



**University of  
Zurich**<sup>UZH</sup>

**Zurich Open Repository and  
Archive**

University of Zurich  
Main Library  
Strickhofstrasse 39  
CH-8057 Zurich  
[www.zora.uzh.ch](http://www.zora.uzh.ch)

---

Year: 2015

---

## **Biological correlates of complex posttraumatic stress disorder-state of research and future directions**

Marinova, Zoya; Maercker, Andreas

**Abstract:** Complex posttraumatic stress disorder (PTSD) presents with clinical features of full or partial PTSD (re-experiencing a traumatic event, avoiding reminders of the event, and a state of hyperarousal) together with symptoms from three additional clusters (problems in emotional regulation, negative self-concept, and problems in interpersonal relations). Complex PTSD is proposed as a new diagnostic entity in ICD-11 and typically occurs after prolonged and complex trauma. Here we shortly review current knowledge regarding the biological correlates of complex PTSD and compare it to the relevant findings in PTSD. Recent studies provide support to the validity of complex PTSD as a separate diagnostic entity; however, data regarding the biological basis of the disorder are still very limited at this time. Further studies focused on complex PTSD biological correlates and replication of the initial findings are needed, including neuroimaging, neurobiochemical, genetic, and epigenetic investigations. Identification of altered biological pathways in complex PTSD may be critical to further understand the pathophysiology and optimize treatment strategies.

DOI: [10.3402/ejpt.v6.25913](https://doi.org/10.3402/ejpt.v6.25913)

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <http://doi.org/10.5167/uzh-110591>

Published Version



Originally published at:

Marinova, Zoya; Maercker, Andreas (2015). Biological correlates of complex posttraumatic stress disorder-state of research and future directions. *European Journal of Psychotraumatology*, 6:25913. DOI: [10.3402/ejpt.v6.25913](https://doi.org/10.3402/ejpt.v6.25913)

REVIEW ARTICLE

## Biological correlates of complex posttraumatic stress disorder—state of research and future directions

Zoya Marinova<sup>1,2\*</sup> and Andreas Maercker<sup>1</sup>

<sup>1</sup>Department of Psychology, Division of Psychopathology and Clinical Intervention, University of Zürich, Zürich, Switzerland; <sup>2</sup>University Clinics for Child and Adolescent Psychiatry, University of Zürich, Zürich, Switzerland

Complex posttraumatic stress disorder (PTSD) presents with clinical features of full or partial PTSD (re-experiencing a traumatic event, avoiding reminders of the event, and a state of hyperarousal) together with symptoms from three additional clusters (problems in emotional regulation, negative self-concept, and problems in interpersonal relations). Complex PTSD is proposed as a new diagnostic entity in ICD-11 and typically occurs after prolonged and complex trauma. Here we shortly review current knowledge regarding the biological correlates of complex PTSD and compare it to the relevant findings in PTSD. Recent studies provide support to the validity of complex PTSD as a separate diagnostic entity; however, data regarding the biological basis of the disorder are still very limited at this time. Further studies focused on complex PTSD biological correlates and replication of the initial findings are needed, including neuroimaging, neurobiochemical, genetic, and epigenetic investigations. Identification of altered biological pathways in complex PTSD may be critical to further understand the pathophysiology and optimize treatment strategies.

**Keywords:** *Complex posttraumatic stress disorder; posttraumatic stress disorder; biological correlate; complex trauma; pathophysiology*

Responsible Editor: Ruth Lanius, Western University of Canada, Canada.

\*Correspondence to: Zoya Marinova, Department of Psychology, Division of Psychopathology and Clinical Intervention, University of Zürich, Binzmuehlestr. 14/17, CH-8050 Zürich, Switzerland, Email: z.marinova@psychologie.uzh.ch

For the abstract or full text in other languages, please see Supplementary files under 'Article Tools'

Received: 2 September 2014; Revised: 7 March 2015; Accepted: 15 March 2015; Published: 16 April 2015

Posttraumatic stress disorder (PTSD) is a mental disorder, which occurs in response to a severe traumatic event and includes several core symptoms: re-experiencing the event accompanied by intense distress, persistently avoiding reminders of the traumatic event, and a state of hyperarousal. PTSD is associated with significant impairment of social as well as occupational functioning, which presents a severe burden for the affected individuals and society (Kessler, 2000). Furthermore, treatment success is often limited, leading to a protracted or recurrent course of symptoms appearing or recurring years after the traumatic event.

The concept of partial (subthreshold) PTSD has long been discussed in order to provide diagnostic coverage for individuals suffering from PTSD symptoms, but not meeting full PTSD diagnostic criteria (Schützwohl & Maercker, 1999; Stein, Walker, et al., 1997). Functional impairment degree and comorbidity rates in partial PTSD have been

found to be intermediate between those of traumatized subjects without PTSD symptoms or with full PTSD (McLaughlin et al., 2015). Partial PTSD has been associated with increased risk for mood and anxiety disorders, substance use, suicide attempts, and medical comorbidities in comparison to traumatized individuals without PTSD symptoms (Pietrzak, Goldstein, Southwick, & Grant, 2011, 2012).

### Complex PTSD—symptoms and its proposed inclusion as a new diagnostic entity in the ICD-11

Exposure to multiple traumatic events, especially in childhood, has been associated with a more complex trauma symptomatology later in life (Briere, Kaltman, & Green, 2008; Cloitre et al., 2009). It was conceptualized in 1992 by Herman that after prolonged traumatic experience, complex PTSD may occur (Herman, 1992). Complex PTSD has been proposed for inclusion as a new diagnostic

entity in the ICD-11 by the working group for “disorders specifically associated with stress” of the World Health Organization (Maercker et al., 2013a, 2013b). The planned complex PTSD category will include three additional clusters of symptoms besides the core PTSD symptoms: persistent and pervasive problems in emotional regulation (increased emotional reactivity, lack of affect, violent outbursts), negative self-concept (feelings of defeat, worthlessness, guilt, or shame), and problems in interpersonal relations (difficulties in establishing or maintaining relationships with others). Complex PTSD will be diagnosed when symptoms from these three additional domains are present in addition to the core symptoms of full or partial PTSD (Table 1). It is important to note that the definition of complex PTSD will be based on the disease symptomatology and not on the specific trauma. However, complex PTSD is most commonly associated with traumatic events of prolonged nature that the victim could not escape. Trauma types associated with complex PTSD include childhood maltreatment, torture, imprisonment, war and refugee status, or long-lasting interpersonal violence (Bryant, 2010).

Multiple diagnostic iterations of complex PTSD-related symptoms have been proposed. Some features related to complex PTSD symptomatology have been encompassed by “Disorders of Extreme Stress Not Otherwise Specified” (DESNOS) (Pelcovitz et al., 1997); “PTSD and Its Associated Features” in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (APA, 2000); and “Enduring Personality Change after Catastrophic Events” (EPCACE) in the ICD-10 (WHO, 1992). In addition, the term “Developmental Trauma Disorder” has been used to describe the clinical presentation in children and adolescents subjected to complex trauma (Van der Kolk, 2005).

An alternative approach is implemented in DSM-5, in which symptoms related to the complex PTSD concept are considered a part of the core symptom profile of PTSD. This is accomplished through introducing a new cluster D of PTSD symptoms, which concern negative mood and cognition changes associated with the traumatic

**Table 1.** Symptom domains related to PTSD and complex PTSD according to the proposed ICD-11 diagnostic criteria

PTSD	Complex PTSD
Re-experiencing a traumatic event	Re-experiencing a traumatic event
Avoiding reminders of the event	Avoiding reminders of the event
Hyperarousal	Hyperarousal
	Affect dysregulation
	Negative self-concept
	Problems in interpersonal relationships

event (including among others negative self-beliefs, feeling of detachment from others, and negative emotional states) (APA, 2013). DSM-5 also includes a dissociative PTSD subtype to diagnose individuals who in addition to the core PTSD symptoms demonstrate significant dissociative symptoms, including depersonalization and/or derealization. Although the proposed for ICD-11 complex PTSD diagnostic criteria do not particularly emphasize dissociation, the DESNOS concept considered dissociative symptoms besides other symptom domains.

We review studies focusing on validating the diagnostic concept and identifying biological correlates of complex PTSD. Key biological correlates of PTSD are pointed out to contextualize complex PTSD findings and to outline potential areas for complex PTSD research. Finally, we present future research directions for the identification of complex PTSD neurobiological correlates.

### Search strategy

Relevant studies were identified by searching the database PUBMED (<http://www.ncbi.nlm.nih.gov/pubmed/>) for the terms “complex posttraumatic stress disorder” OR “complex PTSD” OR “disorders of extreme stress not otherwise specified” OR “SIDES.” Original articles, including the search terms and published through 28 February 2015, were analyzed to select those identifying complex PTSD biological correlates or assessing its validity as a diagnostic concept. In addition, we searched for and separately analyzed original articles including the terms “childhood sexual abuse” AND “PTSD” OR “posttraumatic stress disorder.” PTSD-affected individuals with history of childhood sexual abuse (CSA) are expected to present with especially high rates of complex PTSD symptoms (McLean & Gallop, 2003; Roth, Newman, Pelcovitz, Van der Kolk, & Mandel, 1997; Zlotnick et al., 1996).

### Validating the diagnostic concept of complex PTSD

Several recent studies have assessed the validity of the proposed for ICD-11 complex PTSD as a diagnosis distinct from PTSD. A study by Cloitre, Garvert, Brewin, Bryant, and Maercker (2013) demonstrated the presence of three trauma victims’ classes using latent profile analysis (LPA)—scoring high only on PTSD symptoms, high on complex PTSD symptoms, or low on all PTSD and complex PTSD symptoms. In this investigation, complex PTSD symptomatology was more often associated with chronic trauma and more highly predictive of impairment. Complex PTSD construct validity was also assessed in a group of adults subjected to childhood institutional abuse (Knefel, Garvert, Cloitre, & Lueger-Schuster, 2015; Knefel & Lueger-Schuster, 2013), in which complex PTSD was indicated as a relevant diagnosis by a strong model

fit using confirmatory factor analysis and LPA. In addition, latent class analysis in three distinct trauma groups (victims of sexual assault, physical assault, or bereavement) provided additional evidence for the fit of complex PTSD as a separate class and its association with serious psychological problems (Elklit, Hyland, & Shevlin, 2014). A recent study from our group further supported the validity of complex PTSD as a separate diagnostic entity in a German community sample of 3,012 adolescents and young adults subjected to interpersonal violence. LPA in this sample supported a four-class fit, in which individuals with high degree of PTSD symptoms and individuals with high degree of complex PTSD symptoms were presenting as two distinct classes (Perkonig et al., submitted). Altogether, these studies underscore the validity of the diagnostic concept of complex PTSD and the association of complex PTSD symptoms with additional psychological problems, potentially indicative of higher impairment.

On the other hand, the diagnostic utility of the dissociative PTSD subtype has also been supported by studies utilizing LPA (Steuwe, Lanius, & Frewen, 2012; Wolf et al., 2012).

### Neuroimaging studies and complex PTSD

In adult PTSD patients, reduced hippocampal, left amygdala, and anterior cingulate cortex (ACC) volumes have been detected (Bremner et al., 1995; meta-analysis by Karl et al., 2006). A recent meta-analysis by Meng et al. (2014) corroborated these findings, identifying volume reduction of the left ACC, the left insula, and the right parahippocampal gyrus. Functional brain changes in the hippocampus, amygdala, and prefrontal cortex have also been found in PTSD patients (Bremner, 2007a). A meta-analysis, summarizing functional MRI (fMRI) and positron emission tomography studies on PTSD, confirmed mid- and dorsal ACC and amygdala hyperactivity, as

well as ventromedial prefrontal cortex and inferior frontal gyrus hypoactivity (Hayes, Hayes, & Mikedis, 2012).

Several imaging studies have been conducted on complex PTSD subjects. In childhood abuse-related complex PTSD, decreased gray matter concentration in the right hippocampus, the right dorsal ACC, and the right orbitofrontal cortex (OFC) was observed (Thomaes et al., 2010). These findings imply that complex PTSD may be associated with more severe neural imaging correlates than PTSD. An fMRI study on childhood abuse-related complex PTSD indicated altered activation of the left hippocampus and parahippocampal gyrus, suggesting hippocampal dysfunction (Thomaes et al., 2009). Furthermore, in complex PTSD disturbances in the activation of the left ventral ACC and dorsal ACC, the dorsomedial prefrontal cortex, left ventrolateral prefrontal, and OFC were observed, implying involvement of regions particularly important for emotional processing (Thomaes et al., 2013). Reversal after psycho-educational and cognitive behavioral stabilizing group treatment of some of the neuroimaging alterations in complex PTSD patients was also detected (Thomaes et al., 2012). All four studies assessing neuroimaging correlates associated with complex PTSD (Table 2) focused on childhood abuse-related complex PTSD. Their replication by independent investigations of complex PTSD related to other trauma types is warranted. In addition, these studies included probands with PTSD symptoms and complex PTSD symptoms consistent with the DESNOS conceptualization. Thus, they do not directly support the proposed by the ICD-11 complex PTSD criteria, but rather the broader concept of biological correlates associated with complex PTSD-related symptoms.

The existence of a dissociative PTSD subtype has also been suggested by imaging studies showing distinct patterns of brain activation in patients presenting with

*Table 2.* Studies on biological correlates of complex PTSD

Authors	Sample	Diagnostic tool	Method	Key findings
Thomaes et al., 2009	Child abuse-related complex PTSD	CAPS SIDES	fMRI	- ↑ activation in the left hippocampus and parahippocampal gyrus during preferential recall of negative words
Thomaes et al., 2010	Child abuse-related complex PTSD	CAPS SIDES	Structural MRI	- ↓ hippocampal volume - ↓ ACC volume - ↓ right orbitofrontal cortex volume
Thomaes et al., 2012	Child abuse-related complex PTSD	CAPS SIDES	fMRI	- trend for ↑ left anterior insula and dorsal ACC activation in the classic Stroop task - after therapy ↓ dorsal ACC and left anterior insula activation (during encoding of negative words)
Thomaes et al., 2013	Child abuse-related complex PTSD	CAPS SIDES	fMRI	- ↑ response in the left ventral ACC and dorsal ACC extending to the dorsomedial prefrontal cortex - trend for ↑ left hippocampus activation

fMRI = functional magnetic resonance imaging; complex PTSD = complex posttraumatic stress disorder; ACC = anterior cingulate cortex.

PTSD with or without dissociative symptoms (Lanius, Brand, Vermetten, Frewen, & Spiegel, 2012).

### Areas of interest for future complex PTSD research based on previous PTSD findings

#### *Autonomic and neurochemical measures*

Hyperactivity of the sympathetic branch of the autonomic nervous system has been observed in PTSD patients, including higher blood pressure, heart rate, and increased skin conductance (reviewed in Sherin & Nemeroff, 2011). In addition, PTSD patients show exaggerated response to traumatic reminders, associated with increases in heart rate, blood pressure, and norepinephrine levels.

Norepinephrine and serotonin signaling dysregulation has repeatedly been implicated in PTSD (Krystal & Neumeister, 2009). Alterations in the signaling of amino acids ( $\gamma$ -aminobutyric acid—GABA and glutamate), peptides (neuropeptide Y and endogenous opioid peptides), and thyroid hormones have also been associated with PTSD (Sherin & Nemeroff, 2011). PTSD has been correlated with hypocortisolism, although not all studies have replicated this phenomenon. A meta-analysis suggested the measurement method, sex, and trauma type could influence hypocortisolism detection in PTSD (Meewisse, Reitsma, De Vries, Gersons, & Olf, 2007).

Investigation of the overlap and potential differences in autonomic and neurobiochemical alterations associated with PTSD and complex PTSD is an important research avenue, which can help to understand the pathophysiology of the disorder and may even contribute to novel therapeutic targets identification.

#### *Genetic predisposition*

PTSD symptoms heritability between 30 and 40% has been estimated; however, there has been a relatively small number of genetic variants identified in PTSD patients (Cornelis, Nugent, Amstadter, & Koenen, 2010; Stein, Jang, Taylor, Vernon, & Livesley, 2002; True et al., 1993). Most studies have focused on polymorphisms in genes associated with the neurotransmitters dopamine, serotonin, and norepinephrine; genes related to the hypothalamic-pituitary-adrenal axis (HPA axis); and neurotrophic factors (reviewed in Cornelis et al., 2010). In addition, a single nucleotide polymorphism (SNP) in the retinoid-related orphan receptor alpha gene, implicated in neuroprotection, was identified by a genome-wide association study (GWAS) as a PTSD associated variant (Logue et al., 2013).

So far no studies have specifically investigated the role of genetic predisposition for complex PTSD. Such information would provide insight into the heritability range of complex PTSD and the extent of overlap in

biological pathways involved in the genetic predisposition to PTSD and complex PTSD.

In regards to a dissociative PTSD subtype, a recent GWAS study by Wolf et al. (2014) identified in a trauma-exposed sample for 10 SNPs, a suggestive association with dissociative symptoms, which did not reach genome-wide significance.

Because genetic factors only partially account for PTSD vulnerability, the involvement of epigenetic factors in the pathophysiology of PTSD has also been hypothesized.

#### *Epigenetic factors*

Epigenetic factors reflect the effect of environmental influences on disease occurrence and progression. Recent studies have investigated the role of epigenetic modifications, including DNA methylation, in PTSD. In particular, altered DNA methylation patterns of genes associated with immune function have been identified in PTSD (Rusiecki et al., 2013; Smith et al., 2011; Uddin et al., 2010). Changes in DNA methylation of repetitive elements have also been described (Rusiecki et al., 2012).

So far epigenetic mechanisms have not been investigated specifically in complex PTSD. Assessment of epigenetic patterns in complex PTSD would be of particular importance due to their potential reversibility, rendering them an attractive therapeutic target. A pioneering study by Yehuda et al. (2013) demonstrated an association between DNA methylation and psychotherapy-induced changes in PTSD symptoms. It showed association of *glucocorticoid receptor* and *FK506 binding protein 5 (FKBP5)* DNA methylation levels with prognosis and symptoms' severity respectively after psychotherapy in a group of PTSD-affected combat veterans (Yehuda et al., 2013).

Interestingly, an interaction of *FKBP5* genetic variants and childhood abuse for PTSD vulnerability and symptoms severity has been demonstrated (Binder et al., 2008; Xie et al., 2010). Furthermore, for one of the *FKBP5* genetic variants, a mediating effect of DNA methylation levels for PTSD vulnerability caused by genetic polymorphism and childhood abuse interaction has been identified (Klengel et al., 2013). Such models of gene  $\times$  environmental interaction and mediating effects of epigenetic factors may be highly relevant for complex PTSD vulnerability and will need to be elucidated by further studies.

#### *Telomere shortening*

Human telomeres are repetitive sequences of nucleotides at the ends of chromosomes, which protect them from damage and foster their stability. Recent studies have demonstrated that shortened telomere length may be associated with PTSD (O'Donovan et al., 2011; Zhang et al., 2014). Although childhood trauma has also been associated with telomere shortening, the importance of the presence of childhood trauma for decrease in

telomere length in PTSD patients has yet to be determined. Telomere length in complex PTSD has not been specifically investigated so far. Interestingly, epigenetic alterations or changes in telomere length may also show transgenerational effects (Küffer, Maercker, & Burri, 2014; Yehuda & Bierer, 2008).

Some major biological findings relevant to PTSD and pilot data concerning complex PTSD are summarized in Table 3.

### Timing of the traumatic event, complex trauma, and complex PTSD symptomatology

#### *Developmental stage during which the traumatic event occurs*

The role of the developmental stage, during which a traumatic insult occurs, for complex PTSD vulnerability and for the involvement of specific biological pathways is not completely clarified. Protracted childhood trauma has been associated with increased risk for affect dysregulation,

disorganization of the self-concept, and interpersonal relationship problems; which are symptoms of complex PTSD (Briere & Rickards, 2007). Neuroimaging findings related to PTSD in abused children and adolescents have included decreased cerebral and intracranial volumes in comparison to controls, and correlation of brain volumes with abuse duration and trauma onset (De Bellis et al., 1999).

However, complex PTSD also can be observed after adulthood trauma (for example in victims of torture) even in the absence of childhood abuse (McDonnell, Robjant, & Katona, 2013). Thus, symptoms characteristic of complex PTSD were evident in ex-prisoners of war assessed 30 years after their release from captivity (Zerach & Solomon, 2013), and in female veterans who suffered military sexual assault (Luterek, Bittinger, & Simpson, 2011).

A recent study by Mehta et al. (2013) found almost completely non-overlapping genome-wide DNA methylation profiles between PTSD subjects who suffered childhood maltreatment or only adulthood trauma. The role of

*Table 3.* Neurobiological correlates associated with PTSD and complex PTSD

	PTSD	Complex PTSD (pilot data in need of replication)
Structural imaging studies	<ul style="list-style-type: none"> <li>- ↓ hippocampal volume</li> <li>- ↓ ACC volume</li> </ul>	<ul style="list-style-type: none"> <li>- ↓ hippocampal volume</li> <li>- ↓ ACC volume</li> <li>- ↓ right OFC volume</li> </ul>
Functional imaging studies (implicated areas)	<ul style="list-style-type: none"> <li>- hippocampus and parahippocampal gyrus</li> <li>- amygdala</li> <li>- prefrontal cortex</li> <li>- mid- and dorsal ACC</li> <li>- amygdala</li> <li>- ventromedial prefrontal cortex</li> <li>- inferior frontal gyrus</li> </ul>	<ul style="list-style-type: none"> <li>- hippocampus and parahippocampal gyrus</li> <li>- ventral and dorsal ACC</li> <li>- dorsomedial prefrontal cortex</li> <li>- ventrolateral prefrontal cortex</li> <li>- orbitofrontal cortex</li> </ul>
Autonomic and Neurochemical measures	<ul style="list-style-type: none"> <li>- heart rate</li> <li>- blood pressure</li> <li>- skin conductance</li> <li>- norepinephrine</li> <li>- serotonin</li> <li>- <math>\gamma</math>-aminobutyric acid (GABA)</li> <li>- glutamate</li> <li>- neuropeptide Y</li> <li>- endogenous opioid peptides</li> <li>- cortisol</li> </ul>	
Genetic predisposition	<ul style="list-style-type: none"> <li>- polymorphisms in:</li> <li>- dopaminergic, serotonergic and norepinephrinergic genes</li> <li>- genes related to the HPA axis</li> <li>- neurotrophic factors</li> <li>- the retinoid-related orphan receptor alpha gene</li> </ul>	
Epigenetic factors	<ul style="list-style-type: none"> <li>- DNA methylation of genes associated with immune functions</li> <li>- DNA methylation of repetitive elements</li> </ul>	

Studies assessing complex PTSD reviewed in the table included individuals with PTSD symptoms and complex PTSD symptoms consistent with the DESNOS conceptualization.

*Table 4.* Studies on biological correlates of PTSD related to childhood sexual abuse

Authors	Sample	Key findings
Schaefer et al., 2014	CSA-related PTSD	- ↑ serum levels of the fatty acid ethanolamide oleoylethanolamide
Bremner, Vermetten, & Kelley, 2007b	CSA-related PTSD	- resting afternoon hypocortisolemia with ↑ cortisol pulsatility
Bremner et al., 2005	CSA-related PTSD	- ↑ left amygdala activation with fear acquisition, and ↓ anterior cingulate function with fear extinction
Friedman, Wang, Jalowiec, McHugo, & McDonagh-Coyle, 2005	CSA-related PTSD	- ↑ in total T3 levels, total T3/free thyroxine ratio, free T3/total T3 ratio, and small ↓ in TSH
Klumpers et al., 2004	CSA-related PTSD	- no significant differences in cardiovascular or hormonal response to standardized stress tests
Bremner et al., 2004	CSA-related PTSD	- indications for a dysfunction of a network of brain regions including the visual and parietal cortex and the anterior cingulate
Bremner et al., 2003b	CSA-related PTSD	- indications for a dysfunction of a network of brain regions including the medial prefrontal cortex, hippocampus and cingulate in a study of emotionally valenced declarative memory
Bremner et al., 2003a	CSA-related PTSD	- ↓ hippocampal volume and failure of hippocampal activation during verbal declarative memory tasks
Wilson, Van der Kolk, Burbridge, Fislser, & Kradin, 1999	CSA-related PTSD	- ↑ index of lymphocyte activation (CD45RO/CD45RA)
Shin et al., 1999	CSA-related PTSD	- ↑ orbitofrontal cortex and anterior temporal pole and ↓ increases in anterior cingulate gyrus blood flow compared to non-PTSD traumatized group
Bremner et al., 1999	CSA-related PTSD	- dysfunction of the medial prefrontal cortex, visual association cortex and hippocampus in pathological memories of childhood abuse - ↑ activation in motor cortex and posterior cingulate
Orr et al., 1998	CSA-related PTSD	- larger physiologic responses during abuse-related scripts
Stein, Yehuda, et al., 1997	CSA-related PTSD	- ↑ suppression of plasma cortisol in response to dexamethasone
Lemieux & Coe, 1995	CSA-related PTSD	- sympathetic and adrenocortical activation

CSA = childhood sexual abuse; PTSD = posttraumatic stress disorder.

DNA methylation for PTSD vulnerability appeared to be greater in the childhood maltreated subjects. DNA methylation alterations in genes associated with cell survival, development, adhesion, migration, and immune function were observed in both groups. Unique pathways were related to central nervous system development and tolerance induction (in childhood maltreated PTSD subjects) and growth and apoptosis (in PTSD subjects who had not suffered childhood maltreatment) (Mehta et al., 2013). It is not clear whether these differences are due to the timing of the traumatic event or whether childhood trauma was more commonly related to a complex PTSD phenotype, contributing to the differing DNA methylation patterns.

An important focus of further investigations assessing biological correlates of complex PTSD will be to determine the overlap and differences between pathways involved in complex PTSD symptomatology after traumatic events occurring in childhood or adulthood.

#### *Potential insight from childhood sexual abuse-related PTSD studies*

Due to the limited number of studies focusing on biological correlates of complex PTSD, we also searched for studies assessing PTSD related to CSA. Clear distinction should be made between childhood abuse-related PTSD (including CSA) and complex PTSD, because childhood abuse victims may also develop PTSD without complex PTSD symptoms. However, especially high rates of complex PTSD symptoms in CSA survivors have repeatedly been found. Thus, Zlotnick et al. (1996) established that CSA history was associated with a set of symptoms characteristic of DESNOS. In a study by Roth et al. (1997), 76% of sexually abused individuals with a lifetime diagnosis of PTSD also had the diagnosis of complex PTSD. McLean and Gallop (2003) detected complex PTSD symptoms and borderline personality disorder in 94.7% of a group of women with history of early onset sexual abuse.

Studies focusing on CSA-related PTSD have identified changes in diverse neurobiological domains in comparison to abused individuals without PTSD. These include alterations in neuroimaging, autonomic, and neurobiochemical correlates (summarized in Table 4). CSA-related PTSD studies may provide some insight in biological pathways of interest to focus on in complex PTSD patients. For example, a recent study examined the role of endocannabinoids (anandamide and 2-arachidonylglycerol) and of fatty acid ethanolamides (related to endocannabinoids) in a PTSD sample after CSA (Schaefer et al., 2014). Serum levels of the fatty acid ethanolamide oleoylethanolamide were elevated in the CSA-related PTSD group, supporting previous genetic and imaging studies, implying a role of the cannabinoid system in PTSD.

### Significance of complex PTSD biological correlates identification

A recent review article has outlined the potential significance of using a social cognitive and affective neuroscience integrating approach in assessing complex PTSD (Lanius, Bluhm, & Frewen, 2011). The authors emphasized the importance of identifying deficits in emotional regulation and processing, self-awareness and self-reference, and their interconnections for the diagnosis and treatment of complex PTSD patients. In addition, complex PTSD poses specific treatment challenges, and there are many open questions regarding the therapeutic approach, treatment duration, and expected improvement (Cloitre et al., 2011). The characterization of complex PTSD biological correlates and the common or unique biological pathways involved in the pathogenesis of complex PTSD in comparison to PTSD would provide a better understanding of the disorder. This knowledge may in the end contribute to the identification of novel therapeutic strategies for complex PTSD.

### Conclusions and future research directions

- 1) Recent studies have examined and supported the diagnostic validity of complex PTSD as proposed for inclusion in ICD-11.
- 2) On the other hand, only a few studies have assessed the association of specific neurobiological correlates with complex PTSD. Independent replication and extension of pilot neuroimaging findings will be critical to identify brain circuits involved in the development of complex PTSD symptomatology.
- 3) Combinations of genetic and epigenetic studies are needed to address the role of genetic vulnerability, environmental factors, and their interaction in the development of complex PTSD symptomatology.
- 4) Characterization of autonomic and neurobiochemical correlates of complex PTSD and the overlap or

potential differences with PTSD would help gain insight to the pathophysiology of the disorder and may aid in the identification of therapeutic targets.

- 5) Clearly defined and consistent subjects' inclusion criteria would allow easier comparison of results between studies. In this respect, the introduction of complex PTSD as a diagnostic entity in ICD-11 would facilitate research efforts.
- 6) The potential role of the timing of the traumatic event and trauma type on biological findings associated with complex PTSD needs to be assessed, because initial studies have focused on complex PTSD related to childhood abuse.
- 7) A potential relationship between complex PTSD as proposed for ICD-11 and the dissociative PTSD subtype should be investigated.

### Conflict of interest and funding

The authors have no conflict of interest to report for the present study.

### References

- American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). Washington, DC: Author.
- American Psychiatric Association & American Psychiatric Association Task Force on DSM-5 (APA). (2013). *Diagnostic and statistical manual of mental disorders: DSM-5*. Arlington, VA: American Psychiatric Publishing.
- Binder, E. B., Bradley, R. G., Liu, W., Epstein, M. P., Deveau, T. C., Mercer, K. B., et al. (2008). Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. *The Journal of the American Medical Association*, 299(11), 1291–1305.
- Bremner, D., Vermetten, E., & Kelley, M. E. (2007b). Cortisol, dehydroepiandrosterone, and estradiol measured over 24 hours in women with childhood sexual abuse-related posttraumatic stress disorder. *The Journal of Nervous and Mental Disease*, 195(11), 919–927.
- Bremner, J. D. (2007a). Neuroimaging in posttraumatic stress disorder and other stress-related disorders. *Neuroimaging Clinics of North America*, 17(4), 523–538.
- Bremner, J. D., Narayan, M., Staib, L. H., Southwick, S. M., McGlashan, T., & Charney, D. S. (1999). Neural correlates of memories of childhood sexual abuse in women with and without posttraumatic stress disorder. *The American Journal of Psychiatry*, 156(11), 1787–1795.
- Bremner, J. D., Randall, P., Scott, T. M., Bronen, R. A., Seibyl, J. P., Southwick, S. M., et al. (1995). MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. *The American Journal of Psychiatry*, 152(7), 973–981.
- Bremner, J. D., Vermetten, E., Schmahl, C., Vaccarino, V., Vythilingam, M., Afzal, N., et al. (2005). Positron emission tomographic imaging of neural correlates of a fear acquisition and extinction paradigm in women with childhood sexual-abuse-related post-traumatic stress disorder. *Psychological Medicine*, 35(6), 791–806.



- Bremner, J. D., Vermetten, E., Vythilingam, M., Afzal, N., Schmah, C., Elzinga, B., et al. (2004). Neural correlates of the classic color and emotional stroop in women with abuse-related posttraumatic stress disorder. *Biological Psychiatry*, 55(6), 612–620.
- Bremner, J. D., Vythilingam, M., Vermetten, E., Southwick, S. M., McGlashan, T., Nazeer, A., et al. (2003a). MRI and PET study of deficits in hippocampal structure and function in women with childhood sexual abuse and posttraumatic stress disorder. *The American Journal of Psychiatry*, 160(5), 924–932.
- Bremner, J. D., Vythilingam, M., Vermetten, E., Southwick, S. M., McGlashan, T., Staib, L. H., et al. (2003b). Neural correlates of declarative memory for emotionally valenced words in women with posttraumatic stress disorder related to early childhood sexual abuse. *Biological Psychiatry*, 53(10), 879–889.
- Briere, J., Kaltman, S., & Green, B. L. (2008). Accumulated childhood trauma and symptom complexity. *Journal of Traumatic Stress*, 21(2), 223–226.
- Briere, J., & Rickards, S. (2007). Self-awareness, affect regulation, and relatedness: Differential sequels of childhood versus adult victimization experiences. *The Journal of Nervous and Mental Disease*, 195(6), 497–503.
- Bryant, R. A. (2010). “The complexity of complex PTSD.” *The American Journal of Psychiatry*, 167(8), 879–881.
- Cloitre, M., Courtois, C. A., Charuvastra, A., Carapezza, R., Stolbach, B. C., & Green, B. L. (2011). Treatment of complex PTSD: Results of the ISTSS expert clinician survey on best practices. *Journal of Traumatic Stress*, 24(6), 615–627.
- Cloitre, M., Garvert, D. W., Brewin, C. R., Bryant, R. A., & Maercker, A. (2013). Evidence for proposed ICD-11 PTSD and complex PTSD: A latent profile analysis. *European Journal of Psychotraumatology*, 4, 20706, doi: <http://dx.doi.org/10.3402/ejpt.v4i0.20706>
- Cloitre, M., Stolbach, B. C., Herman, J. L., Van der Kolk, B., Pynoos, R., Wang, J., et al. (2009). A developmental approach to complex PTSD: Childhood and adult cumulative trauma as predictors of symptom complexity. *Journal of Traumatic Stress*, 22(5), 399–408.
- Cornelis, M. C., Nugent, N. R., Amstadter, A. B., & Koenen, K. C. (2010). Genetics of post-traumatic stress disorder: Review and recommendations for genome-wide association studies. *Current Psychiatry Reports*, 12(4), 313–326.
- De Bellis, M. D., Keshavan, M. S., Clark, D. B., Casey, B. J., Giedd, J. N., Boring, A. M., et al. (1999). A. E. Bennett Research Award. Developmental traumatology. Part II: Brain development. *Biological Psychiatry*, 45(10), 1271–1284.
- Elklit, A., Hyland, P., & Shevlin, M. (2014). Evidence of symptom profiles consistent with posttraumatic stress disorder and complex posttraumatic stress disorder in different trauma samples. *European Journal of Psychotraumatology*, 5, 24221, doi: <http://dx.doi.org/10.3402/ejpt.v5.24221>
- Friedman, M. J., Wang, S., Jalowiec, J. E., McHugo, G. J., & McDonagh-Coyle, A. (2005). Thyroid hormone alterations among women with posttraumatic stress disorder due to childhood sexual abuse. *Biological Psychiatry*, 57(10), 1186–1192.
- Hayes, J. P., Hayes, S. M., & Mikedis, A. M. (2012). Quantitative meta-analysis of neural activity in posttraumatic stress disorder. *Biology of Mood & Anxiety Disorders*, 2(1), 9.
- Herman, J. L. (1992). Complex PTSD: A syndrome in survivors of prolonged and repeated trauma. *Journal of Traumatic Stress*, 5, 377–391.
- Karl, A., Schaefer, M., Malta, L. S., Dörfel, D., Rohleder, N., & Werner, A. (2006). A meta-analysis of structural brain abnormalities in PTSD. *Neuroscience & Biobehavioral Reviews*, 30(7), 1004–1031.
- Kessler, R. C. (2000). Posttraumatic stress disorder: The burden to the individual and to society. *Journal of Clinical Psychiatry*, 61(Suppl 5), 4–12.
- Klengel, T., Mehta, D., Anacker, C., Rex-Haffner, M., Pruessner, J. C., Pariante, C. M., et al. (2013). Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. *Nature Neuroscience*, 16(1), 33–41.
- Klumpers, U. M., Tulen, J. H., Timmerman, L., Fekkes, D., Loonen, A. J., & Boomsma, F. (2004). Responsivity to stress in chronic posttraumatic stress disorder due to childhood sexual abuse. *Psychological Reports*, 94(2), 408–410.
- Knefel, M., Garvert, D. W., Cloitre, M., & Lueger-Schuster, B. (2015). Update to an evaluation of ICD-11 PTSD and complex PTSD criteria in a sample of adult survivors of childhood institutional abuse by Knefel & Lueger-Schuster (2013): A latent profile analysis. *European Journal of Psychotraumatology*, 6, 25290, doi: <http://dx.doi.org/10.3402/ejpt.v6.25290>
- Knefel, M., & Lueger-Schuster, B. (2013). An evaluation of ICD-11 PTSD and complex PTSD criteria in a sample of adult survivors of childhood institutional abuse. *European Journal of Psychotraumatology*, 4, 22608, doi: <http://dx.doi.org/10.3402/ejpt.v4i0.22608>
- Krystal, J. H., & Neumeister, A. (2009). Noradrenergic and serotonergic mechanisms in the neurobiology of posttraumatic stress disorder and resilience. *Brain Research*, 1293, 13–23.
- Küffer, A., Maercker, A., & Burri, A. (2014). Transgenerational effects of PTSD or traumatic stress: Do telomeres reach across the generations? *Trauma and Treatment*, 3, 204.
- Lanius, R. A., Bluhm, R. L., & Frewen, P. A. (2011). How understanding the neurobiology of complex post-traumatic stress disorder can inform clinical practice: A social cognitive and affective neuroscience approach. *Acta Psychiatrica Scandinavica*, 124(5), 331–348.
- Lanius, R. A., Brand, B., Vermetten, E., Frewen, P. A., & Spiegel, D. (2012). The dissociative subtype of posttraumatic stress disorder: Rationale, clinical and neurobiological evidence, and implications. *Depression and Anxiety*, 29(8), 701–708.
- Lemieux, A. M., & Coe, C. L. (1995). Abuse-related posttraumatic stress disorder: Evidence for chronic neuroendocrine activation in women. *Psychosomatic Medicine*, 57(2), 105–115.
- Logue, M. W., Baldwin, C., Guffanti, G., Melista, E., Wolf, E. J., Reardon, A. F., et al. (2013). A genome-wide association study of post-traumatic stress disorder identifies the retinoid-related orphan receptor alpha (RORA) gene as a significant risk locus. *Molecular Psychiatry*, 18(8), 937–942.
- Luterek, J. A., Bittinger, J. N., & Simpson, T. L. (2011). Posttraumatic sequelae associated with military sexual trauma in female veterans enrolled in VA outpatient mental health clinics. *Journal of Trauma & Dissociation*, 12(3), 261–274.
- Maercker, A., Brewin, C. R., Bryant, R. A., Cloitre, M., Reed, G. M., Van Ommeren, M., et al. (2013a). Proposals for mental disorders specifically associated with stress in the International Classification of Diseases-11. *Lancet*, 381(9878), 1683–1685.
- Maercker, A., Brewin, C. R., Bryant, R. A., Cloitre, M., Van Ommeren, M., Jones, L. M., et al. (2013b). Diagnosis and classification of disorders specifically associated with stress: Proposals for ICD-11. *World Psychiatry*, 12(3), 198–206.
- McDonnell, M., Robjant, K., & Katona, C. (2013). Complex posttraumatic stress disorder and survivors of human rights violations. *Current Opinion in Psychiatry*, 26(1), 1–6.
- McLaughlin, K. A., Koenen, K. C., Friedman, M. J., Ruscio, A. M., Karam, E. G., Shahly, V., et al. (2015). Subthreshold posttraumatic stress disorder in the World Health Organization World Mental Health Surveys. *Biological Psychiatry*, 77(4), 375–384.
- McLean, L. M., & Gallop, R. (2003). Implications of childhood sexual abuse for adult borderline personality disorder and

- complex posttraumatic stress disorder. *The American Journal of Psychiatry*, 160(2), 369–371.
- Meewisse, M. L., Reitsma, J. B., De Vries, G. J., Gersons, B. P., & Olf, M. (2007). Cortisol and post-traumatic stress disorder in adults: Systematic review and meta-analysis. *The British Journal of Psychiatry*, 191, 387–392.
- Mehta, D., Klengel, T., Conneely, K. N., Smith, A. K., Altmann, A., Pace, T. W., et al. (2013). Childhood maltreatment is associated with distinct genomic and epigenetic profiles in posttraumatic stress disorder. *Proceedings of the National Academy of Sciences USA*, 110(20), 8302–8307.
- Meng, Y., Qiu, C., Zhu, H., Lama, S., Lui, S., Gong, Q., et al. (2014). Anatomical deficits in adult posttraumatic stress disorder: A meta-analysis of voxel-based morphometry studies. *Behavioural Brain Research*, 270, 307–315.
- O'Donovan, A., Epel, E., Lin, J., Wolkowitz, O., Cohen, B., Maguen, S., et al. (2011). Childhood trauma associated with short leukocyte telomere length in posttraumatic stress disorder. *Biological Psychiatry*, 70(5), 465–471.
- Orr, S. P., Lasko, N. B., Metzger, L. J., Berry, N. J., Ahern, C. E., & Pitman, R. K. (1998). Psychophysiological assessment of women with posttraumatic stress disorder resulting from childhood sexual abuse. *Journal of Consulting and Clinical Psychology*, 66(6), 906–913.
- Perkonig, A., Höfler, M., Cloitre, M., Wittchen, H. U., Trautmann, S., & Maercker, A. Further evidence for ICD-11 PTSD and Complex PTSD: Results of latent class analyses with community data from adolescents and young adults. Manuscript submitted for publication.
- Pelcovitz, D., Van der Kolk, B., Roth, S., Mandel, F., Kaplan, S., & Resick, P. (1997). Development of a criteria set and a structured interview for Disorders of Extreme Stress (SIDES). *Journal of Traumatic Stress*, 10, 3–16.
- Pietrzak, R. H., Goldstein, R. B., Southwick, S. M., & Grant, B. F. (2011). Medical comorbidity of full and partial posttraumatic stress disorder in US adults: Results from Wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions. *Psychosomatic Medicine*, 73(8), 697–707.
- Pietrzak, R. H., Goldstein, R. B., Southwick, S. M., & Grant, B. F. (2012). Psychiatric comorbidity of full and partial posttraumatic stress disorder among older adults in the United States: Results from wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions. *The American Journal of Geriatric Psychiatry*, 20(5), 380–390.
- Roth, S., Newman, E., Pelcovitz, D., Van der Kolk, B., & Mandel, F. S. (1997). Complex PTSD in victims exposed to sexual and physical abuse: Results from the DSM-IV field trial for posttraumatic stress disorder. *Journal of Traumatic Stress*, 10(4), 539–555.
- Rusiecki, J. A., Byrne, C., Galdzicki, Z., Srikantan, V., Chen, L., Poulin, M., et al. (2013). PTSD and DNA methylation in select immune function gene promoter regions: A repeated measures case-control study of U.S. Military Service Members. *Frontiers in Psychiatry*, 4, 56.
- Rusiecki, J. A., Chen, L., Srikantan, V., Zhang, L., Yan, L., Polin, M. L., et al. (2012). DNA methylation in repetitive elements and post-traumatic stress disorder: A case-control study of US military service members. *Epigenomics*, 4(1), 29–40.
- Schaefer, C., Enning, F., Mueller, J. K., Bumb, J. M., Rohleder, C., Odorfer, T. M., et al. (2014). Fatty acid ethanolamide levels are altered in borderline personality and complex posttraumatic stress disorders. *European Archives of Psychiatry and Clinical Neuroscience*, 264(5), 459–463.
- Schützwohl, M., & Maercker, A. (1999). Effects of varying diagnostic criteria for posttraumatic stress disorder are endorsing the concept of partial PTSD. *Journal of Traumatic Stress*, 12(1), 155–165.
- Sherin, J. E., & Nemeroff, C. B. (2011). Post-traumatic stress disorder: The neurobiological impact of psychological trauma. *Dialogues in Clinical Neuroscience*, 13(3), 263–278.
- Shin, L. M., McNally, R. J., Kosslyn, S. M., Thompson, W. L., Rauch, S. L., Alpert, N. M., et al. (1999). Regional cerebral blood flow during script-driven imagery in childhood sexual abuse-related PTSD: A PET investigation. *The American Journal of Psychiatry*, 156(4), 575–584.
- Smith, A. K., Conneely, K. N., Kilaru, V., Mercer, K. B., Weiss, T. E., Bradley, B., et al. (2011). Differential immune system DNA methylation and cytokine regulation in post-traumatic stress disorder. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 156B(6), 700–708.
- Stein, M. B., Jang, K. L., Taylor, S., Vernon, P. A., & Livesley, W. J. (2002). Genetic and environmental influences on trauma exposure and posttraumatic stress disorder symptoms: A twin study. *The American Journal of Psychiatry*, 159(10), 1675–1681.
- Stein, M. B., Walker, J. R., Hazen, A. L., & Forde, D. R. (1997). Full and partial posttraumatic stress disorder: Findings from a community survey. *The American Journal of Psychiatry*, 154(8), 1114–1119.
- Stein, M. B., Yehuda, R., Koverola, C., & Hanna, C. (1997). Enhanced dexamethasone suppression of plasma cortisol in adult women traumatized by childhood sexual abuse. *Biological Psychiatry*, 42(8), 680–686.
- Steuwe, C., Lanius, R. A., & Frewen, P. A. (2012). Evidence for a dissociative subtype of PTSD by latent profile and confirmatory factor analyses in a civilian sample. *Depression and Anxiety*, 29(8), 689–700.
- Thomaes, K., Dorrepaal, E., Draijer, N., De Ruiter, M. B., Elzinga, B. M., Sjoerds, Z., et al. (2013). Increased anterior cingulate cortex and hippocampus activation in Complex PTSD during encoding of negative words. *Social Cognitive and Affective Neuroscience*, 8(2), 190–200.
- Thomaes, K., Dorrepaal, E., Draijer, N., De Ruiter, M. B., Elzinga, B. M., Van Balkom, A. J., et al. (2012). Treatment effects on insular and anterior cingulate cortex activation during classic and emotional Stroop interference in child abuse-related complex post-traumatic stress disorder. *Psychological Medicine*, 42(11), 2337–2349.
- Thomaes, K., Dorrepaal, E., Draijer, N., De Ruiter, M. B., Van Balkom, A. J., Smit, J. H., et al. (2010). Reduced anterior cingulate and orbitofrontal volumes in child abuse-related complex PTSD. *Journal of Clinical Psychiatry*, 71(12), 1636–1644.
- Thomaes, K., Dorrepaal, E., Draijer, N. P. J., De Ruiter, M. B., Elzinga, B. M., Van Balkom, A. J., et al. (2009). Increased activation of the left hippocampus region in Complex PTSD during encoding and recognition of emotional words: A pilot study. *Psychiatry Research*, 171(1), 44–53.
- True, W. R., Rice, J., Eisen, S. A., Heath, A. C., Goldberg, J., Lyons, M. J., et al. (1993). A twin study of genetic and environmental contributions to liability for posttraumatic stress symptoms. *Archives of General Psychiatry*, 50(4), 257–264.
- Uddin, M., Aiello, A. E., Wildman, D. E., Koenen, K. C., Pawelec, G., De Los Santos, R., et al. (2010). Epigenetic and immune function profiles associated with posttraumatic stress disorder. *Proceedings of the National Academies of Sciences USA*, 107(20), 9470–9475.
- Van der Kolk, B. A. (2005). Developmental trauma disorder: Toward a rational diagnosis for children with complex trauma histories. *Psychiatric Annals*, 35(5), 401–408.
- Wilson, S. N., Van der Kolk, B., Burbridge, J., Fisler, R., & Kradin, R. (1999). Phenotype of blood lymphocytes in PTSD suggests chronic immune activation. *Psychosomatics*, 40(3), 222–225.

- Wolf, E. J., Miller, M. W., Reardon, A. F., Ryabchenko, K. A., Castillo, D., & Freund, R. (2012). A latent class analysis of dissociation and posttraumatic stress disorder: Evidence for a dissociative subtype. *Archives of General Psychiatry, 69*, 698–705.
- Wolf, E. J., Rasmusson, A. M., Mitchell, K. S., Logue, M. W., Baldwin, C. T., & Miller, M. W. (2014). A genome-wide association study of clinical symptoms of dissociation in a trauma-exposed sample. *Depression and Anxiety, 31*, 352–360.
- World Health Organization. (1992). *The ICD-10 classification of mental and behavioural disorders: Clinical descriptions and diagnostic guidelines*. Geneva: World Health Organization.
- Xie, P., Kranzler, H. R., Poling, J., Stein, M. B., Anton, R. F., Farrer, L. A., et al. (2010). Interaction of FKBP5 with childhood adversity on risk for post-traumatic stress disorder. *Neuropsychopharmacology, 35*(8), 1684–1692.
- Yehuda, R., & Bierer, L. M. (2008). Transgenerational transmission of cortisol and PTSD risk. *Progress in Brain Research, 167*, 121–135.
- Yehuda, R., Daskalakis, N. P., Desarnaud, F., Makotkine, I., Lehrner, A. L., Koch, E., et al. (2013). Epigenetic biomarkers as predictors and correlates of symptom improvement following psychotherapy in Combat Veterans with PTSD. *Frontiers in Psychiatry, 4*, 118.
- Zerach, G., & Solomon, Z. (2013). The relations between posttraumatic stress disorder symptoms and disorder of extreme stress (not otherwise specified) symptoms following war captivity. *The Israel Journal of Psychiatry and Related Sciences, 50*(3), 148–155.
- Zhang, L., Hu, X. Z., Benedek, D. M., Fullerton, C. S., Forsten, R. D., Naifeh, J. A., et al. (2014). The interaction between stressful life events and leukocyte telomere length is associated with PTSD. *Molecular Psychiatry, 19*(8), 856–857.
- Zlotnick, C., Zakriski, A. L., Shea, M. T., Costello, E., Begin, A., Pearlstein, T., et al. (1996). The long-term sequelae of sexual abuse: Support for a complex posttraumatic stress disorder. *Journal of Traumatic Stress, 9*(2), 195–205.