Perry, B.D. (2017) Trauma- and stress-related disorders in infants, children and adolescents in Textbook of Child and Adolescent Psychopathology (Theodore P. Beauchaine and Stephen P. Hinshaw, Eds) Wiley, New York pp 683-705

CHAPTER 20

Trauma- and Stressor-Related Disorders in Infants, Children, and Adolescents

BRUCE D. PERRY

Essentially, all models are wrong, but some are useful.

—George E. P. Box

FOR MORE THAN 150 YEARS, trauma- and stressor-related problems have been studied extensively from multiple perspectives, including those represented by neuroscience, developmental psychology, genetics, epidemiology, the social sciences, medicine, and psychiatry, to name a few. These interdisciplinary perspectives, which are all reflected in the developmental psychopathology approach to conceptualizing mental illness (see Chapter 1 [Hinshaw]) bring different and often complementing insights. Yet, as these various perspectives have converged, defining and delineating "trauma- and stressor-related" disorders has become significantly more challenging and at times controversial. In some important ways, clinical work and research related to trauma among children and adolescents is at an important crossroads; multiple useful directions can, and will, emerge from this junction, but for students, clinicians, and researchers who are interested in trauma "disorders" and trauma-informed practice, program, and policy, this a messy but exciting time.

A brief review of evolving formulations regarding trauma- and stressor-related mental health issues can provide perspective to current efforts to understand complex interrelationships among developmental experiences and physical, emotional, behavioral, social, and cognitive functions.

HISTORICAL CONTEXT

Humankind has always experienced chaos, threat, violence, rape, war, traumatic death, and a host of other known traumatic and stressful events. And humankind has always known the emotional toll that these experiences exact on individuals. Indeed trauma-related symptoms have been documented across all of recorded history. According to Abdul-Hamid and Hacker Hughes (2014), archeological records from Assyria in 1300 B.C. mention combat exposure causing King of Elam's "mind change." Homer's *Iliad* (725 B.C.) describes the emotionally distraught Ajax after losing a competition with Odysseus for the fallen Achilles' armor. Ajax comes under a "spell" from Athena, slaughters a herd of sheep thinking they are the enemy, and then when he comes to his senses, is shamed and commits suicide (later the basis for the famous play *Ajax*, by Sophocles: 450 B.C.). Herodotus (approx. 440 B.C.) describes trauma-like symptoms among warriors following the battle of Marathon. Hysterical blindness was described in one warrior after the man standing next to him was killed, although the blinded warrior "was wounded in no part of his body" (Waterfield & Dewald, 1998). Herodotus also wrote of the Spartan commander Leonidas, who, at the battle of Thermopylae in 480 B.C., dismissed men from combat knowing they were mentally exhausted from previous battles. Trauma-related syndromes similar to the current *DSM-5* diagnosis of post-traumatic stress disorder (PTSD) were described as "irritable heart" of the U.S. Civil War (DaCosta, 1871) and "shell shock" following combat in World War I (Myers, 1915). Early neglect-related conditions similar to the *DSM-5* diagnoses of reactive attachment disorder (RAD) have also been recorded throughout history. Frederick II, the Emperor of Germany, while seeking to determine the "language of God," raised dozens of children in a silent, emotionally neglectful manner. These children spoke no language; and all of them died in childhood (see van Cleve, 1972).

Study of the effects of stress and trauma on mental health played major roles in the emergence of modern neurology and psychiatry. Jean-Martin Charcot (1825–1893), who is often considered the founder of modern neurology, hypothesized that fits of "hysteria" and "hystero-epilepsy," seen in both female and male patients, were associated with earlier traumatic experiences, including industrial accidents and combat exposure (see Ellenberger, 1970; Goetz, 1987). Pierre Janet (1859–1947), a student of Charcot, continued to study hysteria and hypnosis-induced trance states, and ultimately coined the term *dissociation* to describe detachments from reality that occurred when individuals with unspecified mental weaknesses were stressed. Present-day clinicians recognize these as common trauma-related symptoms.

The historical record of the study of trauma in childhood is not as extensive. Sigmund Freud (1909), who was aware of the work of Charcot and Janet, described treatment of a specific phobia in a 5-year-old child, Hans. This was one of the earliest descriptions of potential trauma-related symptoms among children. Although Freud's interpretation was somewhat complex, he made the observation of a previous distressing (if not traumatic) experience that might

account for Han's specific fears related to horses. Hans' family lived across from a coaching inn—a hotel where travelers in coaches could stop for food and lodging. Horses pulling heavily laden carts were most upsetting to Hans. As a younger child when he was outside with his nurse, he observed a horse collapse and die in the street. This horse was pulling a bus of passengers. Hans was frightened by the fallen horse and the clattering of its hooves against the cobbles. Again, the present day, trauma-informed clinician would describe cue-specific reactivity and avoidant symptoms in Hans' behaviors.

Creation of a specific conditioned fear response, and generalization of it to similar stimuli, was a foundational experiment of modern psychology. A pioneer of American psychology, John Watson, intentionally created a phobia in a toddler (Watson & Rayner, 1920). In the classic case study "Little Albert," Watson created cue-specific reactivity by conditioning Albert to be fearful of a neutral cue. Albert demonstrated symptoms of intrusion, altered arousal, and avoidance—key symptoms of PTSD in the *DSM-5*.

> It is probable that many of the phobias in psychopathology are true conditioned emotional reactions either of the direct or the transferred type . . . . Emotional disturbances . . . must be retraced along at least three collateral lines—to conditioned and transferred responses set up in infancy and early youth in all three of the fundamental human emotions
>
> **Watson and Rayner, 1920, p. 317**

Another pioneer of psychology, Mary Cover Jones, reported the first progressive desensitization treatment of a young child when she successfully treated his phobia of rabbits and other soft and, white materials (Cover Jones, 1924). Core principles of this approach form the basis for some current evidence-based or evidence-informed treatments for trauma among both children and adults, including systematic desensitization and trauma-focused cognitive behavioral treatment (TF-CBT). Interestingly, Cover Jones did not believe successful treatment of Peter would persist. She suggested that poverty, maternal depression, permeating distress, chaos, and emotional abuse in the family would undermine his progress:

> His "home" consists of one furnished room which is occupied by his mother and father, a brother of nine years and himself. Since the death of an older sister, he is the recipient of most of the unwise affection of his parents. His brother appears to bear him a grudge because of this favoritism, as might be expected. Peter hears continually, "Ben is so bad and so dumb, but Peter is so good and so smart!" His mother is a highly emotional individual who can not get through an interview, however brief, without a display of tears. She is totally incapable of providing a home on the $25 a week which her husband steadily earns. In an attempt

> to control Peter she resorts to frequent fear suggestions. "Come in Peter, some one wants to steal you." To her erratic resorts to discipline, Peter reacts with temper tantrums. He was denied a summer in the country because his father forgets he's tired when he has Peter around.
>
> **Cover Jones, 1924, pp. 380**

This clinical insight foreshadowed complexities that contribute to our current understanding and study of developmental trauma.

It was in this same era when conceptualizations of homeostasis, stress, and distress were initially articulated. Walter Cannon (1914) coined the term *homeostasis*, and described physiological mobilization of multiple systems in the body under threat as the "fight or flight" response. This term continues to be used to encapsulate a complex array of emotional, behavioral, and physiological changes seen in arousal responses to threat.

A less well-known area of Cannon's work examined an extreme manifestation of dissociative responding—"voodoo" death (Cannon, 1942). The dissociative continuum involves a graded set of adaptive responses, including vasovagal activation, to immobilizing, inescapable, or painful stimuli/threat (Perry, Pollard, Blakely, Baker, & Vigilante, 1995; Porges, 2011). Under extreme threat (perceived or real) both "fight or flight" and dissociative responses can co-occur, leading to a complex mixture of physiological, emotional, behavioral, and cognitive responses (see Perry et al., 1995).

Hans Selye (1936) first used the term *stress* in physiology to describe "nonspecific response of the body to any demand." Selye's organizing framework for understanding effects of stressors on the body—general adaptation syndrome—continues to be useful. This three-phase process begins with the organism at homeostasis. Once a stressor is perceived, the alarm phase begins, which is a sympathetic nervous system dominated "fight or flight" reaction. A second phase, resistance, involves efforts of the body to restore physiological functioning to homeostasis (i.e., back to normal). This involves activation of the parasympathetic nervous system. The third state, exhaustion, occurs if the stressor persists beyond the body's capacity to restore homeostasis. This leads to dysfunction within organ systems in the body and potentially, death (see Chapter 4 [Compas, Gruhn, & Bettis]). As Selye wrote "Every stress leaves an indelible scar, and the organism pays for its survival after a stressful situation by becoming a little older" (Selye, 1936, p. 32). But this was just a start of understanding the complex role of stress and trauma in neuropsychiatric disorders.

ETIOLOGY

Over the past 75 years, a torrent of research in neuroscience and related fields has explored various aspects of stress, distress, trauma, and resilience among both animals and humans. A major area of convergence is the central role that a set of neural

networks plays in maintaining homeostasis, mediating "alarm" and "resistance" responses to stress. These neural networks become altered via allostatic mechanisms when stressors are of sufficient duration, intensity or pattern (for reviews, see Beauchaine, Neuhaus, Zalewski, Crowell, & Potapova, 2011; Mead, Beauchaine, & Shannon, 2010; Chapter 4 [Compas, Gruhn, & Bettis]).

A set of neural systems (including adrenergic, noradrenergic, dopaminergic, and serotonergic) originate in the brainstem and diencephalon and have wide distribution throughout the brain. These networks comprise the core of a "bottom-up" component of the stress response. Along with a top-down set of neural networks (see Beauchaine, 2015; Rauch & Drevets, 2009), they provide integrated responses to novelty, challenge, and threat. Collectively, they modulate and regulate almost all brain functions, including those subserved by neuroendocrine systems including the limbic hypothalamic pituitary adrenal (LHPA) axis, neuroimmune systems, and the autonomic nervous system, thereby playing crucial roles in all of our variegated, heterogeneous stress response capabilities (see also Perry, 2008). Abnormal development or regulation of any component or subcomponent of one or more of these neural networks can result in functional problems and cause symptoms of psychopathology (see Beauchaine et al., 2011). There are many mechanisms through which the functional capacity of these systems can be affected. A brief overview follows.

Genetics

Certain genetic vulnerabilities influence the nature and flexibility of individual's stress responses. To date, most major candidate genes are associated with regulation of adrenergic, noradrenergic, and dopaminergic and serotonergioc neural networks. In animal models, for example, genetic differences in expression of phenylethanolamine N-methyltransferase (PNMT), an enzyme that converts noradrenaline to adrenaline (see Vantini et al., 1983) in two strains of rats lead to a cascade of group differences in stress-response neurobiology that have significant functional consequences, with one strain being more sensitive to stressors (Perry, Stolk, Vantini, Guchhait, & U'Prichard, 1983).

Similar genetically mediated individual differences in sensitivity to stressors among humans are observed. Caspi and colleagues (2001, 2003), for example, reported that the short allele of the serotonin transporter gene (5-HTTLPR) confers vulnerability to depression following stressful life events, a finding that, despite being controversial early on (see e.g., Fergusson, Horwood, et al., 2011; Risch et al., 2009), has since gained acceptance following several replications (see Karg, Burmeister, Shedden, & Sen, 2011). Other gene-environment interactions involving differential sensitivity to stress have been reported for genes involved in production and regulation of monoamine oxidase (MAO-A; e.g., Fergusson,

Boden, et al., 2011; Kim-Cohen, Caspi, Taylor, et al., 2006), corticotropin-releasing hormone (CRHR; Tyrka et al., 2009); and tyrosine hydroxylase (TH; see Cicchetti, Rogosch & Thibodeau, 2012). Nevertheless, much work remains. Smoller (2015) summarized the current status of this area in a recent review:

> Available data suggest that stress-related disorders are highly complex and polygenic and, despite substantial progress in other areas of psychiatric genetics, few risk loci have been identified for these disorders. Progress in this area will likely require analysis of much larger sample sizes than have been reported to date. The phenotypic complexity and genetic overlap among these disorders present further challenges
>
> **Smoller, 2015, p. 297**

EPIGENETICS

Stressors of various kinds affect gene expression and regulation via DNA methylation and modification of histones (proteins that regulate DNA structure; see Chapter 3 [Beauchaine, Gatzke-Kopp, & Gizer]). These *epigenetic* alterations in DNA structure (as opposed to sequence) are best characterized in animal models, where true experiments—including random assignment to stressful and nonstressful conditions—can be conducted (see e.g., Meaney & Szyf, 2005). Maternal stress exposure at key prenatal periods can alter long-term function of several behavior regulation and stress response systems among offspring (e.g., Daskalakis et al., 2013), including both (a) monoamine neural networks implicated in mood and emotion regulation, motivation, social affiliation, and attachment (see Beauchaine et al., 2011); and (b) the LHPA axis, which, as outlined above, coordinates neural and neuroendocrine responses to stress (e.g., Lupien, McEwen, Gunnar, & Heim, 2009).

Although epigenetics is a relatively new field, the potential impact of epigenetic mechanisms of intergenerational transmission of vulnerability (or resilience) to psychopathology may be profound. To date, however, studies among humans remain suggestive, not conclusive (Klengel & Binder, 2015). Although environmentally induced, epigenetic alterations in gene expression clearly accumulate across the lifespan (e.g., Fraga et al., 2005), and are dissociated with adverse rearing conditions (e.g., Tyrka, Price, Marsit, Walters, & Carpenter, 2012), drawing clear links to psychopathology is difficult without the capacity to conduct true experiments. Nevertheless, research demonstrates epigenetic changes in gene expression across an ever broadening range of psychiatric conditions (see Chapter 3 [Beauchaine, Gatzke-Kopp, & Gizer]). In a recent study that received considerable media attention, Yehuda and colleagues (2015) reported prenatally acquired FKBP5 methylation, which was presumed to be trauma-induced among Holocaust survivors and their offspring. It now seems clear that epigenetics will be

a major focus of future research into determinants of stress-responding and other behavior regulation systems.

Early Development

A related area of research on etiologies of trauma- and stress-related disorders is the study of effects of early experience. Seymour Levine, a pioneer in this area, demonstrated that brief stressors in the infant period of rat pup development can result in dramatic alterations in neuroendocrine stress responding (e.g., Levine, 1957, 1994, 2005). Maternal nurturing behaviors (e.g., physical touch, grooming) are key to healthy development of the stress response systems among both rats and nonhuman primates (e.g., Schanberg, Evoniuk, & Kuhn, 1984). In these studies, timing and pattern of stress activation (or deprivation) is critical (Meaney, 2001; Claessens et al., 2011). Some stressors alter neurodevelopment when delivered at certain ages but not others, and some patterns of stress delivery (generally predictable, controllable, and moderate) result in healthier development, whereas other patterns (generally unpredictable, uncontrollable, or extreme) result in apparent sensitization (increased reactivity) of the stress response system to future challenges.

Animal studies of maternal deprivation are homologous to observations of clinicians who work with institutionalized and severely neglected children (see Perry, 2002 for review). Early life stressors, without extreme deprivation, can also lead to abnormalities in stress-responding, and in functioning of other neural networks involved in reward processing, behavior regulation, and social affiliation (see Beauchaine et al., 2011; Broekman, 2011; Meaney, 2001; Perry, 2002; Tronick & Perry, 2015). Among humans, primary caregivers (often mothers) serve as external stress regulators for developing children (Beeghly, Perry & Tronick, 2016). Attentive, attuned, and responsive caregiving provides a pattern of stress response activation/deactivation (i.e., when the infant is hungry, cold, or thirsty, and therefore stressed, she cries—the alarm phase—and the caregiver responds, thereby returning the infant to homeostasis) that encourages a moderate, predictable, and controllable pattern of behavioral responding that leads to resilience. In contrast, overwhelmed, depressed, dysregulated caregivers struggle with consistency in responding, providing their infants with unpredictable, episodic care (and stress response activation/deactivation) that leads to sensitized stress reactivity and a cascade of secondary developmental sequelae (e.g. Perry, Hambrick & Perry, 2015). Other early developmental stressors such as poverty, with related food and housing insecurity, can create a sensitized pattern that leads to risk for health and mental health issues. Nurturing and supportive maternal care can buffer some of the adverse effects of poverty (Miller et al., 2011). Similarly, high quality early childhood programs for at-risk children can buffer some stress-related negative health outcomes associated with early childhood adversity (see Campbell et al., 2014).

Childhood Adversity and Resilience

Developmental adversity following infancy can also precipitate trauma- and stressor-related disorders, especially when coupled with neurobiological vulnerability. An expansive number of studies demonstrate (a) development of trauma-related neuropsychiatric disorders, including PTSD, following various forms childhood trauma (e.g., exposure to domestic violence, sexual abuse, catastrophic public events, maltreatment [for review see Saunders & Adams, 2014]); and (b) a role of childhood trauma as a causal or additive factor in expression of psychiatric disorders that are usually not conceptualized as being trauma- or stressor related, including major depression (see Teicher & Samson, 2013) and schizophrenia/psychotic disorders (see, e.g., Read, Perry, Moskowitz, & Connolly, 2001; Read, Fosse, Moskowitz, & Perry, 2014). Retrospective studies of effects of adversity (i.e., trauma- and stress-related problems) on all aspects of health and welfare has resulted in major shifts in policy and practice. The epidemiological Adverse Childhood Experience (ACE) studies (e.g., Fellitti et al., 1998) demonstrate that adversity in childhood results in "dose-dependent" increases in risk for the top nine major causes of death in adulthood. Risk for suicide, mental health problems, substance abuse, and a host of other untoward outcomes is also increased by childhood adversity (Anda et al., 2006).

In fact, childhood adversity may play a role—at least for many individuals—in expression of most DSM disorders. Green et al. (2010), in a representative sample of 9,282 adults, found that childhood adversities (CAs), especially those in a maladaptive family functioning cluster (parental mental illness, substance abuse disorder, criminality, family violence, physical abuse, sexual abuse, and neglect) correlated strongly with onset of many *DSM-IV* disorders. Furthermore, simulations suggested that CAs are associated with 44.6% of all childhood-onset disorders, and 25.9% to 32.0% of later-onset disorders. These findings complement studies that examine the role of maltreatment in prevalent disorders of childhood (i.e., major depression, ADHD, conduct disorder, anxiety disorders). In a review and analysis of maltreatment as a major co-existing factor in DSM disorders, Teicher and Samson (2014) make the case that for any given disorder, maltreated versus nonmaltreated individuals should be conceptualized as distinct subtypes, and that an ecophenotype modifier be added to the DSM to facilitate research and clinical intervention.

Clearly, developmental adversity, including trauma and exposure to extreme stress, can result in adverse outcomes. However, not all children who are exposed to trauma develop symptoms. In fact, there are identified vulnerabilities and risk factors that increase the likelihood of adjustment problems following trauma (e.g., previous history of exposure to trauma), and factors that predict resilience (e.g., nurturing families, community and cultural connections; see Ungar & Perry, 2012). Understanding resilience is crucial for understanding the etiology of trauma- and stress-related disorders, and for developing more effective treatments.

Cicchetti (2013) in reviewing research on resilience among maltreated children summarized the state of this area:

> "The majority of the research on the contributors to resilient functioning has focused on a single level of analysis and on psychosocial processes. Multilevel investigations have begun to appear, resulting in several studies on the processes to resilient functioning that integrate biological/genetic and psychological domains. Much additional research on the determinants of resilient functioning must be completed before we possess adequate knowledge based on a multiple levels of analysis approach that is commensurate with the complexity inherent in this dynamic developmental process."
>
> **Cicchetti, 2013, pp. 402**

Complex interactions across levels of analysis (i.e., genes, the epigenome, neural systems, physiological networks, organ systems, individuals, families, communities, and cultures), and the developmental timing, patterns, intensity, and nature of stress-activating experiences (i.e., sensitizing vs. resilience-building) for any given individual imply a staggering number of potential phenotypic outcomes following developmental adversity and trauma (i.e., multifinality; see Chapter 1 [Hinshaw]). This is a major challenge to past, present, and proposed efforts to categorize, study, and diagnose trauma- and stressor-related mental disorders among humans.

DIAGNOSTIC ISSUES AND *DSM-5* CRITERIA

The DSM model of conceptualizing, categorizing, and naming psychiatric disorders based solely on symptom clusters has its origins in the 1800s and early 1900s. The first official categorization was the label of "idiocy/insanity," which was part of the 1840 census. The National Commission on Mental Hygiene and the American Psychiatric Association (APA) developed a *Statistical Manual for the Use of Institutions of the Insane* in 1917. This precursor to the DSM included 22 diagnoses. The first DSM (*DSM-I*), published in 1952, specified 108 mental disorders (Grob, 1991). In the *DSM-I*, which was influenced heavily by Adolph Meyer's psychobiology, *all* psychiatric disorders were characterized as reactions to stress (see Chapter 2 [Beauchaine & Klein]). Accordingly, all disorders had the word "reaction" in their titles (e.g., depressive reaction), including the stress-related diagnosis, "gross stress reaction." Interestingly, this diagnosis disappeared in the second version of the DSM (*DSM-II*, 1968). Post-traumatic stress disorder (PTSD), the major trauma-related disorder in the *DSM-5*, did not appear in the DSM until 1980 (*DSM-III*).

In 2013, the APA published the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*). The trauma and stressor-related disorders category reflects the most recent efforts of the APA and its appointed academic

contributors and workgroup members to create diagnostic criteria to categorize neuropsychiatric signs and symptoms—and in some cases life histories—into meaningful clusters to promote further study and development of effective clinical interventions. In the *DSM-5*, trauma- and stressor-related disorders comprise a new category. Five distinct disorders are included: acute stress disorder (ASD), adjustment disorders (AD), disinhibited social engagement disorder (DSED), PTSD, and reactive attachment disorder (RAD). Two indistinct disorders are also included: other specified trauma- and stressor-related disorders and unspecified trauma- and stressor-related disorders. Diagnostic criteria for these disorders are summarized briefly below (each major diagnostic criterion is listed in capital letters).

Acute Stress Disorder

A. Exposure to a trauma (see below for definition)
B. Presence of nine (or more) symptoms from any of the five major symptom categories—intrusion, negative mood, dissociation, avoidance, and arousal—which appear to be associated with the traumatic event
C. Duration of three days to one month after the trauma
D. Impairment in functioning
E. Symptoms not attributable to another cause (e.g., substance of abuse, medical condition, brief psychotic disorder)

Adjustment Disorders

A. Development of emotional or behavioral symptoms in response to an identifiable stressor occurring within 3 months of the onset of stressor
B. Clinically significant level of symptoms
C. Symptoms do not meet criteria for another mental disorder
D. Symptoms are not attributable to normal bereavement
E. Once the stressor is gone, symptoms do not persist past 6 months

Disinhibited Social Engagement Disorder

A. The child actively approaches and interacts with unfamiliar adults, in an overly familiar fashion
B. Such approach behavior is not due to impulsivity (e.g., ADHD)
C. The child has history of insufficient care such as described for RAD
D. Such care is presumed to be causal to A
E. The child has a developmental age of at least nine months

Posttraumatic Stress Disorder

Six years and up:

A. Exposure to a trauma
B. Intrusive symptoms (e.g., intrusive ideations, repetitive play with trauma-related themes, distressing dreams)
C. Avoidant symptoms (e.g. avoidance of evocative cues or trauma-associated people, places, or experiences)
D. Altered mood and cognitions (e.g., guilt, dysphoria, anhedonia)
E. Altered arousal and reactivity (e.g., increase startle response, irritability, hypervigilance)
F. Duration of more than one month
G. Significant functional impairment
H. Symptoms are not due to other causes (e.g., substance use, medical condition)

Criteria for PTSD for children who are younger than age six years are essentially the same, aside from developmentally appropriate emotional, cognitive, and behavioral manifestations of intrusive, avoidant, affective, and arousal symptoms.

Reactive Attachment Disorder

A. A consistent pattern of inhibited, emotionally withdrawn behavior toward adult caregivers, manifested by both
B. Social and emotional disturbance
C. Extremes of insufficient care (e.g., social neglect, institutionalization, repeated changes in primary caregiver); as well as
D. Care in C that is presumed to be causal of A
E. The behavior is not attributable to autism spectrum disorder
F. Symptoms are evident before age five years
G. The child has a developmental age of at least nine months

Specific criteria for, and the very existence of, trauma- and stressor-related disorders in the DSM have changed multiple times since 1980, as newer versions were published. In the *DSM-IV* and *DSM-IV-TR*, for example, PTSD and ASD were categorized as anxiety disorders, whereas RAD was categorized as a disorder usually first diagnosed in infancy, childhood, or adolescence, AD was a stand-alone disorder, and DSED—a new disorder in the *DSM-5*—was previously a subtype of RAD (disinhibited attachment disorder). For ASD, AD, and PTSD, exposure to a traumatic or stressful event is a required diagnostic criterion. However, the definition of trauma is different in the *DSM-5* than in the *DSM-IV* and *DSM-IV-TR* (see below). For RAD and DSED, social neglect (absence of necessary caregiving during

childhood) is a required diagnostic criterion. As this summary implies, individuals who meet diagnostic criteria for trauma- and stressor-related disorders can display a remarkably heterogeneous range of emotional, behavioral, social, and cognitive symptoms, many of which overlap with other *DSM-5* disorders (see discussion of comorbidity below).

PREVALENCE

Prevalence rates of *DSM-5* trauma- and stress-related disorders among children and adolescents are not well established. However, inferences can be drawn from the few studies that addressed prevalences of similar disorders in previous instantiations of the DSM, both among youth and adults. Rates of AD among adult clinical populations, for example, are high; in some cases up to 20% of outpatient samples. Prevalence rates of PTSD among children and adolescents are not well determined, but lifetime prevalence estimates of PTSD range from 8 to 12%. In contrast, RAD is likely rare, given that only about 10% of neglected children are affected (Gleason et al., 2011). Perhaps the more important question for both research and clinical purposes is the prevalence of traumatic experiences.

Exposure to childhood adversity and trauma are common (Saunders & Adams, 2014). Public health surveillance using ACEs in multiple settings demonstrates very high rates of exposure to adversity among children and adolescents. In typical public school classrooms in the state of Washington, for example, only 6 in 30 children have an ACE score of 0, whereas 10 have an ACE score of 4 or more (Family Policy Council: WA). In juvenile justice populations, rates of exposure to multiple trauma are astoundingly high—in excess of 85% (e.g., Baglivio et al., 2014). In the National Survey of Children's Exposure to Violence (NSA), 20% of all youth and 41% of victims of any of four types of victimization that were measured experienced more than one type. In fact, exposure to multiple types of victimization/trauma is very common among children and adolescents, characterizing 20% to 48% of all youth depending on the number of victimization types measured (Finkelhor, Turner, Shattuck, & Hamby, 2015). The prevalence of trauma and its complex heterogeneous outcomes poses a major challenge to the DSM model of delineating mental disorders (see also Chapter 2 [Beauchaine & Klein]).

Clinical and Research Challenges of *DSM* Model

Since 1980, when PTSD was introduced in the *DSM-III*, clinicians and researchers have had to deal with complexities posed by developmental manifestations of trauma-related problems. A simple example is in conceptualization of Criterion A, experiencing a trauma. The *DSM-5* defines trauma as "exposure to actual or threatened death, serious injury, or sexual violence in one or more of four ways: (a) directly experiencing the event; (b) witnessing, in person, the event occurring to others; (c) learning that such an event happened to a close family member

or friend; and (d) experiencing repeated or extreme exposure to aversive details of such events, such as with first responders. Actual or threatened death must have occurred in a violent or accidental manner, and experiencing cannot include exposure through electronic media, television, movies or pictures, unless it is work-related" (*DSM-5*, pp. 271). In order to meet diagnostic criteria for PTSD for adults and children older than age 6 years, the individual must endorse Criterion A. What is considered traumatic is different in the *DSM-5* than in previous versions of the *DSM*; the subjective experience of the individual during the traumatic event is no longer part of Criterion A.

Almost as soon as PTSD among children was described (Terr, 1983), clinicians began to see at least two subtypes. Single traumatic events often result in different presentations compared with multiple traumatic experiences. This led Terr (1991) to refer to Type I and Type II variants of childhood PTSD. Moreover, developmental trauma was associated such complex mixtures of symptoms that it could mimic many other DSM diagnoses. As described above, heterogeneous symptom clusters that are observed following trauma result in very high rates of comorbidity. Attention-deficit/hyperactivity disorder, conduct disorder, major depression, substance abuse disorder, dissociative disorders, and psychotic disorders are commonly co-diagnosed with PTSD. Strict application of DSM criteria yields combinations of comorbid diagnoses that are often of little use to clinicians, and produce major confounds for researchers.

Complex developmental sequelae of trauma and neglect challenge the validity and clinical and research utility of DSM formulations of trauma-related disorders (see van der Kolk, 2005). During development of the *DSM-5*, academics and clinicians who work with traumatized and maltreated children, and others, urged, unsuccessfully, for adoption of a developmental trauma disorder to address some of these complexities (van der Kolk et al., 2009). Yet such an additional disorder cannot address the multidimensional and complex physiological, emotional, social, behavioral, and cognitive effects of developmental adversity, trauma, and neglect. As the statistician George Box said, "Essentially, all models are wrong, but some are useful." For trauma-related disorders, the DSM model may have reached the limits of its utility.

The major limitation of the DSM model involves defining disorders based upon symptoms—not pathophysiology (see Chapter 2 [Beauchaine & Klein]). In stark contrast, diagnosis in medicine focuses on identifying underlying disease processes/pathophysiology (see e.g., Beauchaine & Cicchetti, 2016). This model has evolved over the last 150 years, and was only possible following development of methods that allow more direct and detailed examination of organs and cells, (e.g., microscopes, x-ray, ultrasound, fMRI), and identification of dynamic physiological processes and biomarkers (e.g., chemicals, enzymes, DNA-related factors in blood and other tissue). These advances have allowed clinicians and researchers to move from a symptom and sign dominated model of diagnosing to a specific disease process model (Berger, 1999).

The human brain, however, is both much more complex than any other organ in the body, and much less accessible for direct examination of functioning of its various neural networks. The brain has roughly 86 billion neurons, 420 trillion synapses, and 2.5 quadrillion depolarizations/min, which mediate hundreds of complex functions including speech, abstract cognition, and fine motor control. In comparison, the heart has roughly 2 billion cells and mediates only a handful of much simpler functions such as pumping blood. In 1952, when the DSM was first introduced, no technologies or lab tests existed to provide any basis for clustering neuropsychiatric conditions. At the time, symptom-based diagnosing was therefore logical and necessary. However, reliance on this system is vestigial. By the time newer technologies evolved to directly examine complex neural networks across various brain regions, the field of psychiatry, including its clinical practice, training programs, research frameworks and, medical-economic model, were all dependent on the DSM symptom clustering model. Although good arguments can be made that the so-called medical model of diagnosing disorders is inadequate for the complexities of neuropsychiatric problems, there is value in examining diagnostic practices for other diseases. This simple examination illustrates the nature of clinical and research problems that arises when using symptom-based clustering to define neuropsychiatric disorders.

Problem 1: Similar Signs and Symptoms May Be Caused by Multiple Pathophysiological Processes (Equifinality). If a person presents at the emergency room with severe chest pain (a symptom) and high heart rate (a physical sign), the clinical team will need to determine the underlying cause in order to provide effective treatment. Chest pain and elevated heart rate can be caused by dozens of different pathophysiological processes including coronary artery blockage, pancreatitis, gall bladder problems, lung infections, indigestion, or a gastric ulcer. Although history and additional symptoms help narrow the search for actual causes of these problems, a set of tests that assess biomarkers helps evaluate the physiological status of the various organs and physiological processes that may be involved (e.g., elevated heart muscle enzymes in the blood indicate a heart attack, elevated white blood cells indicate infection, elevated liver enzymes indicate blockage of the gall bladder, ultrasound of the abdomen identify masses or blockages, x-rays of the chest identify lung infection). Biomarkers tell the clinical team about functioning of organ systems that may be responsible for symptoms. Once the actual pathophysiology is determined, a suitable intervention can be started (see also Beauchaine & Marsh, 2006).

Perhaps no other category of *DSM-5* disorders illustrates this potential problem in clinical settings as much as the trauma-related disorders. Consider a teacher who deals with an inattentive, restless, and generally dysregulated 10-year-old boy. His homework is rarely turned in on time, and is always messy and usually incorrect. He doesn't finish tests on time, and his social skills are lagging. The teacher suspects he has ADHD and that he needs medication, and requests that his parents have

him evaluated for ADHD. The mother arranges an appointment with a pediatrician. At best, the busy pediatrician administers a set of attention and impulse-control focused metrics (e.g., the Conners Behavior Rating Scales) to the mother and the teacher, and takes a history of specific symptoms and current presentation in a very brief—perhaps 15 minute—appointment. Based on all information collected, the child meets diagnostic criteria for ADHD, and a psychostimulant is prescribed.

Yet there are dozens of potential pathophysiological processes that can result in these symptoms, many of which are related to developmental stressors and trauma. The child may have experienced intrauterine exposure to alcohol or other teratogens, in which case these symptoms are part of a more complex constellation of problems (see Chapter 9 [Doyle, Mattson, Fryer, & Crocker]). Alternatively, the mother may have experienced serious postpartum depression that reduced her capacity to be attuned and responsive in the first months of her infant's life, resulting in dysregulated stress-responding and ADHD-like symptoms (see Beeghly et al., 2016). The child may have experienced trauma-related alterations in monoamine function and/or stress-responding following exposure to domestic violence, sexual abuse, physical abuse, and/or community violence (see above Beauchaine et al., 2011). Thus, the nature, timing, and severity of a host of adversities during development could result in the symptoms this child is demonstrating (Anda et al., 2006; Teicher & Samson, 2013). It is highly likely that primary informants (i.e., the child, parent, and teacher) are all unaware of relations between past experiences (e.g., domestic violence when the child was ages 4 to 6 years old, community violence, sensitizing distress of poverty), and current symptoms. Even when a clinic screens for some of these events, caregivers may be unwilling to report current traumatic experiences that underlie symptom expression (e.g., ongoing physical or emotional abuse).

Furthermore, imagine a research project in which the pathophysiology of ADHD (or any other *DSM-5* disorder that is affected by developmental trauma) is studied, and this child (and dozens more like him with similar developmental adversities and traumatic experiences) are recruited. Any specific pathophysiology will be drowned out in the complex noise of heterogeneous pathophysiologies of equifinal routes to problems with attention, impulse control, and behavior regulation. Similarly, an outcome study that examines effects of an intervention, whether behavioral or pharmacological, in which children are recruited based on DSM symptom clusters, will have mixed results. Indeed, the greater the number of heterogeneous, equifinal pathophysiologies to a disorder, the less robust any finding will be, and our ability to replicate will be much more difficult because the relative ratios of heterogeneous pathophysiologies in any sample will vary from study to study. The end result is a never-ending, tail chasing research process that is confounded by extensive comorbidities, creation of apparent subtypes of primary disorders, and inability to replicate findings. A brief examination of the literature on most child and adolescent DSM disorders bears this out. For years, few studies in our field that used DSM disorders as a primary differentiator even addressed

developmental adversity, histories of attachment disruption, trauma-related experiences, or histories of resilience factors, which all influence neuropsychiatric phenotypes. Thus, the DSM, symptom-based model poses major obstacles for both basic and applied research.

This illustrates the need for (a) widespread capacity building in health, mental health, and education about relations between trauma, adversity, and neuropsychiatric problems; (b) the need for clinical assessments to include more detailed histories of developmental adversities and resilience-related factors; and (c) the need for research focused on mechanisms to include detailed developmental histories of the nature, timing, and severity of adversities and potential buffering resilience-related factors, in order to create more homogeneous groups.

Problem 2: A Single Disease Process May Have Heterogeneous Manifestations of Symptoms Dependent upon Factors Such as Sex, Developmental Timing, and Potentiating or Attenuating Conditions (Multifinality). When a diagnosis (a disorder or a disease) is connected to an underlying pathophysiology (mechanism) there can be many different clinical presentations (clusters of symptoms and physical signs) as a result (see also Beauchaine & Cicchetti, 2016; Beauchaine & McNulty, 2013). For example, coronary heart disease may not cause chest pain—it may cause numbing and tingling of the left arm or jaw. It may cause nausea. It may merely cause shortness of breath and exhaustion. Symptoms of coronary heart disease often manifest differently in women compared to men. Yet the treatment for coronary heart disease is determined by the extent and specific location of the blockage—not the symptom cluster. Even with the capacity to examine and measure mechanism-related biomarkers, the process of sorting and clustering into similar "diseases" and defining disease-targeting interventions is complex. As the previous sections of this chapter outline, dysregulation of key neural networks can lead to heterogeneous symptoms. Stress-related neural networks are so extensive, and so many factors play roles in their maturation, that regulation and ongoing neuroplasticity render intervention research very difficult.

Development of individualized treatment interventions based on genotypes, phenotypes, and physiologies has emerged in other areas of medicine. Similar efforts are underway in psychiatry, but due to the complexity of development this is a daunting task. A maltreated 12-year-old child, for example, may have the self-regulation capacity of a neurotypical 3-year-old, the social skills of an infant, and cognitive capabilities of a 5-year-old. And, due to unique genetic, epigenetic, and developmental histories of each child, it is usually ineffective to apply a "one-size-fits-all" therapeutic approach (Ungar & Perry, 2012). The Neurosequential Model of Therapeutics© (NMT) is one approach to clinical problem solving that attempts to incorporate this complexity into a practical assessment and treatment planning process (Perry, 2006, 2009; Perry & Dobson, 2013). This assessment method examines and quantifies the timing, nature, and severity of adversity

and resilience-related experiences, as well as current functioning, across multiple functional domains (e.g., sensory motor, regulatory, relational, and cognitive). The NMT creates a matrix of both developmental experience and current functioning across multiple domains, which allows clinical teams to select and sequence therapeutic, educational, and enrichment interventions in a developmentally sensitive fashion. In this regard, the NMT is conceptually similar to the emerging Research Domain Criteria (RDoC) being developed by the National Institutes of Mental Health (NIMH; e.g., Insel et al., 2010).

RESEARCH DOMAIN CRITERIA

Advancing research in developmental trauma, especially mechanism-focused research, will be impossible without addressing confounds of neurodevelopmental heterogeneity. Much larger sample sizes will be required for the multiple levels of analysis research that is required to truly address pathophysiological and other mechanisms related to developmental adversity, including genetic, epigenetic, neurochemical, neurophysiology, neural connectivity, neural networks and regions, individual emotional, social, cognitive and behavioral functioning, caregiver interactions, family composition and function, community strengths and vulnerabilities, and transgenerational cultural and historical factors.

For research purposes, the RDoC have stepped away from the *DSM-5* nosology to adopt a matrix approach to systematically gathering data across multiple levels of analysis for five key behavioral domains (negative valence system; positive valence systems; cognitive systems, social processes, and arousal/regulatory systems). Each domain has primary constructs and subconstructs (e.g., for social processes, social communication is a construct). There are multiple levels of analysis represented, spanning genes through paradigms (see Insel, T. (2013)). The RDoC model will greatly enhance research, and, ultimately, clinical work with children and adolescents who are affected by trauma and adversity. One potential weakness of the RDoC is an apparent benign neglect of the importance of developmental history of adversity and resilience-related experience (see Beauchaine & Cicchetti, 2016). A more intentioned focus on developmental history would add a crucial dimension to the existing matrix.

SYNTHESIS AND FUTURE DIRECTIONS

The human brain is complex. The multiple dimensions of human development and functioning that can be examined and used to cluster individuals into groups is staggering. Efforts of the APA—via the DSM model—to perform this task for trauma-related neuropsychiatric presentations by creating meaningful clusters for further study have come up against the reality of this complexity. In all of the historical and academic descriptions of stress, trauma, and attachment related

problems, mechanisms underlying symptoms were hypothesized. Whether mental health problems were conceptualized as caused by spirits of warriors killed in battle, Athena messing with your head, "mental weakness," unresolved conflicts involving the id, classical conditioning and subsequent generalization of a specific conditioned response, some pathological process was "underneath" the expression of trauma and stress-related symptoms. As in all areas of science, mechanisms matter. Your understanding of the problem determines your solution. If you believe the problem is with gods, you appease the gods by whatever process you think will work, or the spirits of fallen warriors, or resolve internal conflict through an analysis; the point is that the intervention selected is intended to address the source of the problem.

Current understandings of mental disorders recognize the brain as a major mediator of dysfunctions in emotional, behavioral, social, and cognitive functioning. Decades of quality academic work have observed, sorted, sifted, and analyzed symptoms and symptom clusters associated with adversity and trauma. There have been advances from this careful, deliberate work. Yet we are at an impasse. The complex and interactive effects of genetic, epigenetic, intrauterine, early perinatal experience, and ongoing neuroplasticity of key neural networks, including stress-mediating networks, all responsive to both good and bad experiences, collectively mean that human functioning in multiple domains is affected by myriad factors including caregiving, education, social milieus, and cultures, to name but a few. Advancing our capacity to understand trauma and stress-related problems (whether framed as DSM constructs or not) will require taxonomies and nosologies beyond mere clustering of symptoms (Chapter 2 [Beauchaine & Klein]). Adding another DSM diagnosis or two or five will not help much if at all, nor will adding ecophenotype qualifiers to the existing DSM. Major advances in this area will require more dramatic shifts in frame of reference. More developmental- and neuroscience-informed models are required.

REFERENCES

Abdul-Hamid, W. K., & Hacker Hughes, J. G. H. (2014). Nothing new under the sun? Post traumatic stress disorders in the ancient world. *Early Science and Medicine, 19*, 6, 554–557.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders*. (5th ed.). Arlington, VA: American Psychiatric Press.

Anda, R. F., Felitti, V. J., Bremner, J. D., Walker, J. D., Whitfield, C., Perry, B. D., . . . Giles, W. H. (2006). The enduring effects of abuse and related adverse experiences in childhood. A convergence of evidence from neurobiology and epidemiology. *European Archives of Psychiatry and Clinical Neuroscience, 256*, 174–186.

Baglivio, M. T., Epps, N., Swartz, K., Huq, M. S., Sheer, A., & Hardt, N. S. (2014). The prevalence of adverse childhood experiences (ACE) in the lives of juvenile offenders. *Journal of Juvenile Justice, 3*, 1–23.

Beauchaine, T. P. (2015). Future directions in emotion dysregulation and youth psychopathology. *Journal of Clinical Child and Adolescent Psychology, 44*, 875–896.

Beauchaine, T. P., & Cicchetti, D. (2016). A new generation of comorbidity and continuity research in the era of neuroscience and RDoC. *Development and Psychopathology, 28*, 891–894.

Beauchaine, T. P., & Marsh, P. (2006). Taxometric methods: Enhancing early detection and prevention of psychopathology by identifying latent vulnerability traits. In D. Cicchetti & D. Cohen (Eds.) *Developmental psychopathology* (2nd ed., pp. 931–967). Hoboken, NJ: Wiley.

Beauchaine, T. P., & McNulty, T. (2013). Comorbidities and continuities as ontogenic processes: Toward a developmental spectrum model of externalizing behavior. *Development and Psychopathology, 25*, 1505–1528.

Beauchaine, T. P., Neuhaus, E., Zalewski, M., Crowell, S. E., & Potapova, N. (2011). Effects of allostatic load on neural systems subserving motivation, mood regulation, and social affiliation. *Development and Psychopathology, 23*, 975–999.

Beeghly, M., Perry, B. D., & Tronick, E. (2016). Self-regulatory processes in early development. In S. Maltzman (Ed.), *The Oxford handbook of treatment processes and outcomes in psychology*. Oxford Handbooks Online.

Berger, D. (1999). A brief history of medical diagnosis and the birth of the clinical laboratory. Part 1—Ancient times through the 19th century. *Medical Laboratory Observer, 31*, 28–30.

Broekman, B. F. P. (2011). Stress, vulnerability, and resilience, a developmental approach. *European Journal of Psychotraumatology, 2*, 7229.

Campbell, F., Conti, G., Heckman, J. J., Moon, S. H., Pinto, R., Pungello, E., & Pan, Y. (2014). Early childhood investments substantially boost adult health. *Science, 343*, 1478–1485.

Cannon, W. B. (1914). The emergency function of the adrenal medulla in pain and the major emotions. *American Journal of Physiology, 3*, 356–372.

Cannon, W. B. (1942). "Voodoo" death. *American Anthropologist, 44*, 169–181.

Caspi, A., McClay, J., Moffitt, T. E., Mill, J., Martin, J., Craig, I. W., . . . Poulton, R. (2002). Role of genotype in the cycle of violence in maltreated children. *Science, 297*, 851–854.

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., . . . Poulton, R. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science, 301*, 386–389.

Cicchetti, D. (2013). Annual research review: Resilient functioning in maltreated children—past, present, and future perspectives. *Journal of Child Psychology and Psychiatry, 54*, 402–422.

Cicchetti, D., Rogosch, F. A., & Thibodeau, E. (2012). The effects of child maltreatment on early signs of antisocial behavior: Genetic moderation by tryptophan hydroxylase, serotonin transporter, and monoamine oxidase-A genes. *Development and Psychopathology, 24*, 907–928.

Cover Jones, M. (1924). A laboratory study of fear: The case of Peter. *Pedagogical Seminary, 31*, 308–315.

Claessens, S. E. F., Daskalakis, N. P., van der Veen, R., Oitzl, M. S., de Kloet, E. R., & Champagne, D. L. (2011). Development of individual differences in stress responsiveness: An overview of factors mediating the outcome of early life experiences. *Psychopharmacology, 214*, 141–154.

DaCosta, J. M. (1871). On irritable heart: A clinical study of a form of functional cardiac disorder and its consequences. *American Journal of Medical Science, 61*, 17–52.

Daskalakis, N. P., Bagot, R. C., Parker, K. J., Vinkers, C. H., & de Kloet, E. R. (2013). The three-hit concept of vulnerability and resilience: Towards understanding adaptation to early-life adversity outcome. *Psychoneuroendocrinology, 38*, 1858–1873.

Ellenberger, H. (1970) *The discovery of the unconscious: The history and evolution of dynamic psychiatry*. New York, NY: Basic Books.

Fellitti, V. J., Anda, R. F., Nordenberg, D., Williamson, D. F., Spitz, A. M., Edwards, V., . . . Marks, J. S. (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*, 245–258.

Fergusson, D. M., Boden, J. M., Horwood, L. J., Miller, A. L., & Kennedy, M. A. (2011). MAOA, abuse exposure, and antisocial behaviour: 30-year longitudinal study. *British Journal of Psychiatry, 198*, 457–463.

Fergusson, D. M., Horwood, L. J., Miller, A. L., & Kennedy, M. A. (2011). Life stress, 5-HTTLPR, and mental disorder: Findings from a 30-year longitudinal study. *British Journal of Psychiatry, 198*, 129–135.

Finkelhor, D., Turner, H. A., Shattuck, A., & Hamby, S. L. (2015). Prevalence of childhood exposure to violence, crime, and abuse: Results from the National Survey of Children's Exposure to Violence. *JAMA Pediatrics, 169*, 746–754.

Fraga, M. F., Ballestar, E., Paz, M. F., Ropero, S., Setien, F., Ballestar, M. L., . . . Esteller, M. (2005). Epigenetic differences arise during the lifetime of monozygotic twins. *Proceedings of the National Academy of Sciences, 102*, 10604–10609.

Freud, S. (1909). Analysis of a phobia of a five year old boy. In *The Pelican Freud Library* (1977), Vol. 8, Case Histories 1 (pp. 169–306). Harmondsworth, England: Penguin Books.

Gleason, M. M., Fox, N. A., Drury, S., Smyke, A. T., Egger, H. L., Nelson, C. A., . . . Zeanah, C. H. (2011). The validity of evidence-derived criteria for reactive attachment disorder: Indiscriminately social/disinhibited and emotionally withdrawn/inhibited types. *Journal of the American Academy of Child and Adolescent Psychiatry, 50*, 216–231.

Goetz, C. G. (1987). *Charcot, the clinician*. New York, NY: Raven Press.

Green, J. G., McLaughlin, K. A., Berglund, P. A., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., & Kessler, R. C. (2010). Childhood adversities and adult psychiatric disorders in the National Comorbidity Survey Replication I: Associations with first onset of DSM-IV disorders. *Archives of General Psychiatry, 67*, 113–123.

Grob, G. N. (1991). Origins of DSM-I: A study in appearance and reality. *American Journal of Psychiatry, 148*, 421–431.

Insel, T., Cuthbert, B., Garvey M., Heinssen, R., Pine, D. S., Quinn, K., . . . Wang, P. (2010). Research Domain Criteria (RDoC): Toward a new classification framework for research on mental disorders. *American Journal of Psychiatry 167*, 748–751.

Insel, T. (2013). Director's Blog: Transforming Diagnosis. http://www.nimh.nih.gov/about/director/2013/transforming-diagnosis.shtml

Karg, K., Burmeister, M., Shedden, K., & Sen, S. (2011). The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: Evidence of genetic moderation. *Archives of General Psychiatry, 68*, 444–454.

Kim-Cohen, J., Caspi, A., Taylor, A., Williams, B., Newcombe, R., Craig, I. W., & Moffitt, T. E. (2006) MAOA, maltreatment, and gene-environment interaction predicting children's mental health: New evidence and a meta-analysis. *Molelcular Psychiatry, 11*, 903–913.

Klengel, T., & Binder, E. B. (2015). Epigenetics of stress-related psychiatric disorders and Gene × Environment interactions. *Neuron, 86*, 1343–1357.

Levine, S. (1957). Infantile experience and resistance to physiological stress. *Science, 126*, 405.

Levine, S. (1994) The ontogeny of the hypothalamic-pituitary-adrenal axis. The influence of maternal factors. *Annals of the New York Academy of Sciences, 746*, 275–293.

Levine, S. (2005). Developmental determinants of sensitivity and resistance to stress. *Psychoneuroendocrinology, 30*, 939–946.

Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience, 10*, 434–445.

Mead, H. K., Beauchaine, T. P., & Shannon, K. E. (2010). Neurobiological adaptations to violence across development. *Development and Psychopathology, 22*, 1–22.

Meaney, M. J. (2001). Maternal care, gene expression and the transmission of individual differences in stress reactivity across generations. *Annual Review of Neuroscience, 24*, 1161–1192.

Meaney, M. J., & Szyf, M. (2005). Environmental programming of stress responses through DNA methylation: Life at the interface between a dynamic environment and a fixed genome. *Dialogues in Clinical Neurosciences, 7*, 103–123.

Miller, G. E., Lachman, M. E., Chen, E., Gruenewald, T. L., Karlamangla, A. S., & Seeman, T. E. (2011). Pathways to resilience: Maternal nurturance as a buffer against the effects of childhood poverty on metabolic syndrome at midlife. *Psychological Science, 22*, 1591–1599.

Myers, C. S. (1915). A contribution to the study of shell shock. *Lancet, 1*, 316–320.

Perry, B. D. (2002). Childhood experience and the expression of genetic potential: What childhood neglect tells us about nature and nurture. *Brain and Mind, 3*, 79–100.

Perry, B. D. (2006). Applying principles of neuroscience to clinical work with traumatized and maltreated children: The Neurosequential Model of Therapeutics. In N. B. Webb (Ed.), *Working with traumatized youth in child welfare* (pp. 27–52). New York, NY: Guilford Press.

Perry, B. D. (2008). Child maltreatment: A neurodevelopmental perspective on the role of trauma and neglect in psychopathology. In T. P. Beauchaine & S. P. Hinshaw (Eds.), *Child and adolescent psychopathology* (pp. 93–128). Hoboken, NJ: Wiley.

Perry, B. D. (2009). Examining child maltreatment through a neurodevelopmental lens: Clinical applications of the Neurosequential Model of Therapeutics. *Journal of Loss and Trauma, 14*, 240–255.

Perry, B. D., & Dobson, C. (2013). Application of the Neurosequential Model of Therapeutics (NMT) in maltreated children. In J. Ford & C. Courtois (Eds.), *Treating complex traumatic stress disorders in children and adolescents* (pp. 249–260). New York, NY: Guilford Press.

Perry, B. D., Hambrick, E., & Perry, R. D (2015). A neurodevelopmental perspective and clinical challenges. In R. Fong & R. McCoy (Eds.), *Transracial and intercountry adoptions* (pp. 126–153). New York, NY: Columbia University Press.

Perry, B. D., Pollard, R., Blakely, T., Baker, W., & Vigilante, D. (1995). Childhood trauma, the neurobiology of adaptation, and 'use-dependent' development of the brain: How "states" become "traits." *Infant Mental Health Journal, 16*, 271–291.

Perry, B. D., Stolk, J. M., Vantini, G., Guchhait, R. B., & U'Prichard, D. C. (1983). Strain differences in rat brain epinephrine synthesis: Regulation of alpha-adrenergic receptor number by epinephrine. *Science, 221*, 1297–1299.

Porges, S. W. (2011). *The Polyvagal Theory: Neurophysiological foundations of emotions, attachment, communication, and self-regulation*. New York, NY: W. W. Norton.

Rauch, S. L., & Drevets, W. C. (2009). Neuroimaging and neuroanatomy of stress-induced and fear circuitry disorders. In G. Andrews, D. S. Charney, P. J. Sirovatka, & D. A. Regier (Eds.), *Stress-induced and fear circuitry disorders: Refining the research agenda for DSM-V* (pp. 215–254). Arlington, VA: American Psychiatric Press.

Read, J., Perry, B. D., Moskowitz, A., & Connolly, J. (2001). The contribution of early traumatic events to schizophrenia in some patients: A traumagenic neurodevelopmental model. *Psychiatry, 64*, 319–345.

Read, J., Fosse, R., Moskowitz, A., & Perry, B. D. (2014). Traumagenic neurodevelopment model of psychosis revisited. *Neuropsychiatry, 4*, 1–15.

Risch, N., Herrell, R., Lehner, T., Liang, K.-Y., Eaves, L., Hoh, J., . . . Merikangas, K. R. (2009). Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: A meta-analysis. *Journal of the American Medical Association, 301*, 2462–2471.

Saunders, B. E., & Adams, Z. W. (2014). Epidemiology of traumatic experiences in childhood. *Child and Adolescent Psychiatric Clinics of North America, 23*, 167–184.

Schanberg, S., Evoniuk, G., & Kuhn, C. M. (1984) Tactile and nutritional aspects of maternal care: Specific regulators of neuroendocrine function and cellular development. *Proceedings of the Society for Experimental Biology and Medicine, 175*, 135–46.

Selye, H. (1936). A syndrome produced by diverse nocuous agents. *Nature, 196*, 32.

Smoller, J. W. (2015) The genetics of stress-related disorders: PTSD, depression, and anxiety disorders. *Neuropsychopharmacology Reviews, 41*, 297–319.

Teicher, M. H., & Samson, J. A. (2013). Childhood maltreatment and psychopathology: A case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. *American Journal of Psychiatry, 170,* 1114–1133.

Terr, L. (1983). Chowchilla revisited: The effects of psychic trauma four years after a school-bus kidnapping. *American Journal of Psychiatry, 140,* 1543–1550.

Terr, L. (1991). Childhood traumas: An outline and overview. *American Journal of Psychiatry, 148,* 1–20.

Tronick, E., & Perry B. (2015). Multiple levels of meaning-making: The first principles of changing meanings in development and therapy. In G. Marlock H. Weiss, C. Young, & M. Soth (Eds.), *Handbook of body psychotherapy and somatic psychology* (pp. 345–355). Berkeley, CA: North Atlantic Books.

Tyrka, A. R., Price, L. H., Gelernter, J., Schepker, C., Anderson, G. M., & Carpenter, L. L. (2009). Interaction of childhood maltreatment with the corticotropin-releasing hormone receptor gene: Effects on hypothalamic-pituitary-adrenal axis reactivity. *Biological Psychiatry, 66,* 681–685.

Tyrka, A. R., Price, L. H., Marsit, C., Walters, O. C., & Carpenter, L. L. (2012). Childhood adversity and epigenetic modulation of the leukocyte glucocorticoid receptor: Preliminary findings in healthy adults. *PloS One, 7,* 1.

Ungar, M., & Perry, B. D. (2012). Trauma and resilience. In R. Alaggia & C. Vine (Eds.), *Cruel but not unusual: Violence in Canadian families* (pp. 119–143). Waterloo, Ontario, Canada: Wilfred Laurier University Press.

van Cleve, T. C. (1972). *The Emperor Frederick II of Hohenstufen, Immutator Mundi.* New York, NY: Oxford University Press.

van der Kolk, B. A. (2005). Developmental trauma disorder: Towards a rational diagnosis for children with complex trauma histories. *Psychiatric Annals, 33,* 401–408.

van der Kolk, B., Pynoos, R. S, Cicchetti, D., Cloitre, M., D'Andrea, W., Ford, J. D., . . . Teicher, M. (2009). *Proposal to include a developmental trauma disorder diagnosis for children and adolescents in DSM-V.* Unpublished manuscript.

Vantini, G., Perry, B. D., Hurst, J. H., Guchhait, R. B., Elston, R. C., U'Prichard, D. C., & Stolk, J. M. (1983). Genetic differences in phenylethanolamine N-methyltransferase activity in rats. *Psychopharmacology Bulletin, 19,* 616–619.

Waterfield, R. (Trans.), & Dewald, C. (Ed.). (1998). *The Histories by Herodotus.* New York, NY: Oxford University Press.

Watson, J. B., & Rayner, R. (1920). Conditioned emotional reactions. *Journal of Experimental Psychology, 3,* 1–14.

Yehuda, R., Daskalakis, N. P., Bierer, L. M., Bader, H. N., Klengel, T., Holsboer, F., & Binder, E. B. (2015). Holocaust exposure induced intergenerational effects on FKBP5 methylation. *Biological Psychiatry.*

Child and Adolescent Psychopathology

Third Edition

Edited by

Theodore P. Beauchaine
Stephen P. Hinshaw

WILEY

CHILD AND ADOLESCENT PSYCHOPATHOLOGY

THIRD EDITION

EDITED BY
THEODORE P. BEAUCHAINE
STEPHEN P. HINSHAW