LUPINE PUBLISHERS

Online Journal of Neurology and Brain Disorders

DOI: 10.32474/OJNBD.2023.06.000248

ISSN: 2637-6628

Opinion

Complex Posttraumatic Stress Disorder: A Review of the Research

Pilkay S[1]*, Thompson P[2], Seibers A[2] and Nunes S[1]

[1]*David B Falk College of Sport and Human Dynamics, School of Social Work, Syracuse University, USA*

[2]*College of Social Work, University of Tennessee, Tennessee, USA*

***Corresponding author:** Stefanie Pilkay, Assistant Professor, School of Social Work, Syracuse University Falk College, New York, USA

Received: March 09, 2023 **Published:** March 24, 2022

Abstract

Prolonged and repeated childhood maltreatment can lead to lifelong complications including the development of Complex Posttraumatic Stress Disorder (CPTSD). Complex Posttraumatic Stress Disorder (CPTSD) comprises the full spectrum of posttraumatic stress disorder symptoms (PTSD) along with an additional cluster of biopsychosocial and emotional symptoms found resistant to traditional PTSD interventions. This systematic review examines the literature on CPTSD, synthesizes neuroscience knowledge and identifies gaps in the literature to inform practice, and specifies areas for future research. The following search terms were used in varying permutations: Complex PTSD, complex PTSD, complex posttraumatic stress disorder, CPTSD, child*, adolescent*, and adult*. The search terms were utilized in the following databases: Google Scholar (3,002 results), Psych INFO (110 results), Social Work Abstracts (2 results), PubMed (76 results), Sage journals online (26 results), and Psychiatry Online (3 results).

The Inclusion Criteria Encompassed the Following Specifications for all Peer-Reviewed Published Literature:

a) Named Complex PTSD in the abstract or title

b) Named DNA methylation in relation to PTSD or CPTSD in the abstract or title

c) Were cited by sources meeting criteria one and two, not revealed in the original search, and relevant to PTSD or CPTSD.

The final literature collection included 60 articles with a combination of randomized controlled trials, quasi- experimental studies, and correlation studies, represented in quantitative designs. Current research suggests that structural and physiological changes can intensify complex trauma symptoms and does not dispute a theorized progression from PTSD to CPTSD.

Introduction

Adults who have experienced childhood abuse have an increased risk for developing major depressive disorder, bipolar disorder, post-traumatic stress disorder (PTSD), and substance abuse [1]. Other heightened consequences of child abuse that contribute to biopsychosocial and emotional impairments include severe obesity [2], cardiovascular disease, and arthritis [3]. In 2014, the National Institute of Health estimated direct and indirect costs of lost wages, increased use of health care services, and disability benefits of trauma survivors of child maltreatment and war veterans at $317 billion. Researchers agree that not all traumatic experiences are equal in the magnitude of effects on an individual. Type, frequency, duration of trauma, and the failure to prevent or effectively intervene influences where an individual's consequences will lie on the continuum. Herman (1992) [4] described captive relationships as chronically severe cases where children are subjected to prolonged and repeated trauma that they cannot escape resulting in chronic activation of the stress response that can lead to dysregulated stress reactivity. The additional cluster of biopsychosocial and emotional symptoms that manifest as a result from chronic traumatic experiences involving captive relationships were referred to as Complex PTSD (CPTSD). CPTSD comprises the

full spectrum of PTSD symptoms (i.e., intrusion, avoidance, negative alterations in cognitions and mood, altered arousal, and reactivity) along with altered systems of meaning, diminished sense of self, impaired self-regulation of behavior and affect, somatization, pathological dissociation, impaired self-concept, cognitive difficulties, and chaotic or avoidant dysfunctional relationships [5,6]. A clinical presentation of this would appear as an individual with externalizing behaviors, mood swings, physical sickness or pain without a medical illness, distorted beliefs about the self, difficulties with attention and memory, hypervigilance, but little to no hyperarousal symptoms due to dissociation. The DSM-IV-R classified CPTSD under the diagnosis Disorder of Extreme Stress Not Otherwise Specified (DES-NOS); however, this classification was excluded from the Diagnostic Statistical Manual (DSM)-5 and dissociation was added to the potential symptoms of PTSD.

While changes to the DSM-5 no longer include DES-NOS or recognize CPTSD (Association, 2013) the recently published International Classification of Diseases (ICD) version 11 includes CPTSD as its own distinct diagnosis [7]. The decision to add CPTSD to the ICD 11 was due to ongoing research that identified, and replicated findings, showing CPTSD has its own unique set of symptoms separate from PTSD within chronically traumatized populations [8-11]. Specifically, Powers et al. [11] concluded that PTSD and CPTSD, as trauma-related disorders of dysregulated stress activation, were two distinct constructs in all clinical domains. Therefore, this systematic review examines and integrates the literature on CPTSD and relevant epigenetic findings, identifies gaps in the literature to inform practice, and specifies areas for future research.

Methods

Multiple key words were utilized initially to identify what type of literature was associated with those terms and to determine which terms would produce the most relevant literature. The search process is depicted in (Figure 1). The following search terms were used in varying permutations: Complex PTSD, complex PTSD, complex posttraumatic stress disorder, CPTSD, child*, adolescent*, and adult*. The search terms were utilized in the following databases: Google Scholar (3,002 results), Psych INFO (110 results), Social Work Abstracts (2 results), PubMed (76 results), Sage journals online (26 results), and Psychiatry Online (3 results). A total of 3,219 articles were identified, without setting a parameter of publication years, prior to applying the inclusion criteria.

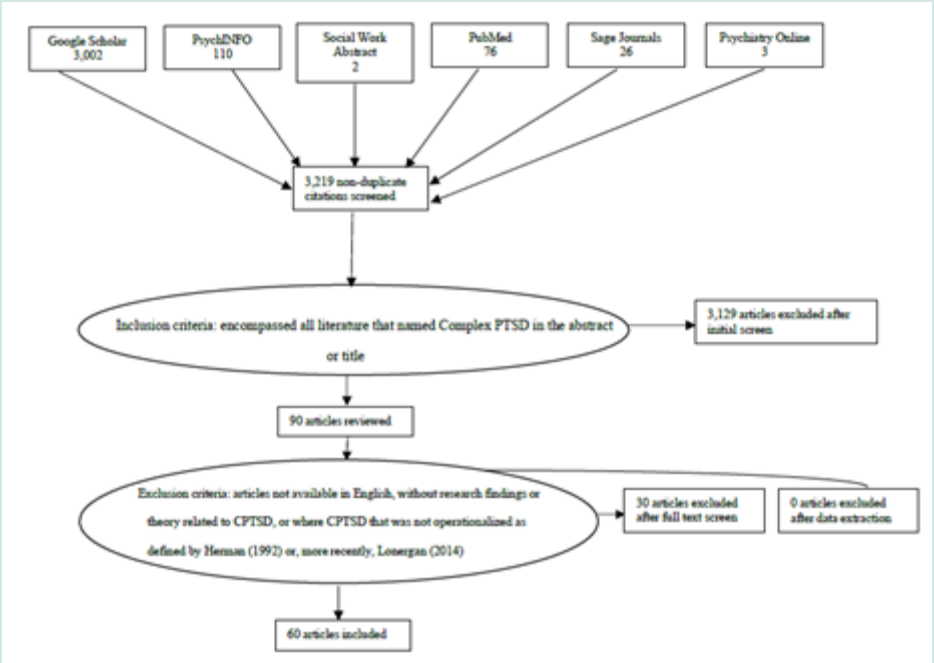

Figure 1: Overall results of the systematic review.

Inclusion Criteria Encompassed the Following Specifications for All Peer-Reviewed Published Literature:

a) Named Complex PTSD in the abstract or title.

b) Named DNA methylation in relation to PTSD or CPTSD in the abstract or title;

c) Were cited by sources meeting criteria one and two, not revealed in the original search, and relevant to PTSD or CPTSD resulting in 90 identified articles that included 3 articles referencing DES-NOS.

Literature exclusion criteria were set to exclude articles from the search that were not available in English, where CPTSD was not operationalized as defined by Herman (1992) [4] or, more recently [5], or included an emphasis on medical or health stressors versus trauma or early life-stress such as accompanies CPTSD. Some literature included the term Complex PTSD in the abstract, but the reference was to a severity in PTSD symptoms and not the actual symptom clusters associated with CPTSD. The final literature collection included 60 articles with a combination of literature reviews, randomized controlled trials, quasi-experimental studies, meta-analysis, and correlation studies (Figure 1).

Results

Multiple themes emerged in the literature and afforded a logical outline to synthesize the results. The following sections will inform the reader on the experiential predictors of CPTSD, the neurobiological correlates of CPTSD versus PTSD symptomology, and the biological risk, as measured in DNA methylation, for the development of CPTSD symptoms. The literature is also organized in (Table 1) for quick reference.

Table 1: Synthesis of CPTSD literature.

Author(s)	N	Result(s)
CPTSD Predictors		
Child Abuse		
Amariglio, (2014) [12]	62	Childhood sexual abuse associated with development of CPTSD
Boroske-Leiner et al. (2008) [13]	72	Early life exposure, cumulative/severity of childhood abuse associated with CPTSD
Bruns, (2002) [28]	113	Parent-child relatioship moderates CPTSD development
Castelda, (2006) [27]	47	Cumulative/severity of childhood abuse associates with CPTSD
Cloitre et al., (2009) [14]	734	Cumulative/severity of childhood abuse associates with CPTSD
Dorahy et al., (2009) [15]	81	Childhood sexual abuse, emotional neglect, and cumulative/severity of childhood abuse associates with CPTSD
Hall, (1999) [85]	99	Cumulative/severity of childhood abuse associates with CPTSD
Leahy, (2008) [16]	164	Childhood abuse mediates association between domestic violence in adulthood and CPTSD
Mahoney, (2006) [17]	234	Early life exposure and childhood sexual abuse associates with CPTSD
Mayfield-Schwarz, (2007) [18]	41	Early life exposure and duration of trauma, cumulative/severity of childhood abuse associate with CPTSD
McLean & Gallop, (2003) [19]	65	Early life exposure and childhood sexual abuse associate with CPTSD
McTeague et al., (2010) [26]	125	Early life exposure, cumulative/severity of childhood abuse associate with CPTSD
Pelaprat, (2010) [20]	60	Duration of trauma, cumulative/severity of childhood abuse associate with CPTSD
Petchkovsky & San Roque,(2002) [21]	9	Early life exposure and duration of trauma, cumulative/severity of childhood abuse associate with CPTSD
Rosenkranz et al., (2014) [22]	216	Early life exposure and duration of trauma, cumulative/severity of childhood abuse associate with CPTSD
Van Der Kolk et al., (2005) [23]	528	Duration of trauma, cumulative/severity of childhood abuse associate with CPTSD
Vielhauer, (1996) [24]	60	Childhood sexual abuse associates with CPTSD
Winnett, (2014) [25]	92	Betrayal by perpetrator, failure to protect by non-offending caregiver
Adult Trauma		
McDonnell et al., (2013) [29]	Literature Review	Human rights violations victims develop cptsd without childhood abuse
Leahy, (2008) [16]	164	Repeated domestic violence in adulthood without childhood abuse links to CPTSD
Developmental Stage		
Maercker et al., (2013) [9]	Literature Review	Developmental stage at time of trauma event affects development of CPTSD
Giurou et al., (2018) [6]	Literature Review	Timing, severity, and duration of trauma interact with genetic components could result in progression from PTSD to CPTSD to borderline personality disorder
Variations in Symptomology		
Ford & Courtois, (2014) [30]	Literature Review	Identified clear symptom distinctions among PTSD, CPTSD, and borderline personality disorder.
Van Dijke et al., (2012) [31]	472	Identified clear symptom distinctions among PTSD, CPTSD, and borderline personality disorder.

Ashfield et al., (2020)	11	Identified clear symptom distinctions among PTSD and CPTSD
Knefel et al., (2019) [10]	1591	Identified clear symptom distinctions among PTSD and CPTSD
Ekimova & Luchnikova, (2020)	Literature Review	Identified clear symptom distinctions among PTSD and CPTSD
Lehrner & Yehuda, (2020)	Literature Review	Identified clear symptom distinctions among PTSD and CPTSD
Treatment Interventions		
Talbot, (2020)	Literature Review	Identified Integrative Treatment of Complex Trauma for Adolescents (ITCT-A) and Eye Movement Desensitization and Reprocessing (EMDR) as promising treatment interventions.
Karatzias et al., (2018)	171	Identified phase-based or sequenced approach interventions as promising treatment interventions.
Neurobiology		
Thomaes et al., (2010) [34]	59	CPTSD reduced gray matter OFC, attenuation in hippocampus and ACC, ACC volume negatively correlates with child abuse severity and PTSD hyper arousal, anger negatively correlates with hippocampus and OFC volume, greater impulsivity with decreased hippocampal volume
Villarreal et al., (2002) [32]	22	PTSD reduced hippocampal volume
Woodward et al., (2006) [33]	99	PTSD reduced ACC volume compared to controls
McDonnell et al., (2013) [29]	Literature Review	CPTSD increased activation of hippocampus and ACC not found in PTSD
Thomaes et al., (2013) [37]	49	Functional c in hippocampus and acc in CPTSD patients linked with increased dissociation scores, severity of childhood abuse positively correlated with activity in the ventral ACC and hippocampus
Castelda, (2006) [27]	47	Increased childhood abuse, greater severity of ptsd, and more personality disorder diagnoses negatively correlated with decreased heart rate changes during auditory startle procedures
McTeague et al., (2010) [26]	125	Single event trauma and ptsd linked to robust startle, increased skin conductivity, and increased heart rate. Multiple traumas showed blunted defensive reactivity associated with chronic and severe ptsd, increased mood and anxiety disorder comorbidity, and increased depression, blood oxygenation level dependent response sensitive to fear related cues in cptsd patients compared to healthy controls
Medina et al., (2001) [40]	52	Childhood physical abuse and intimate partner violence correlated with PTSD symptoms, but symptom severity negatively correlated with magnitude of eye-blink responses
Schauer and Elbert, (2015) [41]	Theoretical	Defense cascade model based on sympathetic and parasypathetic nervous system responses
Epigenetics		
Zovkic et al., (2013) [46]	Literature Review	Epigenetic mechanisms mediate trauma adaptation and are involved in differential risk and resilience to ptsd
Blaze et al., (2015) [47]	Literature Review	Stress response is sensitive to epigenetic tags from early life adversity
Wu et al., (2014) [48]	14	Animal models show early life stress associates with methylation patterns that increase gene activity of the ACTH protein
Murgatroyd et al., (2010) [49]	8-16 mice per goup (4 groups)	Animal models show early life stress associates with methylation patterns that increase gene activity of the corticosterone levels
Perroud et al., (2013) [51]	167	DNA methylation in the central nervous system can influence neurogenesis and synaptogenesis
Naumova et al., (2012) [52]	28	Methylation patterns can emerge immediately after the trauma occurs
Essex et al., (2013) [53]	109	Methylation patterns can emerge later after the childhood trauma during adolescence
Perroud et al., (2011) [54]	215	Childhood trauma can associate with methylation patterns in adulthood on genes associated with psychopathology
Tyrka et al., (2012) [55]	99	Childhood trauma can associate with methylation patterns in adulthood on genes associated with psychopathology
Heinrich et al., (2015) [59]	95	Reduced methylation on glucocorticoid receptor gene NR3C1 in individuals with externalizing disorders, compared to controls and depressive disorder
Martín-Blanco et al., (2014) [60]	281	Childhood physical abuse positively correlated with methylation on NR3C1 which is positively associated with severity of mental health symptoms

Tyrka et al., (2015) [61]	184	Childhood maltreatment positively correlated with methylation on NR3C1 that positively correlated with individual stress
Perroud et al., (2015) [62]	346	Chidhood trauma associated with DNA methylation and specific gene variant involved in serotonin activity
Miller et al., (2013) [69]	1686 (meta- analysis)	Reduced expression of serotonin transporter gene SLC6A4 correlated with increased stress reactivity
Ouellet-Morin et al., (2013) [70]	28 twin pairs	Greater methylation on the serotonin gene correlated with blunted cortisol reactions during stress
Boyle et al., (2005) [71]	6	Rodents with reduced glucocorticoid receptors exhibited depression-like symptoms related to poor inhibition of the HPA axis
Ridder et al., (2005) [72]	14	Rodents with reduced glucocorticoid receptors exhibited depression-like symptoms related to poor inhibition of the HPA axis
Labonte et al., (2012) [73]	106	Early life maltreatment has been associated with increased methylation and reduced expression of glucocorticoid receptors in the hippocampus
McGowan et al., (2009) [74]	36	Early life maltreatment has been associated with increased methylation and reduced expression of glucocorticoid receptors in the hippocampus
Toda et al., (2014) [76]	17	Maternal deprivation has been associated with increased methylatio of NTSR1 in the amygdala and NTSR1 activity is negatively associated with conditioned fear-freezing behavior
Tseilikman, et al., (2020)	35	Dynamical interactions between hypocorticonemia, plasma glucocorticoids, and brain neurotransmitters play vital roles in the development of PTSD-susceptible phenotypes in rodents

Childhood Trauma as a Predictor of CPTSD

Evolving theory on CPTSD etiology provides an important context for understanding the mechanisms of its symptomology. Substantial research has focused on associations between childhood abuse and CPTSD [12-25]. Timing, type, and duration of trauma each play roles in the development of CPTSD [12,13,20].

Childhood is a critical time for development resulting in a natural captive relationship [4] created by the need to be cared for and protected. Traumatic experiences that have a captive element to the relationship show a greater link to the development of CPTSD. In general, early childhood or adolescent trauma [13,17-19,26] and duration of abuse have been shown to increase distress in adulthood [18,20,23].

The type of childhood trauma has also been shown to independently influence the development of CPTSD. For example, several studies have identified childhood sexual [12,15,17,19,24], emotional neglect [15], perception of betrayal by the perpetrator, and perception of failure to protect by a non-offending caregiver [25] as contributors to psychopathology development. Eight studies also show that the amount of trauma [13,14,18,20,23,26,27], such as repeated or cumulative experiences, and the severity of childhood abuse [15,18] correlate with the development of CPTSD. However, it is important to note that the pathway to developing CPTSD is complex and includes other experiences. For example, the parent–child relationship moderates the development of CPTSD [28], and childhood abuse mediates the relationship between domestic violence in adulthood and CPTSD [16].

Adulthood Trauma as a Predictor of CPTSD

Hermans et al., (1992) [4] conceptualization of CPTSD requires an inescapable harm in adulthood trauma that includes prisoners of war, sex slavery, refugee status, domestic violence victims and genocide survivors. [29] evaluated 33 articles and found that victims of human rights violations could develop CPTSD without a history of childhood abuse. Moreover, Leahy (2008) found that repeated domestic violence in adulthood with no history of childhood abuse was also associated with CPTSD, though a history of child abuse exacerbated the symptoms. While trauma can be experienced at any age, the impact can be greatly affected by developmental stage [9,6] theorized that the timing, severity, and duration of traumatic exposure coupled with genetic predisposition could progress past CPTSD into permanent personality modifications, clinically similar to Borderline Personality Disorder (BPD). While many studies have examined PTSD, CPTSD, and BPD symptomology [30,31] few have examined the neurobiology that distinguishes the clinical diagnoses from one another.

Neurobiology Research

Limited research has explored the neurobiology of individuals with CPTSD. This could be due to numerous factors such as the removal of the diagnostic option from the DSM-V, the research expense, the lack of available equipment and willing participants. Eight studies were identified as conducting research on neurobiology related variables as measured with functional magnetic resonance imaging (fMRI), direct examination of post-mortem tissue, and stress reactivity measures (startle eye blink, auditory startle, and heart rate). Although more research is needed, these studies are integrated to compare and contrast findings for CPTSD and PTSD. Brain images show alterations in the brain that vary according to PTSD and CPTSD and help define the differences in symptoms and biological etiology. Previous research has found

that patients with PTSD have reduced hippocampal volume [32] and anterior cingulate cortex (ACC) volume compared to non-PTSD controls [33]. The ACC facilitates some amygdala inhibition, in addition to emotion regulation, which can moderate some emotionally driven behaviors.

An investigation of CPTSD revealed differences when compared to individuals with PTSD. Thomaes et al. [34] used fMRI scans to compare the brains of 31 individuals who met the criteria for child-abuse-related CPTSD with the brains of 28 healthy non-traumatized controls. Results indicated that patients with CPTSD had reductions in the gray matter of the orbitofrontal cortex (OFC), along with attenuation in the hippocampus and ACC. In conjunction with the ACC, the OFC provides significant inhibition for the amygdala as part of the brain's top-down processing [35]. An impaired or diminished functioning of these two brain regions can lead to a loss of inhibition of the amygdala, causing the amygdala to dominate, which in turn can cause anxiety-related disorders and impulsive or criminal behaviors [36]. The fMRI findings are only correlational and do not provide enough evidence to prove causation for any pathways among child abuse, gray matter volume, and CPTSD. However, the correlation does provide insight into a plausible explanation for the CPTSD symptom of impaired self-regulation of behavior and affect. In the same study, Thomaes et al. [34] found that severity of child abuse and PTSD hyper-arousal negatively correlated with ACC volume. As the severity of abuse or arousal increased, the ACC volume decreased. They further discovered that anger negatively correlated with hippocampus and OFC volume, which supports these biological changes as potential drivers of the emotional dysregulation that is common to CPTSD.

Interestingly, because scientists believe that the OFC might facilitate extinguishing the learned fear response, alterations in the OFC may support a theory of a neurobiological compensatory response. In theory, if the reduced volume of the OFC results in diminished functioning then PTSD would be resistant to traditional exposure therapies because of an impaired ability to extinguish the learned fear response. Chronic PTSD would lead to chronic stress reactivity which in turn can lead to excitotoxicity. Excitotoxicity occurs when cortisol levels remain elevated for extended periods of time. Cortisol essentially hoards the glucose in our system to build up energy reserves for our possible need to flee or fight. A large amount of glucose is needed to breakdown the glutamate in our brains and when cortisol is elevated for extended periods the glutamate builds up. This excess glutamate is what creates excitotoxicity which degrades neurons and breaks the connections between neurons. A compensatory response would be for the brain to override the stress activation to reduce the damage that occurs from excitotoxicity. One such example could be dissociation, which is severe for individuals with CPTSD. CPTSD involves increased activation of the hippocampus and ACC that does not occur in PTSD [29]. These functional differences were found to be associated with increased scores on dissociation measures [37]. These findings could explain the pathological dissociation that is common with CPTSD and could support the theory of a potential neurobiological compensatory response.

The identified functional and structural differences in the hippocampus may also explain why individuals with CPTSD have cognitive difficulties. This part of the brain is well known to be associated with learning and memory deficits in individuals with attenuation-associated chronic stress activation [38]. Interestingly, the hippocampus serotonergic system also has been found to play a role in mood, impulsivity, aggression, and anxiety disorders [39]. This may explain the behavior dysregulation in CPTSD, as suggested by research that identified a correlation between impulsivity and decreased hippocampus volume [34]. If a compensatory response involves disengagement like dissociation, then the biological processes associated with stress activation would involve a dampened or inhibited effect. An investigation of physical stress responses did find a change that suggested some type of inhibition [27,26]. In a group comparison study of individuals with CPTSD versus non-traumatized controls and CPTSD versus individuals with PTSD only, individuals with CPTSD who were exposed to trauma stimuli exhibited hypo-responsivity compared to controls and those with PTSD [26,27]. [40] were first to examine the phenomena by studying 52 women for startle eye-blinks in response to auditory probes in relation to PTSD symptomology. Childhood physical abuse and intimate partner violence both correlated with PTSD symptoms. However, PTSD symptom severity correlated negatively with the magnitude of eye-blink responses. Essentially, as PTSD symptoms increased, the magnitude of the startle eye-blink response decreased, showing increased hypo-responsivity [40].

Castelda et al. [27] showed that increased events of child abuse, greater severity of PTSD, and more personality disorder diagnoses negatively correlate with decreased heart rate changes during auditory startle procedures, further confirming hypo-responsiveness in these individuals. McTeague et al., (2010) [26] expanded upon these findings when they investigated 22 incidents of single-trauma exposure and 27 multiple-trauma exposed individuals with PTSD. Acoustic startle probes were used, and stress reactions (eye-blink, heart rate, skin conductivity, and facial expressivity) were measured. Participants who had experienced single-event trauma and those diagnosed with PTSD had a robust startle, increased skin conductivity, and increased heart rate. Individuals with multiple traumas reported greater arousal but showed blunted defensive reactivity associated with chronic and severe PTSD, increased mood and anxiety disorder comorbidity, and increased depression. Interestingly, the comorbid symptoms associated with this blunted response include symptoms that are unique to CPTSD (e.g., emotion dysregulation). The most symptomatic patients with a history of severe and cumulative trauma showed dissonant physiological hypo-reactivity. The researchers concluded that sustained high stress and persistent negative affect may have compromised individuals' biological defensive reactions [26]. This conclusion further suggests the

disengagement or dissociative compensatory response changes in relation to the trauma severity.

Schauer and Elbert et al. [41] offered a theorized model, the defense cascade, to help explain this divergent manifestation of stress-related disorders. The defense cascade comprises six steps in the stress activation cycle: freeze, flight, fight, fright, flag, and faint. The sympathetic nervous system activates the first four stages, and the parasympathetic nervous system activates the last two stages. Parasympathetic activation is considered to be involved in the dissociative response and a form of shutting down. Schauer and Elbert et al., (2015) [41] theorized that the physiological response that is experienced during the trauma (sympathetic or parasympathetic) also is elicited during later traumatic cues and triggers. Recently, researchers discovered clusters within a sample of patients with PTSD that supports the defense cascade model [29]. The cluster with a type 1 response exhibited sympathetic activation that manifested as a loss of top-down processing, low activation of the medial prefrontal cortex and ACC, and increased activation of the limbic system, including the amygdala. The cluster with a type 2 response exhibited parasympathetic activation with increased activation of the ACC and medial prefrontal cortex, resulting in hyper inhibition of the limbic system including the amygdala [29]. However, these groupings may be too parsimonious to capture complex interactions of experience and biology.

The defense cascade model considers only the experience during the traumatic event but not how the body's response to trauma (i.e., hypervigilance, hyperarousal, anxiety) influences biological changes. It also does not account for differences between single and multiple trauma events. It instead allows the possibility that a single event can evoke a devastating response, resulting in activation of the parasympathetic nervous system, thereby causing all future trauma triggers to elicit the same response. Current knowledge suggests that complex trauma is instead associated with dissociative-type reactivity. Furthermore, the defense cascade model does not explain why individuals with CPTSD and those with PTSD have the same attenuation in the hippocampus and ACC, where the changes match the repetitive activation of the sympathetic response. Research has begun to identify relationships between biological changes and the timing, complexity, and symptom severity of trauma. The literature describes how changes in the neurobiological structures and functions of a traumatized individual change over time. As previously mentioned, a compensatory response may explain the differences between CPTSD and PTSD. Similar neurological changes in these conditions could represent a once shared similar response pattern of over-activation of the sympathetic nervous system. McTeague et al. [26] inferred the potential of sustained high stress and chronic negative affect to alter defensive reactivity.

However, hypo-responsivity does not necessarily cause diminished attention to fear-related stimuli. McTeague et al., (2010) [26] conducted a comparison of the blood- oxygenation-level-dependent response in 28 individuals with CPTSD and 21 healthy, non- traumatized controls found sensitivity to fear-related cues in the group with CPTSD. An fMRI measurement of brain activity during presentations of negative (fear-related) and neutral words showed that participants with CPTSD were more likely to falsely report hearing a negative word in previous presentations. Additionally, blood-oxygenation-level-dependent responses showed increased activity in the left ventral and dorsal ACC, extending to the dorsal medial prefrontal cortex, and increased left hippocampus activation during recall of negative words (McTeague et al., 2010). Most importantly, the severity of childhood abuse positively correlated with activity in the ventral ACC and hippocampus [37].

Genetic and Epigenetic Patterns as Predictors

Consideration of a potential etiological route for CPTSD must include biological risk. Vulnerability to PTSD has been associated with childhood trauma, panic disorder, major depressive disorder, conduct disorder, and paternal depression. Of these, early onset of childhood trauma supports a developmental perspective of risk and vulnerability. Additionally, anxiety and mood disorders suggest a biological imbalance within the individual and potential for inherited vulnerabilities, such as depression [42].

Epigenetics refers to chemical groups that attach to the DNA and alter gene function without changing the DNA sequence itself [43]. Epigenetic tags influence our genes by determining which genes are active, when they are activated, and to what degree they are active [44]. These tags influence brain structure, function, and behavior [45]. Epigenetic mechanisms mediate trauma adaptation, and they are involved in differential risk and resilience to PTSD [46]. DNA methylation is the most studied epigenetic mechanism. It occurs when a methyl group attaches to a gene in the DNA strand to create a stable influence on that gene that can last a lifetime [43]. DNA methylation is an epigenetic marker, and it has been identified as one mechanism that alters stress reactivity and possibly subsequent brain structure and function [43]. It is highly sensitive to experience [47].

Research examining DNA methylation provides insight into dysfunction in the stress response system. The stress response in the hypothalamus-pituitary-adrenal axis is sensitive to epigenetic tags from early-life adversity [47]. Animal models have associated early-life stress with methylation patterns that increase gene activity of the ACTH protein [48] and corticosterone levels [49]. Initially, this results in a strong and efficient stress response, but chronic activation can disrupt negative feedback by blunting the cortisol response [50]. Moreover, DNA methylation in the central nervous system can influence neurogenesis and synaptogenesis [51]. Neurogenesis refers to the process of forming new neurons and synaptogenesis refers to the growth of connections between neurons. It can develop immediately after a childhood experience occurs [52], later during adolescence [53], or in adulthood on genes that are associated with psychopathology [54,55]. Alterations to neurogenesis and synaptogenesis can have positive or negative consequences.

During childhood, reduced neurogenesis and synaptogenesis reportedly alters brain development [56]. During adulthood, these processes may protect against stress, as greater neurogenesis following a stress event increases sensitivity to stress [57]. Altered gene activity in glucocorticoid receptors is a suspected mechanism of stress- related disorders and may cause structural and functional changes in the brain. Glucocorticoid receptors play instrumental roles in stress-response negative feedback [58]. Altered gene activity in these receptors could lead to stress sensitization or chronic activation, which can develop into psychopathology. For example, [59] found reduced methylation on glucocorticoid receptor gene NR3C1 in individuals with externalizing disorders, compared with controls and others with depressive disorder. Traumatic events and associated mental health symptoms also demonstrate similar epigenetic patterns. Childhood physical abuse has been positively correlated with methylation on NR3C1, which is positively associated with the severity of mental health symptoms [60]. In a large sample of children with diverse ancestry, childhood maltreatment positively correlated with methylation on NR3C1 that likewise positively correlated with individual stress [61]. DNA methylation associated with childhood trauma has been found to alter serotonin activity [62]. Serotonin affects appetite [63], memory [64], mood [65], sleep [66], social behavior [67], and sexual interest and function [68].

Research suggests that mood disruptions, like those associated with trauma-related disorders, can occur when serotonin levels are dysregulated. More recently, [62] has linked methylation on the serotonin gene to childhood abuse and increased symptom severity in individuals who carry a specific variation of the gene. Miller et al. [69] confirmed in a meta-analysis that reduced expression of serotonin transporter gene SLC6A4 correlated with increased stress reactivity. A comparison of monozygotic twins revealed greater methylation on the serotonin gene correlated with blunted cortisol reactions during stress [70]. More important, animal research suggests that glucocorticoid receptors and serotonin may be linked somehow. Rodents with reduced glucocorticoid receptors exhibited depression-like symptoms related to poor inhibition of the hypothalamus-pituitary- adrenal axis [71,72]. Future research could help deepen understanding of trauma-related stress disorders and mood dysregulation by including both glucocorticoid receptors and serotonin-related genes in epigenetic investigations of trauma.

Epigenetics and the Brain

DNA methylation may be involved in multiple functions of the central nervous system, which could help explain the development and chronicity of trauma-related psychopathology. The challenge is interpreting what these gene regulation patterns might mean for brain development and function. Research has identified that the hippocampus, medial prefrontal cortex, dorsal medial prefrontal cortex, anterior cingulate cortex, and orbitofrontal cortex have different structures or functions in CPTSD, compared to PTSD. DNA methylation may be one mechanism for these differences. For example, early-life maltreatment has been associated with increased methylation and reduced expression of glucocorticoid receptors in the hippocampus [73,74]. These changes affect the gray matter volume in the hippocampus [75]. Maternal deprivation has been associated with increased methylation of NTSR1 in the amygdala. NTSR1 activity also is negatively associated with conditioned fear- freezing behavior [76].

Conclusion

This review is the first to integrate epigenetic, neurobiological, and phenotype research regarding the current knowledge of the etiology of CPTSD and the potential pathways for similar and dissimilar symptoms with PTSD. Multiple studies have investigated CPTSD and PTSD [77-80], and some discussed criticism surrounding the overlap between the two disorders' symptomology [81-90]. This review has demonstrated that while PSTD and CPTSD have some symptom similarities, preliminary findings suggest these disorders are neurobiologically different. Furthermore, the DNA methylation research on stress responsivity suggests a pathway for the theorized progression of PTSD into CPTSD and provides some context for the structural and functional neurobiological differences between the disorders. Most importantly, understanding how CPTSD may be biologically driven to develop and manifest specific symptomology will help to identify preventions and interventions to improve quality of life for individuals.

Current research suggests that structural and physiological changes could explain the intensity of complex trauma symptoms. The brain could engage a compensatory response to manage chronic stress activation, which could result in dissociation symptoms and related treatment challenges. However, more evidence is needed to determine if CPTSD is a progression of PTSD. Practice will benefit from future research that identifies how increasing symptom severity of PTSD can progress to CPTSD. A cross-disciplinary approach that includes neuroscience observations, such as DNA methylation and fMRI, will advance our understanding of the complex paths from trauma to behavioral dysfunction and poor quality of life. The greater detail we can observe about the development and outcomes of CPTSD the greater the opportunities for discovering novel prevention and intervention measures.

References

1. Felitti V, Anda R, Nordenberg D, Williamson D, Spitz A, et al. (1998) Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: The adverse childhood experiences (ACE) study. American Journal of Preventive Medicine 14(4): 245-258.
2. Richardson AS, Dietz WH, Gordon Larsen P (2014) The association between childhood sexual and physical abuse with incident adult severe obesity across 13 years of the National Longitudinal Study of Adolescent Health. Pediatric obesity 9(5): 351-361.
3. Afifi TO, Mota N, MacMillan HL, Sareen J (2013) Harsh physical punishment in childhood and adult physical health. Pediatrics 132(2): 333-340.

4. Herman JL (1992) Complex PTSD: A syndrome in survivors of prolonged and repeated trauma. Journal of Traumatic Stress 5(3): 377-391.
5. Lonergan M (2014) Cognitive behavioral therapy for PTSD: The role of complex PTSD on treatment outcome. Journal of Aggression, Maltreatment and Trauma 23(5): 494-512.
6. Giourou E, Skokou M, Andrew SP, Alexopoulou K, Gourzis P, et al. (2018) Complex posttraumatic stress disorder: The need to consolidate a distinct clinical syndrome or to reevaluate features of psychiatric disorders following interpersonal trauma?. World journal of psychiatry 8(1): 12-19.
7. Complex Posttraumatic Stress Disorder (2018). ICD11.
8. Brewin CR, Cloitre M, Hyland P, Shevlin M, Maercker A, et al. (2017) A review of current evidence regarding the ICD-11 proposals for diagnosing PTSD and complex PTSD. Clinical Psychology Review 58: 1-15.
9. Cloitre M, Garvert DW, Brewin CR, Bryant RA, Maercker A (2013) Evidence for proposed ICD-11 PTSD and complex PTSD: A latent profile analysis. European Journal of Psychotraumatology 4(1): 20706.
10. 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 (4).
11. Powers A, Fani N, Carter S, Cross D, Cloitre M, Bradley B (2017) Differential predictors of DSM-5 PTSD and ICD-11 complex PTSD among African American women. European journal of psychotraumatology 8(1): 1338914.
12. Amariglio N (2014) Thematic analysis among survivors of childhood sexual abuse. AAI3591784.
13. Boroske-Leiner K, Hofmann A, Sack M (2008) Ergebnisse zur internen und externen validität des interviews zur komplexen posttraumatischen belastungsstörung (I-kPTBS). PPmP: Psychotherapie Psychosomatik Medizinische Psychologie 58(5): 192-199.
14. Cloitre Stolbach, Herman Kolk VD, Pynoos Wang, Petkova (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.
15. Dorahy MJ, Corry M, Shannon M, MacSherry A, Hamilton G, et al. (2009) Complex PTSD, interpersonal trauma and relational consequences: Findings from a treatment-receiving Northern Irish sample. Journal of Affective Disorders 112(1-3): 71-80.
16. Leahy KL (2008) Complex posttraumatic stress symptoms among a community sample of battered women. AAI3298071, 684.
17. Mahoney KL (2006) Trauma, post-traumatic stress disorder, and Disorders of Extreme Stress (DES) among incarcerated men and women. AAI3184800, 4490.
18. Mayfield Schwarz L (2007) Severity of trauma exposure and complex posttraumatic stress disorder symptomatology in women who prostitute. AAI3264335, 2659.
19. McLean LM, 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.
20. Pelaprat M (2010) Complex trauma among court-involved youth. AAI3382657, 6563.
21. Petchkovsky L, San Roque, C (2002) Tjunguwiyanytja , attacks on linking: Forced separation and its psychiatric sequelae in Australia Stolen Generations. Transcultural Psychiatry 39(3): 345-366.
22. Rosenkranz SE, Muller RT, Henderson JL (2014) The role of complex PTSD in mediating childhood maltreatment and substance abuse severity among youth seeking substance abuse treatment. Psychological Trauma: Theory, Research, Practice, and Policy 6(1): 25-33.
23. Van der Kolk B, Roth S, Pelcovitz D, Sunday S, Spinazzola J (2005) Disorders of extreme stress: The empirical foundation of a complex adaptation to trauma. Journal of Traumatic Stress 18: 389-399.
24. Vielhauer MJ (1996) Complex post-traumatic stress disorder associated with childhood sexual and physical abuse in male veterans with histories of substance abuse disorders pp. 750.
25. Winnett L (2014) Betrayal trauma, attachment, and symptom complexity among child sexual abuse survivors.
26. McTeague, Lang, Laplante, Cuthbert, Shumen, Bradley (2010) Aversive imagery in posttraumatic stress disorder: Trauma recurrence, comorbidity, and physiological reactivity. Biological Psychiatry 67(4): 346-356.
27. Castelda BA (2006) Construct validation of the Sexual Abuse Questionnaire (SAQ) using an acoustic startle procedure and measures of complex posttraumatic stress disorder (PTSD).
28. Bruns CM (2002) Perceived mutuality in child-adult relationships and severity of abuse as predictors of complex PTSD symptoms in women who were sexually abused as children.
29. McDonnell Robjant, Katona (2013) Complex posttraumatic stress disorder and survivors of human rights violations. Current opinion in psychiatry 26(1): 1-6.
30. Ford JD, Courtois CA (2014) Complex PTSD, affect dysregulation, and borderline personality disorder. Borderline Personality Disorder and Emotion Dysregulation 1(1): 1-17.
31. Van Dijke A, Ford JD, van der Hart O, van Son M, van der Heijden P, et al. (2012) Complex posttraumatic stress disorder in patients with borderline personality disorder and somatoform disorders. Psychological Trauma: Theory, Research, Practice, and Policy 4(2): 162.
32. Villarreal G, Hamilton DA, Petropoulos H, Driscoll I, Rowland LM, et al. (2002) Reduced hippocampal volume and total white matter volume in posttraumatic stress disorder. Biological Psychiatry 52(2): 119-125.
33. Woodward SH, Kaloupek DG, Streeter CC, Martinez C, Schaer M, et al. (2006) Decreased Anterior Cingulate Volume in Combat-Related PTSD. Biological Psychiatry 59(7): 582-587.
34. K Dorrepaal E, Draijer N, de Ruiter MB, van Balkom AJ, et al. (2010) Reduced anterior cingulate and rbitofrontal volumes in child abuse-related complex PTSD. Journal of Clinical Psychiatry 71(12): 1636-1644.
35. Carlson NR (1986) Physiology of behavior: Allyn & Bacon.
36. Stone MH (2014) The spectrum of borderline personality disorder: A neurophysiological view Electrophysiology and Psychophysiology in Psychiatry and Psychopharmacology. Springer 23-46.
37. Thomaes K, Dorrepaal E, Draijer N, de Ruiter MB, Elzinga BM, 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.
38. Cook A, Spinazzola J, Ford J, Lanktree C, Blaustein M, et al. (2005) Complex trauma. Psychiatric Annals 35(5): 5.
39. Charil A, Laplante DP, Vaillancourt C, King S (2010) Prenatal stress and brain development. Brain Research Reviews 65(1): 56-79.
40. Medina AM, Mejia VY, Schell AM, Dawson ME, Margolin G (2001) Startle reactivity and PTSD symptoms in a community sample of women. Psychiatry Res 101(2): 157-169.
41. Schauer M, Elbert T (2015) Dissociation following traumatic stress. Journal of Psychology, 218(2).
42. Koenen KC, Harley R, Lyons MJ, Wolfe J, Simpson JC, et al. (2002) A twin registry study of familial and individual risk factors for trauma exposure and posttraumatic stress disorder. The Journal of nervous and mental disease 190(4): 209-218.
43. Bale (2015) Epigenetic and transgenerational reprogramming of brain development. Nat Rev Neurosci 16(6): 332-344.

44. Bonasio R, Tu S, Reinberg D (2010) Molecular signals of epigenetic states. Science 330(6004): 612-616.

45. Nikolova YS, Hariri AR (2015) Can we observe epigenetic effects on human brain function?. Trends in cognitive sciences 19(7): 366-373.

46. 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.

47. Blaze J, Asok A, Roth TL (2015) The long-term impact of adverse caregiving environments on epigenetic modifications and telomeres. Front Behav Neurosci 9: 79.

48. Wu Y, Patchev AV, Daniel G, Almeida OF, Spengler D (2014) Early-life stress reduces DNA methylation of the Pomc gene in male mice. Endocrinology 155(5): 1751-1762.

49. Murgatroyd C, Patchev AV, Wu Y, Micale V, Bockmuhl Y, et al. (2010) Dynamic DNA methylation programs persistent adverse effects of early-life stress. Nature neuroscience 13(5): 649.

50. Ouellet Morin Odgers, Danese Bowes, Shakoor Papadopoulos, Arseneault (2011) Blunted Cortisol Responses to Stress Signal Social and Behavioral Problems Among Maltreated/Bullied 12-Year-Old Children. Biological Psychiatry 70(11): 1016-1023.

51. Perroud Salzmann A, Prada P, Nicastro R, Hoeppli ME, Furrer S, et al. (2013) Response to psychotherapy in borderline personality disorder and methylation status of the BDNF gene. Translational Psychiatry 3(1): e207.

52. Naumova OY, Lee M, Koposov R, Szyf M, Dozier M, et al. (2012) Differential patterns of whole-genome DNA methylation in institutionalized children and children raised by their biological parents. Development and Psychopathology 24(1): 143-155.

53. Essex MJ, Boyce WT, Hertzman C, Lam LL, Armstrong JM, et al. (2013) Epigenetic vestiges of early developmental adversity: Childhood stress exposure and DNA methylation in adolescence. Child Dev 84(1): 58-75.

54. Perroud Paoloni Giacobino A, Prada P, Olie E, Salzmann A, Nicastro R, et al. (2011) Increased methylation of glucocorticoid receptor gene (NR3C1) in adults with a history of childhood maltreatment: A link with the severity and type of trauma. Transl Psychiatry 1(12): e59.

55. Tyrka AR, Price LH, Marsit C, Walters OC, Carpenter LL (2012) Childhood Adversity and Epigenetic Modulation of the Leukocyte Glucocorticoid Receptor: Preliminary Findings in Healthy Adults. PLoS One 7(1): 30148.

56. Cohen Cory S, Kidane AH, Shirkey NJ, Marshak S (2010) Brain-derived neurotrophic factor and the development of structural neuronal connectivity. Developmental Neurobiology 70(5): 271-288.

57. Levone BR, Cryan JF, O Leary OF (2015) Role of adult hippocampal neurogenesis in stress resilience. Neurobiology of Stress 1(Supplement C): 147-155.

58. Meaney MJ, Diorio J, Francis D, Widdowson J, LaPlante P, et al. (1996) Early Environmental Regulation of Forebrain Glucocorticoid Receptor Gene Expression: Implications for Adrenocortical Responses to Stress. Dev Neurosci 18(1-2): 61-72.

59. Heinrich A, Buchmann AF, Zohsel K, Dukal H, Frank J, et al. (2015) Alterations of glucocorticoid receptor gene methylation in externalizing disorders during childhood and adolescence. Behavior Genetics 45(5): 529-536.

60. Martín Blanco A, Ferrer M, Soler J, Salazar J, Vega D, et al. (2014) Association between methylation of the glucocorticoid receptor gene, childhood maltreatment, and clinical severity in borderline personality disorder. Journal of Psychiatric Research 57: 34-40.

61. Tyrka AR, Parade SH, Eslinger NM, Marsit CJ, Lesseur C, Armstrong DA, et al. (2015) Methylation of exons 1D, 1F, and 1H of the glucocorticoid receptor gene promoter and exposure to adversity in preschool-aged children. Development and Psychopathology 27(2): 577-585.

62. Perroud Zewdie S, Stenz L, Adouan W, Bavamian S, Prada P, et al. (2015) Methylation of serotonin receptor 3a in adhd, borderline personality, and bipolar disorders: Link with severity of the disorders and childhood maltreatment. Depression and Anxiety 33(1): 45-55.

63. Crane JD, Palanivel R, Mottillo EP, Bujak AL, Wang H, et al. (2015) Inhibiting peripheral serotonin synthesis reduces obesity and metabolic dysfunction by promoting brown adipose tissue thermogenesis. Nature medicine 21(2): 166-172.

64. Seyedabadi M, Fakhfouri G, Ramezani V, Mehr SE, Rahimian R (2014) The role of serotonin in memory: Interactions with neurotransmitters and downstream signaling. Experimental brain research 232(3): 723-738.

65. Hieronymus F, Emilsson JF, Nilsson S, Eriksson E (2016) Consistent superiority of selective serotonin reuptake inhibitors over placebo in reducing depressed mood in patients with major depression. Molecular psychiatry 21(4): 523-530.

66. Rancillac A (2016) Serotonin and sleep-promoting neurons. Oncotarget 7(48): 78222.

67. Donaldson ZR, Piel DA, Santos TL, Richardson Jones J, Leonardo ED, et al. (2014) Developmental effects of serotonin 1A autoreceptors on anxiety and social behavior. Neuropsychopharmacology 39(2): 291.

68. Clayton AH, Croft HA, Handiwala L (2014) Antidepressants and sexual dysfunction: Mechanisms and clinical implications. Postgraduate medicine 126(2): 91-99.

69. Miller Wankerl M, Stalder T, Kirschbaum C, Alexander N (2013) The serotonin transporter gene-linked polymorphic region (5-HTTLPR) and cortisol stress reactivity: A meta-analysis. Molecular psychiatry 18(9): 1018-1024.

70. Ouellet-Morin Wong, Danese Pariante, Papadopoulos Mill, Arseneault (2013) Increased serotonin transporter gene (SERT) DNA methylation is associated with bullying victimization and blunted cortisol response to stress in childhood: A longitudinal study of discordant monozygotic twins. Psychological Medicine 43(9): 1813-1823.

71. Boyle MP, Brewer JA, Funatsu M, Wozniak DF, Tsien JZ, et al. (2005) Acquired deficit of forebrain glucocorticoid receptor produces depression-like changes in adrenal axis regulation and behavior. Proc Natl Acad Sci USA 102(2): 473-478.

72. Ridder S, Chourbaji S, Hellweg R, Urani A, Zacher C, et al. (2005) Mice with genetically altered glucocorticoid receptor expression show altered sensitivity for stress-induced depressive reactions. The Journal of Neuroscience 25(26): 6243-6250.

73. Labonte B, Yerko V, Gross J, Mechawar N, Meaney MJ, et al. (2012) Differential glucocorticoid receptor exon 1B, 1C, and 1h expression and methylation in suicide completers with a history of childhood abuse. Biological Psychiatry 72(1): 41-48.

74. McGowan PO, Sasaki AD, Alessio AC, Dymov S, Labonté, B, et al. (2009) Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nature neuroscience 12(3): 342-348.

75. Dannlowski U, Kugel H, Redlich R, Halik A, Schneider I, et al. (2014) Serotonin transporter gene methylation is associated with hippocampal gray matter volume. Human Brain Mapping 35(11): 5356-5367.

76. Toda H, Boku S, Nakagawa S, Inoue T, Kato A, et al. (2014) Maternal Separation Enhances Conditioned Fear and Decreases the mRNA Levels of the Neurotensin Receptor 1 Gene with Hypermethylation of This Gene in the Rat Amygdala. PLoS One 9(5): 97421.

77. Dijke V (2012) Dysfunctional affect regulation in borderline personality disorder and in somatoform disorder. European Journal of Psychotraumatology 3(Suppl 2).

78. Elklit Hyland Shevlin (2014) Evidence of symptom profiles consistent with posttraumatic stress disorder and complex posttraumatic stress disorder in different trauma samples. Eur J Psychotraumatol 5.

79. Knefel Garvert Cloitre, Lueger Schuster (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).

80. Wolf Miller, Kilpatrick Resnick, Badour, Marx Friedman (2015) ICD–11 Complex PTSD in US National and Veteran Samples Prevalence and Structural Associations With PTSD. Clinical Psychological Science 3(2): 215-229.

81. American Academy of Social Work & Social Welfare (2017) 12 Challenges.

82. Association AP (2013) Diagnostic and statistical manual of mental disorders (DSM-5®): American Psychiatric Pub.

83. Cloitre Garvert, Weiss Carlson, Bryant (2014) Distinguishing PTSD, complex PTSD, and borderline personality disorder: A latent class analysis. European Journal of Psychotraumatology 5.

84. Dorrepaal E, Thomaes K, Smit JH, Veltman DJ, Hoogendoorn AW, et al. (2014) Response to Treatment compliance and effectiveness in complex PTSD patients with co-morbid personality disorder undergoing stabilizing cognitive behavioral group treatment: A preliminary study. European Journal of Psychotraumatology 5: 23792.

85. Hall DK (1999) Complex posttraumatic stress disorder/disorders of extreme stress (CP/DES) in sexually abused children: An exploratory study. Journal of Child Sexual Abuse: Research, Treatment, & Program Innovations for Victims, Survivors, & Offenders 8(4): 51-71.

86. Hieronymus F, Emilsson JF, Nilsson S, Eriksson E (2016) Consistent superiority of selective serotonin reuptake inhibitors over placebo in reducing depressed mood in patients with major depression. Molecular psychiatry 21(4): 523-530.

87. Koenen KC, Harley R, Lyons MJ, Wolfe J, Simpson JC, et al. (2002) A twin registry study of familial and individual risk factors for trauma exposure and posttraumatic stress disorder. The Journal of nervous and mental disease 190(4): 209-218.

88. Kulkarni J (2017) Complex PTSD-a better description for borderline personality disorder?. Australasian Psychiatry 25(4): 333-335.

89. Levone BR, Cryan JF, O Leary OF (2015) Role of adult hippocampal neurogenesis in stress resilience. Neurobiology of Stress 1(Supplement C): 147-155.

90. Prados J, Stenz L, Courtet P, Prada P, Nicastro, et al. (2015) Borderline personality disorder and childhood maltreatment: A genome!wide methylation analysis. Genes, Brain & Behavior 14(2): 177-188.

DOI: 10.32474/OJNBD.2023.06.000248