that epigenetic mechanisms are also involved in establishing individual differences in PTSD risk and resilience by mediating long-lasting effects of genes and early environment on adult function and behavior (Skelton *et al* 2012; Zovkic *et al* 2013). Epigenetic mechanisms play an important role in the regulation of gene expression in response to environmental signals and drugs and represent the interface of the genome and the environment without gene´s mutation. In other words, epigenetic modification describes an environmentally induced change in DNA which alters the function without the change of gene´s structure. These changes can be specific to critical developmental periods, can be stable, enduring, and site-specific, and may be intergenerationally transmitted. There are 3 main basic epigenetic molecular mechanisms, including DNA methylation, histone modification and microRNA dysregulation, each of which could be involved in the pathophysiology of many pathological conditions, including psychiatric disorders. It is known that various stressors can operate through epigenetic mechanisms (Fagiolini *et al* 2009; Jakovljevic *et al* 2010; Jobe *et al* 2012; Skelton *et al* 2012). Skelton *et al* (2012) summarize that epigenetic mechanisms could be active from very early developmental period as shown in work of Meaney and colleagues (2005). In the rat model, maternal care characterized by higher amounts of licking and grooming produced lower levels of cortisol in the rat pups, but only if occurred during a specific, early developmental window. These rat infants also demonstrated enhanced suppression of cortisol in response to dexamethasone, as well as greater expression of the glucocorticoid receptor´s gene and a greater number of hippocampal glucocorticoid receptors as a result of hypomethylation in promoter region of the hippocampal glucocorticoid receptor´s gene. Skelton *et al* (2012) also point out that neuroendocrine alterations in this animal model are interestingly parallel to those in PTSD with low basal cortisol and enhanced suppression of cortisol in response to a synthetic glucocorticoid. The lower levels of glucocorticoid receptor´s mRNA were also found in the hippocampus of suicide victims who had a history of childhood abuse. On the other hand, some studies indicate that the association between a history of psychological trauma and suicidal behavior in children is not clearly understood (McGowan *et al* 2009; Koutek *et al* 2009). It can be hypothesized that the epigenetic-mediated changes in HPA axis reactivity could be associated with increased vulnerability to PTSD following subsequent traumatic exposure, probably by the stress-induced elevations in noradrenergic neurotransmission leading to overconsolidation of fear memories, together with increased arousal and distress. These findings could also help to explain the mechanism by which early life trauma is a strongly validated risk factor for the subsequent development of PTSD in adulthood by recalibrating the set point and stress-responsivity of the HPA axis in an enduring manner that increases vulnerability to PTSD. Moreover, it is generally accepted that early adverse experience, including prenatal stress and stress throughout childhood, has prominent and long-lasting effects on the development of neurobiological systems, which exerts substantial effects on "programming" subsequent stress reactivity and vulnerability to develop PTSD (Yehuda *et al* 2010; Sherin & Nemeroff 2011). Moreover, transgenerational epigenetic effects have been also associated with pathological condi-

tions, including psychiatric disorders (Murgatroyd *et al* 2010; Peter & Akbarian 2011; Welnhold 2012). Very interesting data brought study of transgenerational transmission of trauma by Yehuda *et al* (2008). The authors found increased risk for PTSD, as well as low cortisol levels, in the offspring of female, but not male, Holocaust survivors with PTSD. Multiple data analyses supported suggestion that the main pathophysiological mechanism could be explained by epigenetic changes of glucocorticoid receptor´s gene. As with the rat model, this increased risk may be produced by alternations in maternal care associated with the mother's PTSD, which may disrupt child-maternal attachment, a known risk factor for PTSD (Charuvastra & Cloitre 2008). These effects may also produce enduring changes in HPA axis responsivity to stressors that may influence risk for PTSD following subsequent traumatic exposure (Brand *et al* 2010). Animal models of PTSD also suggest that epigenetic regulation of the BDNF gene may be also crucial for this disorder. For example, specific exon-containing BDNF mRNAs seem differentially regulated in fear processes in rats depending on the procedure, previous stress, and which brain region is analyzed (Andero & Ressler 2012; Maddox *et al* 2013). The combined recent progress in research of epigenetic modulation of memory with the advances in fear neurobiology suggest that this area may be critical to progress in our understanding of fear-related disorders with implications for new approaches to treatment and prevention (Maddox *et al* 2013).

Neuroanatomical studies suggest hippocampal dysfunction in PTSD which is supported by consistent findings of decreased volume of hippocampus secondary to trauma. There are also increasing data showing decreased volume in medial and ventral prefrontal cortex (Stein & Rauch 2008). Reduced volume and activity of hippocampus lead to alteration in stress responses and extinction. Hippocampal volume reduction in PTSD may reflect the accumulated toxic effects of repeated exposure to increased glucocorticoid levels or increased glucocorticoid sensitivity, though recent evidence also suggests that decreased hippocampal volumes might be a pre-existing vulnerability factor for developing PTSD (Sherin & Nemeroff 2011). Amygdala hyperresponsiveness has been identified in numerous studies of patients who suffered from PTSD. Increased activity of amygdala promotes hypervigilance and impairs discrimination threat. Greater activation of the amygdala in response to viewing fearful faces corresponded with poor prognosis in cognitive behavioral therapy (CBT) and some studies have also shown that severity of PTSD symptoms predicts the magnitude of amygdala activation when encoding memories unrelated to the traumatic event (Bryant *et al* 2008; Dickie *et al* 2008; Martin *et al* 2009). The rostral anterior cingulate cortex (ACC) volume also predicted success of CBT. Functional imaging studies have shown that greater activation of the ventral ACC in response to viewing fearful faces corresponded with a poorer response to CBT. It is possible that decreased rostral ACC volume results in a decreased ability for extinction learning. Patients who have PTSD and who have a smaller ACC volume may be less able to regulate fear during therapy, which could make the CBT process less effective (Martin *et al* 2009). Reduced volume of prefrontal cortices could be connected with executive functions dysregulations, followed by possible reduced anterior cingulate volume and decreased medial prefrontal activation (Sherin & Nemeroff 2011). It has been hypothesized that symptoms of PTSD, including intrusive thoughts and reexperiencing trauma, result from an inability of higher cognitive structures to repress negative emotional memories, which exerts significantly different patterns in comparison to healthy controls. The severity of PTSD symptoms was also found to be positively correlated with the degree of activation in the ventral frontolimbic areas while patients were presented with emotional stimuli in comparison to neutral stimuli. In patients with PTSD, reduced activation of the dorsal executive network (the middle frontal gyrus, dorsal anterior cingulate gyrus, and inferior parietal lobule) also correlated with symptom severity. These results suggest that brain areas that are restricted to executive functioning in healthy subjects are used for emotional/affective processing in patients who have PTSD, and it consequently decreases the capacity of executive control (Martin *et al* 2009; Morey *et al* 2008). According to Falconer *et al* (2008), sensory gating deficits observed in patients with PTSD result from information processing systems being overpowered by hypervigilance for threat related stimuli and hyperarousal. These patterns are suggested from experiments which demonstrated deficits of inhibitory control in PTSD patients. In control subjects, inhibitory processing activated the right frontotemporoparietal cortical network. In patients who had PTSD, the left ventrolateral prefrontal cortex was activated, and the frontotemporoparietal cortical network was less active (reviewed by Martin *et al* 2009).

Comprehensive research points out that a lot of factors in PTSD pathophysiology must be taken into account. Mutual interplay and various influences in neurobiological systems following trauma exposure modulate individual constellation of different factors including genetic susceptibility, gender (higher risk for females), prior trauma, early developmental stage at the time of traumatic exposure, and physical injury (including traumatic brain injury-TBI) at the time of psychological trauma. The point of special interest is the interconnection between PTSD and TBI. TBI presents an increased risk for the development of PTSD. Moreover, several pathological features found in PTSD patients overlap with features found in patients with TBI, including common endocrine, neurochemical, and circuit abnormalities (Sherin & Nemeroff 2011). It is only partially true that the more severe the head

injury, the less likely it is that PTSD will develop, because patients with marked brain damage are more likely to have an amnesia for the psychological trauma of the accident. Many patients with severe head injuries have PTSD, but it is often overlooked in the setting of much more obvious cognitive and physical changes (Cummings & Trimble 2002). Based on the current knowledge, PTSD could be conceptualized as a pathological condition characterized by dysregulation of multiple stress-mediating systems following a psychological shock in setting of genetic, epigenetic, and experiential predispositions when exposed to certain extreme conditions. It is hypothesized that the main pathophysiological patterns of PTSD could be explained as a relative lack of baseline cortisol at the time of a psychological trauma, which may consequently facilitate overactivation of the central CRH-NE cascade, resulting in enhanced and prolonged stress responses. This increased stress responsiveness may be further accentuated by inadequate regulatory effects of GABA, serotonin, and NPY. Additionally, altered norepinephrine and stress hormone activity may be critically involved in processes of learning and extinction, both of which are abnormal in PTSD, together with dysfunctions of the hippocampus, amygdala, prefrontal cortex and other brain regions (Sherin & Nemeroff 2011).

Very promising research area is an identification of complex factors underlying the resilience. Stressful life events, trauma, and chronic adversity can have a substantial impact on brain function and structure, and can result in the development of posttraumatic stress disorder (PTSD), depression and other psychiatric disorders. However, most individuals do not develop such illnesses after experiencing stressful life events, and are thus thought to be resilient. Resilience is defined as the capacity and dynamic process of adaptively overcoming stress and adversity while maintaining normal psychological and physical functioning. It is of special importance that research of biological background of resilience strongly overlap with features investigated in PTSD (neurochemical systems, NPY, BDNF, CRH, HPA axis and others) and multiple interacting factors including genetics, epigenetics, developmental environment, psychosocial factors, and functional neural circuitry, play critical roles in developing and modulating resilience in an integrated way. Current data suggest that research in resilience neurophysiology offers unique opportunities to create efficient treatment and preventive strategies (special treatment targeting involved neurobiological systems together with complex behavioral and social strategies) to facilitate the development of evidence-based interventions for enhancing resilience and mitigating risk for stress-related psychiatric disorders (Wu *et al* 2013). Such complex biological, social and integrative strategies are also markedly important to prevent the stigma in patients with mental illness as well as other distinct adverse effects of social stress, and improve the quality of patient´s life (Praško *et al* 2011; Auxéméry 2012; Klop *et al* 2012; Šestáková *et al* 2012).

Consequences of childhood traumatization

Several retrospective and (for now only sporadic) prospective studies have confirmed connections between adverse childhood experience and numerous mental disorders such as borderline personality disorder, certain types of depression, dissociative disorders, some types of bipolar affective disorder, schizophrenia, substance dependency and others. Recently, some studies have focused on similar connections in somatic illnesses.

Childhood psychological traumatization might sometimes indirectly lead to somatic illness through problematic behavior such as smoking, alcohol and drug consumption, and sexual promiscuity (sexually transmitted diseases).

Early psychological traumata and their accumulation might cause life-lasting wounds that are not healed with time. Or, to put it more cautiously, they are not always healed with time. There are reasons to doubt the common consolation, "time heals all wounds".

Vincent J. Fellitti and Robert F. Anda (1998) and their Adverse Child Experience (ACE) Study deserve credit for studying this problem. Between 1995 and 1997, 26 000 patients undergoing a routine health screening were asked about adverse experience in childhood. Informed consent for use of personal data for study purposes was given by 71% of patients (54% females and 46% males, average age 57 years), representing a sample of 18 175 subjects. All patients possessed health insurance, and thus were not necessarily representative of the American population; most belonged to the middle or upper middle classes. However, 64% listed at least one childhood traumatic event. One third of the subjects had two or more traumatic events in childhood (younger than 18 years). A part of the sample was followed prospectively and the whole sample retrospectively. Eight categories of childhood abuse and adverse experience of parent-child relationship were studied: emotional and physical abuse, sexual violence/abuse; substance abuse, serious mental illness, violence toward the mother, a family member in prison, and parental separation or divorce were considered indicators of disintegrated family system. The ACE Score attributes one point for each category of exposure to child abuse and/or neglect. Thus, if a person indicated three types of traumatization, his/her score was 3 etc.

An excerpt from the ACE Study

Questionnaire listing the percentage of positive response in the sample N=18 175

Adverse childhood experience – maltreatment, abuse

Emotional – 10.3%

Did a parent or other adult in the household often or very often…

Swear at you, insult you, put you down, or humiliate you?

Act in a way that made you afraid that you might be physically hurt?

Physical – 28.0%

Did a parent or other adult in the household…

Push, grab, slap, or throw something at you?

Ever hit you so hard that you had marks or were injured?

Sexual – 20.4%

Did an adult or person at least 5 years older than you ever

Touch or fondle you or have you touch their body in a sexual way?

Attempt or actually have oral, anal, or vaginal intercourse with you?

Severely damaged family system / domestic violence

Dependency – 26.6%

Did you live with anyone who was a problem drinker or alcoholic or who used street drugs?

Mental illnesses – 19.0%

Was a household member depressed or mentally ill, or did a household member attempt suicide?

Violence towards the mother – 12.6%

Was your mother or stepmother:

Often or very often pushed, grabbed, slapped, or had something thrown at her?

Sometimes, often, or very often kicked, bitten, hit with a fist, or hit with something hard?

Ever repeatedly hit at least a few minutes or threatened with a gun or knife?

Household member in prison – 4.5%

Did a household member go to prison?

Parental separation or divorce – 22.8%

Were your parents ever separated or divorced?

The results of the ACE Study indicate that there is a connection between psychological traumatization in childhood and pregnancies in adolescence. Adolescence pregnancies, for their part, are connected with long-lasting psychosocial consequences and an increased fetal death risk. – The higher the ACE Score, the higher lithium and antipsychotic prescription rates. When ACE Score is 5 and higher, there is a tenfold increase in these prescription rates. – The Ace Score also positively correlates with frequency of work- and relationship-related problems in adulthood, financial problems, absences from work, emotional stress, somatic symptoms, and substance abuse. The higher frequency of somatic and mental illnesses leads to a higher mortality. – The ACE Score also positively correlates with nicotine dependency. Nicotine might be understood as "self-medication"; it is probably an attempt to influence the negative emotional consequences of neurobiological and social adverse child experience influences. – Each ACE Point increases the probability of drug abuse two- to fourfold. Intravenous drug abuse, on its part, leads to a higher hepatitis and endocarditis risk. – Hallucinations represent a nonspecific psychopathological symptom, as they can be found in affective disorders, schizophrenia, schizoaffective disorders, serious post-traumatic stress disorders, dissociative and other disorders. If the ACE Score is 7 and more, the risk of psychotic symptoms increases fivefold. – Each ACE Point increases the risk of suicidal behavior. This relationship remains even after correcting for alcohol and drug dependency depression. Two thirds of all suicidal attempts in adulthood can be understood as long-term consequences of childhood adverse experience. – Liver diseases, especially cirrhosis, are one of the prevailing causes of death both in Europe and the USA. The most frequent cause of cirrhosis is hepatitis and alcoholism. For hepatitis C, the risk of chronic course is 70%. Similarly, 40% of patients suffering from a liver disease have hepatitis C.

Illegal drug consumption and hazardous sex behavior increase the risk of hepatitis B and C. Combination with alcohol consumption accelerates cirrhosis and increases the risk of hepatic cancer. The ACE Score positively correlates with chronic liver illnesses. – Risk factors of cardiac disease need to be revised, too. "Conventional" risk factors, such as smoking, diabetes, physical inactivity and hypertension explain only half of the variance of the cardiac disease incidence. According to Schickendanz *et al* (in Seidler *et al* 2011), several prospective studies suggest that psychosocial factors such as depression, anger and hostility support development of a coronary illness. Furthermore, they may play a role in frequency of fatal complications, such as heart attack. The ACE Score of 9 significantly increases the risk of a coronary illness (Fellitti *et al* 1998) – There is a direct connection between the chronic obstructive pulmonary disease and nicotine abuse – cigarette smoking. The ACE Score of 4 increases its risk by 93%. – The ACE Study shows that there is a connection between all illness-related deaths (deaths due to coronary illness, cancer, chronic pulmonary disease, accidents with a skeletal injury) and frequency of childhood traumatic experiences.

In a big sample of somatically ill patients, the ACE Study confirms what we suspected based on the clini-

cal practice. According to Schickendanz and Plassmann (in Seidler *et al* 2011): "The results clearly show that psychosocial stressors in childhood are destructive. Furthermore, they have life-long consequences. They are the most important factor deciding about health, wellbeing, and individual and social efficiency (p. 447).

According to some critics derogating the findings of this and similar studies, due to the methodology subjects might tend to exaggerate childhood traumatic events. However, this criticism is not fully justified. Patients with positive family experience have little reason to speak badly of them. On the contrary, we should assume higher rates of traumatization than those found in the ACE Study. This is due to the fact that many victims experience amnesia after a traumatic event. Partial or complete amnesia, either permanent or in some periods of life, is found in 5–20% of traumatized subjects, most frequently after sexual abuse (Hofmann 2006).

There were no direct questions assessing emotional or physical neglect, which might be considered a minor flaw of the ACE Study. The methodology only allows indirect inference of neglect.

Therapy of posttraumatic stress disorder

PTSD treatment, similarly to treatment of other mental disorders, might include psychotherapy and pharmacotherapy.

In pharmacological studies of PTSD treatment, a 30% reduction of symptomatology is considered an improvement. In randomized controlled trials, such an improvement is observed in 50% of cases. *Sertraline* and *paroxetine* have been found to have the most positive effects. The effectiveness of mirtazapine and venlafaxine is similar. Pharmacological treatment in PTSD is not as effective as it is in depression. Compared to the treatment of depressions, the PTSD treatment requires higher dosage, starting from a low dose and keeping the full dose for at least eight weeks, since the medication may not be immediately effective. The recommended duration of pharmacological treatment is 1–2 years. There is an increased relapse risk after the discontinuation of the medication. In case of psychosis-like symptomatology, an atypical antipsychotic might be considered. Some findings suggest that *olanzapine* and *quetiapine* have an additional positive effect on sleep. In case of aggression, *valproate* may be used (Benkert & Hippius 2011).

Psychotherapy of posttraumatic stress disorder

The authors of the monograph on supportive psychotherapy, the most prevalent psychotherapeutic approach in the USA (Novalis *et al* 1999), describe several principles that are used by other psychotherapeutic approaches, too. They include communication style leading to strong therapeutic alliance, repeated psychoeducation, and encouragement to verbalize details of the traumatic event and related emotions. The therapist has to be ready to listen to the story again and again, to repeatedly reassure and to retain a realistic therapeutic optimism. Sigmund Freud was the first one to point out the therapeutic importance of *reliving* and *re-suffering* of the traumatic event. This is often connected with an affective catharsis. He encouraged the patients to make the trauma fully accessible to the consciousness including all its aspects and details, verbalizations and related affective reactions (in Freud 1969). This happens within a safe therapeutic relationship.

In psychotherapy of a trauma, it is important to consider a specific way of confronting the patient with the traumatic memories. This enables new learning and reworking of the dysfunctional memory material (Bob 2011). Typically, traumatic memories emerge uncontrollably. Their repeated presentation does not, however, have a positive effect on emotional burden and on extinguishing of the conditioned reaction. On the contrary, re-traumatization happens. The negative affective memories are strengthened, and they are generalized to other stimuli. One of the most common flaws in psychotherapy potentially leading to a iatrogenic damage is an uncontrolled emotional abreaction including full reliving and free expression of related emotions with no therapeutic guidance of the process. The therapeutic effect of the sole "emotional discharge" has been questioned (Van der Hart & Brown 1992). Remembering the traumatic event must always be preceded by a sufficient stabilization of the patient. This is the case especially in massively and repeatedly traumatized patients. The stabilization includes building sufficient affective tolerance and the ability to maintain dual attention though the whole period of trauma confrontation. Dual attention means a sufficient contact with the traumatic memories on one hand, and contact with the situation here and now on the other. This ability to integrate the past into the full consciousness of the present represents the main therapeutic goal. Important aspects are activation of inner sources of safety (positive inner objects) and of the present safe therapeutic relationship (psychotherapy as a secure base, Bowlby) (Hašto 2005). This goal is being reached in three phases of trauma therapy: the stabilization, confrontation with the trauma, and reintegration. These therapy stages were proposed already by P. Janet (Van der Hart & Dorahy, in Dell & O´Nell 2009).

Methodical guidelines for PTSD treatment were formulated by authors belonging to various therapeutic schools. Some of them are mainly dynamically oriented; others describe themselves as cognitive-behavioral. The biggest body of empirical evidence confirms the effectiveness of cognitive-behavioral techniques, especially exposition and cognitive therapy (Benedek & Wynn 2011). Often, we encounter integrative approaches or pragmatic eclecticism. The aforementioned supportive

psychotherapy can be classified as a dynamic approach, or as a supportive pole of dynamic (Gabbard 2005) or psychoanalytic (Wöller & Kruse 2011) psychotherapy. It chooses the best techniques according to what is needed to solve a specific problem (Novalis *et al* 1999). Methodically structured guidelines of PTSD treatment that could be classified rather as psychodynamic have been formulated by Horowitz (2004), Levenson *et al* (2005), Reddemann (2004), Sachsse (2004), and Steiner & Krippner (2006). The latter three references use techniques originating from the katathym-imaginative psychotherapy (KIP). According to Lamprecht (2000), the EMDR (Hofmann 2006; Shapiro 1998) can be understood as an integration of psychodynamic and cognitive approaches. It is based on free associations focused on the trauma and work with cognitions. Several useful techniques originate in hypnotherapy (Phillips & Frederic 2007) that also has an interactively-eclectic character. Approaches described by the authors with a background in KIP and hypnotherapy are oriented rather on type II trauma, they use especially stabilization techniques and techniques activating the inner resources. Other approaches in PTSD treatment include the Imagery Rescripting and Reprocessing Therapy (IRRT) (Smucker *et al* 1995) and the Narrative Exposition Therapy (NET) (Schauer *et al* 2005). They also use the exposition principle. A theoretical concept and treatment methodology for patients with serious structural personality dissociations (usually as a result of type II trauma beginning in early childhood) have been formulated by Helga Matthess together with Ellert Nijenhuis (in Wöller 2006).

Methodically precise concept of PTSD exposition therapy and work with cognitions and homework within the frame of cognitive-behavioral therapy has been described by Ehlers (1999). In most circumstances, there are 15 sessions lasting 90 minutes each. The first 8–12 take place weekly, the last 3 monthly. The in vivo exposure can take additional 2 hours. While the metaanalysis of CBT for PTSD treatment conducted by Etten and Taylor in 1998 found the effect size d=1.27, Ehlers' work group reports effect size d=2.6–2.8. The effects stay stable even in a one year follow up. After the treatment, 80–90% of the patients do not fulfill PTSD diagnostic criteria. Drop-out rate was only 5%.

The modern CBT, similarly to Guided Imagery Psychotherapy (Katathym-imaginative Psychotherapie), uses systematically and thoughtfully the work with imaginations that leads to a kind of "rescripting" of traumatic memory traces and their associative connections. The method is concisely reviewed also with vignettes in Praško *et al* (2012).

In the last two decades, the development of psychotraumatology has markedly accelerated, and the effectiveness of psychotherapeutic techniques used in PTSD treatment has been subject of intense scientific interest. The authors of an overview of present knowledge on PTSD treatment (Frommberger & Maercker, in Vorderholzer & Hohagen 2011) state PTSD symptoms can be reduced by both psychotherapy and pharmacotherapy (paroxetine, sertraline). They quote the review of neurobiological studies conducted by Jetzke *et al*., and state that the anterior gyrus cinguli activity is increased, while the amygdala remains unchanged. Thus, the emotion control improves, but we can hardly count with influencing the anxious conditioning of the amygdala. Considering psychotherapy, the biggest effect sizes have been found for CBT and EMDR. According to Lamprecht (2000), the EMDR accelerates the therapeutic process. Thus, less time is needed for the therapy. Meta-analyses comparing CBT exposure techniques and EMDR suggest that the EMDR reaches the same results in 40–50% of the time needed when using CBT.

Having in mind Baldwin´s point (Baldwin 2013) of psychobiological origin of posttraumatic symptomatology and important role of autonomic nervous system in the dysregulation emerging after trauma, psychotherapeutic methods that address physiology directly might present crutial asset in treating PTSD. There is empirical and research evidence that EMDR affects the balance of parasympathetic / sympathetic regulation (Elofsson *et al* 2008). At the same time, using relaxation (like autogenic training) to train ventral vagal mode of experiencing may be very beneficial for dysregulated trauma victims.

In our patient, we used EMDR as well as autogenic training. Therefore, we shortly describe both methodologies. The EMDR is an integrative method which involves a specific approach for confronting trauma. Following a structured manualized approach, the therapist is helping the patient to remember the traumatic event in as much detail (tactile, cognitive, affective and somatic) as possible. After the memory is fully active in patient's consciousness, the therapists starts the bilateral stimulation at a frequency of approximately 1Hz. (The therapist usually asks the patient to follow his fingers with his or her eyes. The fingers move alternately from side to side so that the patient's eyes also move back and forth. The stimulation can also be tactile or auditory. The therapist either alternately touches patient's right and left hand, or the patient has headphones and listens to sounds played alternately to his/her left and right ear.) One set usually consists of 25–30 stimuli, followed by a pause of several seconds. In this time, the therapist and the patients talk about the experience. In the stimulation phase, the patient's task is to freely associate and to impartially observe the associations (free associations and activation of the watchful ego). In this phase, the therapist does not interfere, trusting to patient's salutogenic ability facilitated by the therapeutic situation and the bilateral stimulation. The therapist only takes short pauses in the stimulation and asks the patient about any changes in his/her feelings. This process continues until the memory is fully emotionally neutral. In the next step, the original memory is

paired with a new – positive – cognitive evaluation. The body reaction to the memory is tested, since traumatic memories are most deeply kept on the somatic level. The EMDR uses two subjective scales measuring the therapeutic effect. One of them is the Subjective Units of Disturbance Scale (SUDS) originating from Wolpe. It is a scale of 0 to 10, where 0 means "no distress" and 10 means "maximal distress". The other one is the Validity of Cognition Scale (VoC) measuring the validity of the positive cognition connected to the traumatic event. It is a scale of 1 to 7, where 1 means "completely false" and 7 equals "completely true". The desensitization phase ends when the SUDS has reached 0 and VoC has reached 7. This result might be reached after one session, but sometimes several sessions are needed.

Hypotheses about a possible "mechanism of action" of the EMDR remain open. Further research is needed to confirm them. According to the present knowledge, bilateral stimulation during trauma reliving leads to specific activation changes in the central nervous system. These changes, caused mainly by autonomic nervous system regulations (Vojtová & Hašto 2009), increase the information processing capacity. Already ten seconds after the beginning of the bilateral stimulation of frequency 1Hz during the trauma reliving, there is a decrease of sympathicotonia, decrease of heart rate and increase in vagal activation (Elofsson *et al* 2008; Sack *et al* 2008). The brain information processing system is probably activated. Orientation reaction is provoked and neural activity similar to the REM sleep (Stickgold 2002). Panksepp (1998) points out that similar neural structures are activated by play, exploratory behavior and REM sleep. Connections with neural networks where positive experiences are stored. Thus, the trauma is being rewritten (Ralaus 2006). According to one of the hypothesis, there is a greater participation of the left hemisphere in the problem solving (Hofmann 2006). All this happens within the accepting and safe frame potentiated by the rhythmic bilateral signals and therapist's presence. Furthermore, the therapist explicitly verbalizes his/her trust in patient's salutogenic processes that can now be activated. From the attachment theory point of view (Hašto 2005), this can be understood as a ritualized attachment behavior: A competent, supporting person is close to an extremely distressed individual. If we move to the endocrine-molecular level, oxytocin (Brüne 2012) may play an important role here.

Autogenic training (AT) according to J.H. Schultze (Hašto 2006) is a well-known and empirically tested method of concentrative self-relaxation. It uses mental repeating of autosuggestion formulas to reach full physical and mental relaxation, so called auto-hypnoid state. In AT basic stage, the patient repeats sentences creating heaviness and warmth sensations, calm heart rate and breathing, feelings of radiating warmth in the abdomen, and feelings of freedom and clarity in the head. In further course, it is possible to use "individually tailored" formulas corresponding to patient's specific difficulties (intermediate stage). Finally, it is possible to deepen and broaden the consciousness using imaginative meditations (higher stage). The result of autogenic training is a state of deep psychophysical wellbeing having both therapeutic and preventive effect on stress-related difficulties. However, we consider the Autogenic training as contradictory in florid PTSD symptomatology. In our case study, we will show its usefulness in the last phase of treatment and also its importance as a preventing factor.

Acknowledgment

Translated by Svetlana Žuchová, MSc., MD., PhD. and Ted Erler, PhD.

REFERENCES

1 American Psychiatric Association (2000/2010). Diagnostic and Statistical Manual of Mental Disorders. DSM-IV-TR. Fourth Edition (Arlington: APA).
2 American Psychiatric Association (2013). Diagnostic and Statistical Manual of Mental Disorders. DSM-5. (Washington DC, London: APA).
3 Andero R, Ressler KJ (2012). Fear extinction and BDNF: Translating animal models of PTSD to the clinic. *Genes Brain Behav*. **11**(5): 503–512. doi: 10.1111/j.1601-183X.2012.00801.x.
4 Auxéméry Y (2012). Posttraumatic stress disorder (PTSD) as a consequence of the interaction between an individual genetic susceptibility, a traumatogenic event and a social context. *Encephale*. 38(5): 373–380. doi: 10.1016/j.encep.2011.12.003.
5 Benedek DM, Wynn GH (2011). Clinical Manual for Management of PTSD. Washington: American Psychiatric Publishing. p.468.
6 Benkert O, HIPPIUS H (2011). Kompendium der Psychiatrischen Pharmakotherapie. 8. Auflage. Berlin: Springer. p.720.
7 Bleuler M (1978). Die schizophrenen Geistesstörungen im Lichte langjähriger Kranken-und Familiengeschichten. Stuttgart: Thieme. p.673.
8 Bob P (2011). Brain, mind and consciousness. New York: Springer. p. 151.
9 Brand S, Brennan P, Newport DJ, Smith AK, Weiss T, Stowe ZN (2010). The impact of maternal childhood abuse on maternal and infant HPA axis function in the postpartum period. *Psychoneuroendocrinology* **35**(5): 686–693. doi: 10.1016/j.psyneuen.2009.10.009.
10 Bryant RA, Felmingham K, Kemp A, Das P, Hughes G, Peduto A, Williams L (2008). Amygdala and ventral anterior cingulated activation predicts treatment response to cognitive behaviour therapy for post-traumatic stress disorder. *Psychol Med.* **38**: 555–561.
11 Brüne M (2012). Evolučná psychiatria. Pôvod psychopatológie. [(Textbook of Evolutionary Psychiatry. The Origins of Psychopathology.) (in Slovak, translated from original, Oxford, New York, Oxford University Press, 2008.)] Trenčín: Vydavateľstvo F. p.424.
12 Cummings JL, Trimble MR (2002). Head Injury and Its Sequelae. In: Neuropsychiatry and Behavioral Neurology, 2nd Edition. Washington, London: American Psychiatric Publishing. p. 217–225.
13 Dickie EW, Brunet A, Akerib V, Armony JL (2008). An fMRI investigation of memory encoding in PTSD: influence of symptom severity. *Neuropsychologia*. **46**: 1522–1531.
14 Ehlers A (1999). Posttraumatische Belastungsstörung. Fortschritte der Therapie. Göttingen: Hogrefe. p.99.
15 Elbert T (2009). Von Jagern und Gejagten. Wie lebensbedrohliche Erfahrung Geist und Gehirn modifizieren. Berlin: DGPPN Kongress, Eröffnungsvortrag, 25.11.2009.
16 Elofsson UO, Von Scheele B, Theorell T & Sondergaard HP (2008). Physiological correlates of eye movement desensitization and reprocessing. *J Anxiety Disord.* **22** (4): 622–634.
17 Etain B, Henry C, Bellivier F, Mathieu F, Leboyer M (2008). Beyond genetics: childhood affective trauma in bipolar disorder. *Bipolar Disord*. **10** (8): 867–876.

18 Fagiolini M, Jensen CL, Champagne FA (2009). Epigenetic Influences on Brain Development and Plasticity. *Curr Opin Neurobiol.* **19**(2): 207–212. doi: 10.1016/j.conb.2009.05.009.

19 Falconer E, Bryant R, Felmingham KL, Kemp AH, Gordon E, Peduto A, Olivieri G, Williams LM (2008). The neural networks of inhibitory control in posttraumatic stress disorder. *J Psychiatry Neurosci.* **33**: 413–422.

20 Fedor-Freybergh PG (1999). Psychoimmuno-neuroendocrinology: An integrative approach to modern philosophy in medicine and psychology. *Neuroendocrinol Lett.* **20** (3–4): 205–213.

21 Fedor-Freybergh PG, Maas L (2011). Continuity and Indivisibility of Integrated Psychological, Spiritual and Somatic Life Processes. *Int J Prenat Perinat Psychol Medicine*. **23** (Suppl 1): 135–142.

22 Fedor-Freybergh PG (2013). Psychosomatické charakteristiky prenatálneho a perinatálneho obdobia ako prostredia dieťaťa. [(Psychosomatic Characteristics of Prenatal and Perinatal Period as the Environment of Infant.) (In Slovak.)] Trenčín: Vydavateľstvo F. p. 3–28.

23 Fellitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, Koss MP, Marks JS (1998). Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. *Am J Prev Med*. **14**: 245–258.

24 Flatten G, Gast U, Hofmann A, Knaevelsrund Ch, Lampe A, Liebermann P, Maercker A, Reddemann L & Wöller W (2013). Posttraumatische Belastungsstörung. S3-Leitlinie und Quellentexte. 3. Auflage. Stuttgart: Schattauer. p.146.

25 Freud S (1969). Studie o hysterii. In S. Freud S., ed. Vybrané spisy II–III. [(Studies about hysteria, In Freud S., ed. Selected files II–III.) (in Czech.)] Praha: Avicenum. p. 11–133.

26 Frommberger U, Maercker A (2011). Posttraumatische Belastungsstörung. In Vorderholzer U, Hohagen F, eds. Therapie psychischer Erkrankungen. State of the Art, 6. Auflage. München: UrbanFischer, 209–218.

27 Fujisawa TX, Nishitani S, Obara T, Shinohara K (2012). Loneliness depends on salivary estradiol levels in adolescent females. *Neuroendocrinol Lett.* **33**(5): 525–529.

28 Gabbard GO (2005). Dlhodobá psychodynamická psychoterapia. Základný text. Jadrové kompetencie v psychoterapii. [(Long – Term Psychodynamic Psychotherapy. A Basic Text. Core Competencies in Psychotherapy.) (In Slovak, translated from original, Washington DC – London: American Psychiatric Publishing, Inc., 2004)] Trenčín: Vydavateľstvo F. p.208.

29 Gutman AR, Yang Y, Ressler KJ, Davis M (2008). The role of neuropeptide Y in the expression and extinction of fear-potentiated startle. *J Neurosci* **28**: 12682–12690.

30 Hašto J, Švančarová O, Suško J, Gyén D (2011). Posttraumatická stresová porucha – prevalencia u psychiatrických hospitalizovaných pacientov. [(Post-traumatic stress disorder – prevalence in hospitalised psychiatric patients.) (In Slovak with English abstract.)] *Psychiatria pre prax.* **12** (4): 161–164.

31 Hašto J (2005). Vzťahová väzba. Ku koreňom lásky a úzkosti. [(Attachment. Investigating the roots of love and anxiety.) (In Slovak.)]Trenčín: Vydavateľstvo F. p. 300.

32 Hašto J (2013). Autogénny tréning. [(Autogenous training.) (In Slovak.)] 3.doplnené vydanie. Trenčín: Vydavateľstvo F. p. 65.

33 Herman JL (2001). Trauma a uzdravenie. Násilie a jeho následky – od týrania v súkromí po politický teror. Bratislava: Aspekt. [(Trauma and healing. Violence and its consequences – from private tyranny to political terror.) (In Slovak.)] Bratislava: Aspekt. p.342.

34 Hoebel BG, Avena NM, Rada P (2007). Accumbens dopamine-acetylcholine balance in approach and avoidance. *Curr Opin Pharmacol*. **7**: 617–27.

35 Hofmann A (2006). EMDR. Terapia posttraumatických stresových syndrómov. Trenčín: Vydavateľstvo F. Orig. (2006). EMDR, Therapie psychotraumatischer Belastungssyndrome. Stuttgart: Georg Thieme Verlag KG. p. 252.

36 Horowitz MJ (2004). Liečba syndrómov podmienených stresom. [(Treatment of stress response syndromes.) (In Slovak, translated from original, Washington: American Psychiatric Publishing, Inc., 2003)] Trenčín: Vydavateľstvo F. p. 111.

37 Charuvastra A, Cloitre M. Social bonds and posttraumatic stress disorder. *Annu Rev Psychol.* **59**: 301–328

38 Ironson G, Cruess D, Kumar M (2007). Immune and Neuroendocrine Alterations in Post-traumatic Stress Disorder. In: Adler R, editor. Psychoneuroimmunology, 4th Edition. Amsterdam, Boston, Heidelberg, London, New York, Oxford, Paris, San Diego, San Francisco, Singapore, Sydney, Tokyo: Elsevier Academic Press. p. 531–547

39 Jakovljević M, Reiner Ž, Miličić D, Crnčević Ž (2010). Comorbidity, Multimorbidity and Personalized Psychosomatic Medicine: Epigenetics rolling on the horizon. *Psychiatr Danub.* **22**(2): 184–189.

40 Jobe EM, Andrea L, McQuate AL, Zhao X (2012). Crosstalk among epigenetic pathways regulates neurogenesis. *Front Neurosci.* **6**(59): 1–14.

41 Kampfhammer HP (2006). Zur Neurobiologie von Trauma, Dissociation und Somatisierung. In Remmel A, Kernberg OF, Vollmoeller W & Strauss B, ed. Handbuch Körper und Persönlichkeit. Entwicklungspsychologie, Neurobiologie und Therapie von Persönlichkeitsstörungen. Stuttgart: Schattauer, 345–365.

42 Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB (1995). Postraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry.* **52** (12): 1048–60.

43 Klopp C, Garcia C, Schulman AH, Ward CP, Tartar JL (2012). Acute social stress increases biochemical and self report markers of stress without altering spatial learning in humans. *Neuroendocrinol Lett*. **33** (4): 425–30.

44 Koutek J, Kocourkova J, Hladikova M, Hrdlicka M (2009). Suicidal behavior in children and adolescents: does a history of trauma predict less severe suicidal attempts? *Neuroendocrinol Lett.* **30** (1): 99–106.

45 Krystal JH, Neumeister A (2009). Noradrenergic and Serotonergic Mechanisms in the Neurobiology of Posttraumatic Stress Disorder and Resilience. *Brain Res.* **1293**: 13–23. doi: 10.1016/j.brainres.2009.03.044.

46 Lamprecht F (2000). Praxis der Traumatherapie. Was kann EMDR leisten? Stuttgart: Pfeiff er bei Klett-Cotta. p. 238.

47 Lanius R, Vermetten E, Loevenstein R, Brand B, Schmahl Ch, Bremmer D, Spiegel D (2010). Emotion Modulation in PTSD: Clinical and Neurobiological Evidence for a Dissociative Subtype. *Am J Psychiatry.* **167**(6): 640–647.

48 Levenson H, Butler SF, Powers TA, Beitman BD (2005). Krátka dynamická a interpersonálna psychoterapia. Stručný sprievodca. [(Concise Guide to Brief Dynamic and Interpersonal Therapy.) (In Slovak, translated from original Washington DC – London: American Psychiatric Publishing, Inc., 2002.)] Trenčín: Vydavateľstvo F. p. 174.

49 Luxenberg T, Spinazzola T, Van Der Kolk BA (2001). Complex Trauma and Disorders of Extreme Stress (DESNOS) Diagnosis, Part One: Assessment. *Directions in Psychiatry.* **21**: 373–393.

50 Maddox SA, Schafe GE, Ressler KJ (2013). Exploring epigenetic regulation of fear memory and biomarkers associated with posttraumatic stress disorder. *Front Psychiatry.* 4: 62. doi: 10.3389/fpsyt.2013.00062. eCollection 2013

51 Mareš J (2012). Posttraumatický rozvoj člověka. [(Post-traumatic human development.) (In Czech.)] Praha: Grada Publishing. p. 198.

52 Martin EI, Ressler KJ, Binder E, Nemeroff ChB (2009). The Neurobiology of Anxiety Disorders: Brain Imaging, Genetics, and Psychoneuroendocrinology. *Psychiatr Clin North Am.* **32**(3): 549–575. doi: 10.1016/j.psc.2009.05.004.

53 Matthess H & Nijenhuis E (2006). Wie behandeln wir Patienten mit schwerer struktureller Dissoziation der Persönlichkeit? Therapeutische Möglichkeiten bei schwerer dissoziativer Persönlichkeitsdesinlegration. In Wöller W, ed. Trauma und Persönlichkeitsstörungen. Psychodynamischintegrative Therapie. Stuttgart: Schatauer, 465–482.

54 McGowan PO, Sasaki A, D´Alessio AC, Dymov S, Labonté B, Szyf M, Turecki G, Meaney MJ (2009). Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nature Neurosci.* **12**(3): 342–348. doi: 10.1038/nn.2270.

55 Meaney MJ, Szyf M (2005). Maternal care as a model for experience-dependent chromatin plasticity? *Trends in Neurosci.* **28**(9): 456–463.

56 Mol SSL, Arntz A, Metsemakers JFM, Dinant G-J, Vilters-Van Montfort PAP, Knottnerus JA (2005). Symptoms of posttraumatic stress disorder after non-traumatic events: evidence from an open population study. *Br J Psychiatry*. **186**: 494–499.
57 Morey RA, Petty CM, Cooper DA, Labar KS, McCarthy G (2008). Neural systems for executive and emotional processing are modulated by symptoms of posttraumatic stress disorder in Iraq war veterans. *Psychiatry Res.* **162**: 59–72.
58 Moskowitz A, Schafer I & Dorahy MJ (2008). Psychosis, trauma and dissociation. West Sussex: Wiley and Sons. p. 358.
59 Murgatroyd Ch, Wu Y, Bockmühl Y, Spengler D (2010). Genes learn from stress. How infantile trauma programs us for depression. *Epigenetics*. **5**(3): 194–199.
60 Mylle J, Maes M (2004). Partial posttraumatic stress disorder revisited. *J Affect Disord*. **78** (1): 37–48.
61 Novalis PN, Rojcewicz SJ & Peele R (1999). Klinická príručka podpornej psychoterapie. [(Clinical Manual of Supportive Psychotherapy.) (In Slovak, translated from original Washington DC – London, American Psychiatric Press, Inc.. 1993.)] Trenčín: Vydavateľstvo F. p.421.
62 Panksepp J (1998). Affective neuroscience. The foundations of human and animal emotions. Oxford: Oxford University Press. p. 466.
63 Peter CJ, Akbarian S (2011). Balancing Histone Methylation Activities in Psychiatric Disorders. *Trends Mol Med.* **17**(7): 372–379. doi: 10.1016/j.molmed.2011.02.003.
64 Phillips M, Frederic C (2007). Handbuch der Hypnotherapie bei posttraumatischen und dissoziativen Störungen. [(Healing the Divided Self.) (In German, translated from original New York, WWNorton & Company, 1995)]. 2. Auflage. Heidelberg: Carl-Auer. p. 424.
65 Praško J, Mainerová B, Diveky T, Kamarádová D, Jelenová D, Grambal A, Látalová K, Sigmundová Z, Šilhán P (2011). Panic disorder and stigmatization. *Act Nerv Super Rediviva.* **53**(4): 194–201.
66 Prasko J, Grambal A, Kamaradova D, Jelenova D (2012). Imagery rescripting of traumatic or distressing stories from childhood. *Act Nerv Super Rediviva.* **54**(3): 113–120.
67 Raison CL, Miller AH (2003). When not enough is too much: the role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. *Am J Psychiatry.* **160**: 1554–1565.
68 Ralaus D (2006). Spracovanie traumatických zážitkov pomocou očných pohybov EMDR. . [(Processing traumatic experience via EMDR eye motion.) (In Slovak with English abstract.)] Psychiatria. **13**(3–4): 167–176.
69 Šestáková B, Židková A, Týblová I, Tymkivová M (2012). What is the life quality of the patients who have gone through intensive care? *Act Nerv Super Rediviva.* **54**(1): 31–34.
70 Shapiro F (1998). EMDR Eye Movement Desensitization and Reprocessing. Grundlagen und Praxis. Handbuch zur Behandlung traumatisierter Menschen. [(Eye Movement Desesitization and Reprocessing-Basic Principles, Protocols and Procedures.) In German, translated from original New York, Guilford, 1995)]. Paderborn: Junfermann. p. 485.
71 Sherin JE, Nemeroff ChB (2011). Post-traumatic stress disorder: the neurobiological impact of psychological trauma. *Dialogues Clin Neurosci.* **13**(3): 263–278.
72 Schauer M, Neuner F & Elbert T (2005). Narrative Exposure Therapy. A Shortterm Intervention for Traumatic Stress Disorders after War, Teror, Torture. Cambridge-Göttingen, Hogrefe: Huber Publishers. p. 110.
73 Schlegel L (2005). Základy hlbinnej psychológie, s osobitným zreteľom na neurózológiu a psychoterapiu. Diel I, II, III. [(Grundriss der Tiefenpsychologie, Band I, II, III.) (In Slovak translated form original Tübingen, Francke Verlag, 1973, 1978, 1985)]. Trenčín: Vydavateľstvo F. p.533.
74 Skelton K, Ressler KJ, Norrholm SD, Jovanovic T, Bradley-Davino B (2012). PTSD and Gene Variants: New Pathways and New Thinking. *Neuropharmacology*. **62**(2): 628–637. doi: 10.1016/j.neuropharm.2011.02.013.
75 Smolík P (2002). Duševní a behaviorální poruchy. Průvodce klasifikací. Nástin nozologie. Diagnostika. [(Mental and behavioral disorders. A guide to classification. Outline of nosology. Diagnostics.) (In Czech.)] Praha: Maxdorf. p. 506.
76 Smucker MR, Dancu C, Foa EB, Niederee JL (1995). Imagery Rescripting: A new treatment for survivors of childhood sexual abuse suffering from posttraumatic stress. *Journal of Cognitive Psychotherapy*. **9**: 317.
77 Stein DJ, Rauch SL (2008). Neuropsychiatric aspects of anxiety disorders. In: Yudofsky SC, Hales RE, editors. Neuropsychiatry and Behavioral Neurosciences, 5th Edition. Washington, London: American Psychiatric Publishing. p. 1025–1043.
78 Steiner B, Krippner K (2006). Psychotraumatherapie. Tiefenpsychologischimaginative Behandlung von traumatisierten Patienten. Stuttgart: Schattauer. p. 355.
79 Stickgold R (2002). EMDR: A putative neurobiological mechanism of action. *J Clin Psychol.* **58** (1): 61–75.
80 Strawn JR, Geracioti TD (2008). Noradrenergic dysfunction and the psychopharmacology of posttraumatic stress disorder. *Depress Anxiety.* **25**: 260–271.
81 Tagay S, Repic N & Senf W (2011). Traumafolgestörungen bei Erwachsenen, Kindern und Jugendlichen. *Psychotherapeut*, 1–12.
82 Teicher MH, Samson JA, Polcari A & Mcgreenery CE (2006). Sticks, stones and hurtful words. Relative effects of various forms of childhood maltreatment. *Am J Psychiatry.* **163**: 993–1000.
83 Terr LM (1991). Childhood traumas: An outline and overview. *Am J Psychiatry.* **148**: 10–20.
84 Ungerer O, Deter HC, Fikentscher E & Konzag TA (2010). Verbesserte Diagnostik von Traumafolgestörungen durch den Einsatz der Life-Stressor Checklist. Psychotherapie, Psychosomatik, Medizinische Psychologie 60: 434–441.
85 Van der Hart O, Brown P (1992). Abreaction re-evaluated. *Dissociation*. **5**: 127–40.
86 Van der Hart O, Dorahy MJ (2009). History of the concept of dissociation. In Dell P & O´Nell J, eds. Dissociation and the Dissociative Disorders: DSM-V and beyond. New York: Routledge. p. 3–26.
87 Vojtová H & Hašto J (2009). Neurobiology of Eye Movement Desensitization and Reprocessing. *Act Nerv Super.* **51**(3): 98–102.
88 Warner D, Schmidt I & Heim C (2006). Psychobiologie der Posttraumatischen Belastugsstörung. In Remmel A, Kernberg OF, Vollmoeller W & Strauss B, ed. Handbuch Körper und Persönlichkeit. Entwicklungspsychologie, Neurobiologie und Therapie von Persönlichkeitsstörungen. Stuttgart: Schattauer, 321–344.
89 Welnhold B (2012). A Steep Learning Curve. Decoding Epigenetic Influences on Behavior and Mental Health. *Environmental Health Perspectives.* **120** (10): A 397–A401.
90 Wittchen H-U, Wunderlich U, Gruschwitz S & Zaudig M (1997). Skid-I. Strukturiertes Klinisches Interview für DSM-IV. Achse I: Psychische Störungen. Interviewheft. Göttingen: Hogrefe. p. 122.
91 Wöller W & Kruse J (2011). Hlbinná psychoterapia. Základy a návody pre prax. [(Tiefenpsychologisch fundierte Psychotherapie. Basisbuch und Praxisleitfanden.) (In Slovak translated from original Stuttgart – New York, Schattauer, 2005.)] Trenčín: Vydavateľstvo F. p. 536.
92 Wöller W (2006). Trauma und Persönlichkeitsstörungen. Psychodynamischintegrative Therapie. Stuttgart: Schatauer. p.582.
93 World Health Organisation (1991) Tenth Revision of the International Clasification of Diseases. Chapter V (F) Mental and Behavioral Disorders including Disorders of Psychological Development. Clinical Descriptions and Diagnostic Guidelines. Geneva. p.346.
94 Wu G, Feder A, Cohen H, Kim JJ, Calderon S, Charney DS, Mathé AA (2013). Understanding resilience. *Front Behav Neurosci.* **7**: 10. doi: 10.3389/fnbeh.2013.00010. eCollection 2013.
95 Yehuda R, Brand S, Yang RK (2006). Plasma neuropeptide Y concentrations in combat exposed veterans: relationship to trauma exposure, recovery from PTSD, and coping. *Biol Psychiatry.* **59**: 660–663.
96 Yehuda R, Flory JD, Pratchett LC, Buxbaum J, Ising M, Holsboer F (2010). Putative biological mechanisms for the association between early life adversity and the subsequent development of PTSD. *Psychopharmacology (Berl.).* **212** (3): 405–417. doi: 10.1007/s00213-010-1969-6.
97 Zovkic IB, Meadows JP, Kaas GA, Sweatt JD (2013). Interindividual Variability in Stress Susceptibility: A Role for Epigenetic Mechanisms in PTSD. *Front Psychiatry.* **4**: 60. doi: 10.3389/fpsyt.2013.00060. eCollection 2013.