Pathways from Adverse Childhood Experiences to Nervous System Dysregulation

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Abstract

The type, timing, duration, and frequency of exposures to adverse childhood experiences (ACEs) or early life stress (prenatal/postnatal) are likely antecedents of nervous system dysregulation manifesting across multiple systems. These are mediated through multiple *neuroendocrine axes* (hypothalamic-pituitary-adrenal, hypothalamic-pituitary-thyroid, pituitary-growth hormone/insulin-like growth factor-1 (IGF), hypothalamic-pituitary-gonadal) and the *autonomic system* (sympathetic or parasympathetic), but they also affect *neuro-immune interactions* (innate and adaptive immunity) and the *neuroenteric system* (gastric, intestinal, and hepato-pancreatic).
Even in the absence of abuse or neglect, children are increasingly exposed to three overarching trends: 1) parental use of psychotropic drugs and substances; 2) inconsistent or distracted parenting; and 3) deprivation from natural environments, social engagements, and unstructured play (that is not technology-dependent). Thus, children may fail to acquire developmentally appropriate self-regulation, coping skills, or peer engagement skills; they often receive pharmaceuticals for behavioral compliance, as opposed to mindfulness, self-reflection, or cognitive-behavioral therapy to guide self-development. Children presenting with clinically unexplained symptoms across multiple domains (executive dysfunction, sleep disturbances, autonomic dysregulation, somatization, digestive symptoms, emotional dysregulation) are susceptible to permanent reductions in grey matter volume, cognitive/behavioral problems, and poorer physical and mental health. Early life stress disrupts their first-time learning experiences; acclimatizes them toward pathways of negative (fear-motivated, anxiety-inducing) reinforcement of affiliated experiences, with atypical internalizing or externalizing behaviors, and impaired self-regulation. Positive experiences in the presence of supportive, nurturing parents with consistent parenting styles/practices can reverse this trend and avoid the long-term consequences of nervous system dysregulation.

Keywords: Stress systems, Central Nervous System (CNS) dysregulation, Hypothalamic-Pituitary-Adrenal (HPA) Axis, Hypothalamic-Pituitary-Thyroid (HPT) Axis, Hypothalamic-Pituitary-Gonadal (HPG) axis, Autonomic Nervous System (ANS), clinical domains, early life stress (ELS), adverse childhood experiences (ACEs), toxic stress, developmental origins of disease.

1. Introduction

Children with a history of adverse childhood experiences (ACEs) may present with unexplained symptoms across multiple domains (namely, executive dysfunction, sleep disturbances, autonomic dysregulation, somatization, digestive symptoms, and emotional dysregulation).[1] The involvement of multiple clinical domains suggests overall dysregulation of the central nervous system (CNS) as opposed to isolated effects on stress-responsive systems like the hypothalamic-pituitary-adrenal (HPA) axis or the sympathetic-adrenal medullary (SAM) axis. Preschool children are particularly vulnerable to the long-term effects of ACEs because of their behavioral immaturity, limited coping skills, and brain plasticity with immature sensory, motor, and neuroendocrine systems.[2-4] For example, the HPA axis does not mature until 4-5 years of age[5] and its dysregulation may interrupt further sequential development of higher limbic system structures such as the amygdala,[6] the hippocampal complex,[6,7] and the prefrontal cortex (PFC).[8]

In 2015, Ortega-Martinez presented the hypothesis known as the "the double neurogenic niche hypothesis" which states that each kind of fetal and childhood stressor influences a specific neurogenic pool that later becomes a precursor for adult hippocampal neurogenesis.[9] Disruption of neurobehavioral development induces permanent alterations in adult biological and behavioral phenotypes, linked to the types of stressful stimuli experienced, the timing of stressful events, and general environmental conditions, with several psychopathologies, like psychosis and mood disorders appearing in adolescence.[8] Reduced grey matter volume in the anterior ventromedial PFC correlated inversely with PTSD duration in children, suggesting ongoing neurotoxic processes in youth with PTSD.[10] HPA axis dysregulation may influence subsequent cortical maturation, grey matter volumes, cognitive ability, and emotional well-being. Consequently, children presenting with medically unexplained symptoms should be assessed for unreported ACEs as well as the biomarkers of chronic emotional (e.g., cortisol) and biologic stress (e.g., telomere length).

Early life stress (ELS) and ACEs do not mean the same thing, although each carries a potential for triggering CNS dysregulation. "ELS" is a general term used for stress occurring in the prenatal and early postnatal periods. For example, ELS may include parental dependency or risk-taking behaviors known to compromise the *in utero* environment, postnatal care or home environment of the baby. For example, maternal postnatal depression, which influences a mother's parenting-style and newborn bonding, is also considered as ELS. The term "ACEs", however, is generally used to characterize specific types of stressors, first defined in the ACEs study.[11,12] The ACEs questionnaire retrospectively surveyed adults for 8 specific adverse experiences in childhood and found that persons who had experienced four or more ACEs compared to those who had experienced none, had 4- to 12-fold increased health risks for alcoholism, drug abuse, depression, and suicide attempts; a 2- to 4-fold increases in smoking, poor self-rated health, multiple sexual partners, and

sexually transmitted diseases, as well as increases in physical inactivity and severe obesity.[11] ACEs also showed a graded relationship to the prevalence of chronic non-communicable adult-onset diseases including ischemic heart disease, type-II diabetes, cancer, chronic lung disease, or liver disease. The ACEs were strongly interrelated and persons with multiple categories of childhood exposure were likely to have multiple health risk factors later in life.[12]

The type, timing, duration, and frequency of exposures to ELS and/or subsequent ACEs are likely to determine the advent of nervous system dysregulation manifesting through multiple pathways, including: 1) the neuroendocrine axes (hypothalamic-pituitary-adrenal, pituitary-thyroid, pituitary-growth hormone, hypothalamic-pituitary-gonadal); 2) the autonomic system (sympathetic or parasympathetic); 3) neuro-immune interactions (innate and adaptive immunity at the cellular and humoral level); and 4) the neuro-enteric system (gastric, intestinal, and hepato-pancreatic). **Figure 1** summarizes a model for the antecedent and contributing factors leading to the advent of CNS dysregulation. This review examines nervous system dysregulation primarily from a psychoneuroendocrine perspective, and does not explore other pathways associated with neuroinflammatory mechanisms, genetic and epigenetic regulation, regulation of the neurenteric system or the human microbiome.

Figure 1:

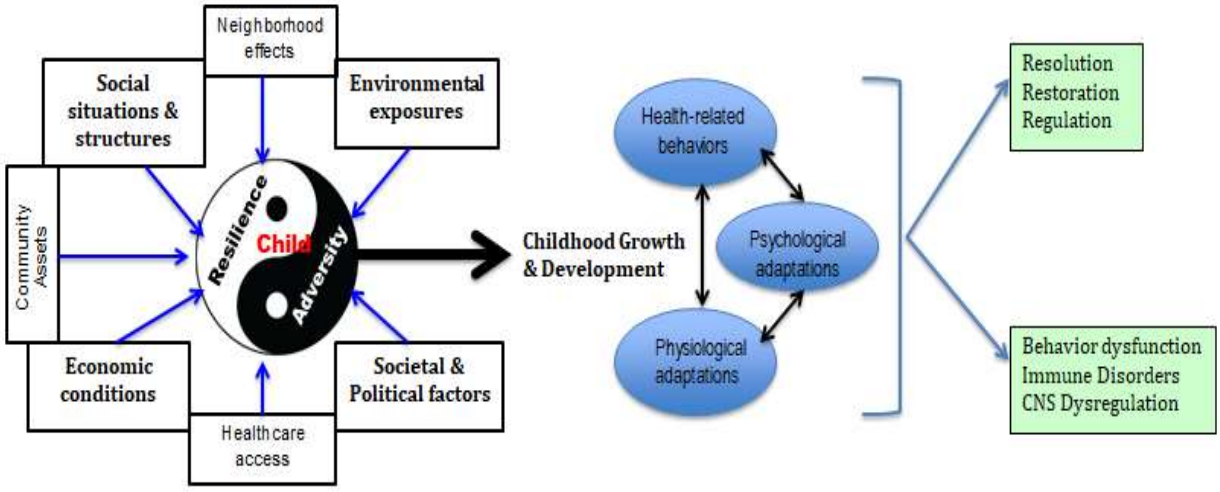

Figure 1: A proposed model for CNS dysregulation, showing the common antecedent factors drawn from the social determinants of health and their impact on growth and development occurring in early life. Positive and negative influences within critical windows of development can trigger *physiological adaptations* (involving the neuroendocrine, autonomic, neuroimmune, and neurenteric regulation systems), *psychological adaptations* (internalizing or externalizing behaviors, impaired coping mechanisms, secondary gain, vulnerability to various psychopathologies), and health-promoting vs. health-harming behaviors (diet, substance abuse, exercise, sleep habits, etc.), eventually leading to resolution vs. dysregulation.

1.1 Hypothalamic-Pituitary-Adrenal (HPA) Axis

Aberrant development in response to prenatal or postnatal ELS leads to HPA axis dysregulation,[13] associated with cognitive impairment,[14,15] childhood behavioral and developmental problems,[16-19] impaired immunity,[20] mood disorders,[21] depression during adolescence,[22] with greater risks of adult chronic non-communicable diseases[13] and neurodegenerative disorders.[14] Apart from heritable genetic and epigenetic traits, cumulative and sequential exposures to a variety of stressors such as social adversity, socioeconomic insecurity, isolation/neglect, perceived discrimination, physical and emotional trauma, chronic pain, critical illness and other stressful events in early life are likely to perturb neurogenesis in the subventricular zones.[23,24] These trigger changes in pathway development within developing brain systems, within cortical and subcortical areas, including the hypothalamus.[25,26] We propose that prenatal and post-natal stress may cause "neurogenesis abruption", constrict the proliferation of neural stem progenitor cells, their differentiation, migration. and maturation as neuronal precursors, and their integration into functional pathways and systems within the prefrontal cortex, hippocampus, amygdala, corpus callosum, anterior commissure, thalamus, hypothalamus and basal ganglia, thus altering HPA axis development and regulation.[27-29]

The HPA axis appears to be a central regulator of stress-responsive systems.[28,30] The physiological mechanisms of stress are well documented even though the normative ranges of specific stress hormones, like cortisol in children are still being debated.[31] Stressful events stimulate the parvocellular neurons, located in the hypothalamic paraventricular nucleus (PVN), to secrete corticotropin releasing hormone (CRH).[32] CRH stimulates the anterior pituitary corticotrope cells to release ACTH, which then triggers glucocorticoid production in the adrenal cortex.[32] ACTH can also stimulate gene expression of the norepinephrine biosynthesis enzymes, crosslinking with the sympathetic-adrenal medullary (SAM) axis to escalate the stress response.[33] Disconnects in regulation between ACTH and cortisol and vice versa lead to chronic, abnormally high levels of cortisol or a blunting of diurnal variations, both defined as HPA axis dysregulation. HPA axis dysregulation mediates epigenetic changes that can be transmitted intergenerationally[34] and is known to alter the formation of neurocircuitry.[35] Maternal-infant bonding and maternal sensory stimulation establish enduring changes in "experience-induced neuroplasticity"[36] and are mediated through activation of the arginine vasopressin (AVP)/oxytocin pathway.[37] Nurturing parental behaviors are linked to oxytocin release in young children.[38-41] Oxytocin directly and indirectly inhibits ACTH release and cortisol responses by acting as an vasopressin antagonist in the PVN and anterior pituitary.[42] Oxytocin is also strongly linked with memories of anxiety, fear and fear extinction.[43,44]

Reciprocal regulation of the HPA axis and AVP/oxytocin systems is amply illustrated in animal studies, but also following

exposure to ELS in humans. For example, 8 year-old children enduring physical abuse had gender specific cortisol and oxytocin levels during controlled stress: girls, but not boys, showed a higher oxytocin and lower cortisol responses.[45] Functioning of the amygdala is different between boys and girls, such that girls are more likely to interpret abuse as fearful thereby triggering anxiety and depression in adulthood.[46] PTSD, other affective disorders, and underactive stress hormone levels (suppression of the HPA axis) occurred commonly in women that experienced childhood sexual abuse.[47,48] School children raised with domestic and/or neighborhood violence had shortened telomere length (indicates premature cellular aging and biologic stress), an inability to reduce cortisol following reactivity test and a steeper diurnal cortisol decline.[49] Exposure to chronic childhood stress is linked with alterations in brain development, challenges to well-being and sound health, school readiness and academic success, and shaping of social relationships.[50] Chronic exposures to various stressors can alter the development and regulation of several brain regions and the HPA axis.[32,33,51]

Prenatal brain development is particularly vulnerable to long-term programming by stress, particularly glucocorticoid effects mediated via the hypothalamic-pituitary-adrenal (HPA) axis (for review see Moisiadis and Matthews, 2014).[52] Basically, cortisol is the most abundant glucocorticoid hormone mediating stress-related changes in homeostasis associated with wide-ranging genomic regulation.[53,54] The promoter regions of many genes contain cortisol response elements (CREs) known to up- or down-regulate gene expression, explaining how cortisol release can be physiologically adaptive, maladaptive, or toxic – by altering homeostasis (blood pressure, calcium absorption, anti-inflammatory activity, lipogenesis/lipolysis, gluconeogenesis, glycogenolysis, protein breakdown, insulin resistance, glomerular filtration, etc.),[55,56] as well as brain development.[57-61] Cortisol regulates the autonomic stress system (epinephrine, norepinephrine) to alter intermediary metabolism as well as physiological responses, but also contributes to memory formation and learning following short-term stressful events (adaptive response).[62,63] Normally functioning HPA axis limits cortisol exposure through a negative feed-back loop to the hypothalamus and anterior pituitary,[55,56] but this negative feed-back loop is ineffective in children with a dysregulated HPA axis.[64,65] Based on a longitudinal study of 100 maternal-child dyads, Karlen et al. concluded that development of the HPA axis is guided by heritable traits with "maternal calibration" of early childhood set-points for cortisol responses in their offspring that stabilize with increasing age.[66] The antecedents of HPA axis dysregulation often reside in early life adversity,[59,67-71] increasing the lifetime risks for chronic non-communicable diseases, poor physical and mental health,[72,73] drug abuse or other risk-taking behaviors,[74,75] leading to significant morbidity and early mortality.[76-86]

1.2 Hypothalamic-Pituitary-Thyroid (HPT) Axis

The hypothalamic-pituitary-thyroid axis controls somatic growth, brain development, energy homeostasis and thermogenesis by regulating intermediary metabolism and mitochondrial function[87] through the synthesis of thyrotropin releasing hormone (TRH) by the PVN, which releases thyroxine (T4) and triiodothyronine (T3) from the thyroid gland. Genomic studies found T3-response element genes enriched in astrocytes and neurons of the subplate zone and in specific neurons from neuroendocrine areas sustaining a transition from fetal to adult patterns of gene expression.[88] Steady declines in TRH secretion were implicated in the neurodegenerative conditions of aging, coupled with loss of its neuroprotective effects against oxidative stress, glutamate toxicity, caspase-induced cell death, and neuroglial inflammation in the diencephalon and spinal cord.[89] A neuroprotective role for TRH or T3 during toxic stress or critical illness, states often associated with altered thyroid hormones and mitochondrial function, has not been investigated.

Exposure to ACEs or traumatic life events during critical windows in human development[2] often leads to subsequent manifestation of thyroid dysregulation[90-92] and activation of the HPA axis.[90] Wang reported an association between ACEs and hyperthyroidism, also documented historically,[93,94] suggesting that changes in thyroid regulation are contextual (fright or flight) and time sensitive (age of exposure and proximity to precipitating events).[92] Early life trauma was associated with reduced T3 levels in adolescents even after adjusting for potential confounders like pubertal status, gender, socioeconomic status and BMI,[95] confirmed in sexually abused adolescent females, where measures of PTSD and depression were negatively correlated with thyroid hormone levels (T3, T4).[96] Conversely, elevated T3 levels and hyperthyroidism occurred in women with histories of physical or sexual abuse leading to menstrual-related mood disorders, PTSD, depression, or other psychiatric diagnoses.[97-101] Thus, it is likely that childhood abuse leads to early suppression of the HPT axis and thyroid function, with later changes in HPT regulation resulting in a hyperthyroid state.

1.3. Hypothalamic-Pituitary-Gonadal axis

The hypothalamic-pituitary-gonadal (HPG) axis is functional mainly in the perinatal, prepubertal and pubertal periods.[102] The hypothalamus regulates both HPA and HPG axes through complex cross-talk of socially and psychologically responsive neuroendocrine factors, neurotransmitters, and neurohormones. One hypothesis explaining gender differences in developmental or mental health conditions (e.g., depression, anxiety, schizophrenia, anorexia/bulemia, autism, ADHD, OCD, and others) relates to context-specific interactions between the HPA and HPG axes. For example, the PVN of women had larger arginine vasopressin (AVP) neurons,[103] contributing to greater HPA axis stress responses and associated with altered HPA reactivity during the menstrual cycle and in pregnancy. Hypothalamic activation of the HPG axis for the release of gonadotropin-releasing hormone (GnRH) launches gonadal development at the onset of puberty which “is gated by the state of

body energy reserves and sensitivity to metabolic cues".[104]

HPA axis hormones (cortisol and ACTH) increase gonadotropin-inhibitory hormone (GnIH)[105,106] and via GnIH receptors are located in the limbic system, telencephalon, diencephalon and midbrain areas,[106] control behavioral stress responses. Chronic stress can also inhibit the onset of puberty, compromise fertility during childbearing years, disrupt reproductive functions and behaviors, may trigger preterm labor, and also lead to HPA axis dysregulation in the offspring.[105,107-110] Indeed, prenatal maternal trauma was associated with elevated hair cortisol levels in their preschool children[111] and dysregulated HPA-HPG interactions in late childhood.[112] Another study reported preliminary evidence suggesting that prenatal maternal stress reduces the age at menarche in their offspring, mediated through its effects on elevated BMI in early childhood.[113] Epidemiologic studies reported that girls exposed to ACEs or other early life stressors had altered pubertal development, such that sexual abuse was associated with earlier puberty whereas physical abuse was associated with early or delayed puberty.[114-116] Dismukes et al. explored HPA-HPG axis coupling and stress responses in 64 males and 56 females; they found that testosterone and DHEA positively predicted cortisol responses, whereas early life adversity, marital discord and family life stress increased the coupling between cortisol and testosterone.[117] Much further work is required to elucidate the relationships between the exposures to ELS and neuroendocrine regulation of the HPG axis.

1.4 Autonomic System Dysregulation

The sympathetic and parasympathetic components work in tandem within a healthy autonomic nervous system (ANS) for the regulation of body temperature, breathing and heart rates, digestion, reproduction, and responses to stress. Stress-induced ANS dysregulation can be indexed by measuring salivary alpha-amylase (sAA).[118,119] Dysregulation of each stress system may differentially contribute to the symptoms of CNS dysregulation. Sexually dimorphic adaptations may occur during pregnancy. "Women carrying female fetuses displayed greater autonomic arousal and flatter (but more elevated) diurnal cortisol patterns compared to women carrying males. Women with flatter daytime cortisol trajectories and more blunted sAA awakening responses also had infants with lower birth weight. These maternal adaptations are consistent with sexually dimorphic fetal/developmental/evolutionary adaptation strategies that favor growth for males and conservation of resources for females."[120]

Relatively rare forms of childhood ANS dysregulation include postural orthostatic tachycardia syndrome (POTS; five times higher in females than males),[121] congenital central hypoventilation syndrome,[122,123] rapid-onset obesity with hypothalamic dysregulation, hypoventilation, and autonomic dysregulation (ROHHAD),[124-126] neurocardiogenic syncope (NCS),[127] and others. More prevalent forms of ANS dysfunction are associated with symptoms such as cyclic nausea and vomiting,[128] altered heart rate variability (HRV),[118,129] and vagal tone,[130] recurrent headache

disorders,[131] chronic fatigue syndrome.[132] ELS can trigger life-threatening conditions of ANS dysregulation[131,133-139] and HPA axis dysregulation,[18,131,134,140-147] suggestive of overall CNS dysregulation. Context specific, physical but not sexual abuse during childhood induces ANS hyporesponsivity (i.e., heart and respiratory rate deceleration),[137,138] internalizing and disruptive behavior disorders.[138] Women with higher child maltreatment scores had greater difficulties with emotional regulation and reduced cortisol reactivity, which contributed to their blunted postpartum physiological reactivity.[18] Altered ANS reactivity and regulation have been documented in a variety of psychosomatic conditions associated with the involvement of multiple systems, many of which were associated with exposures to ELS.[148-156] Indeed, autonomic dysregulation may be the most consistent feature of the psychological, clinical, cognitive and behavioral outcomes resulting from any exposure to ACEs or other early life stressors.

2. Comment

The American Academy of Pediatrics (AAP) maintains that toxic stress in early life contributes the origin of many adult-onset diseases, determining both physical and mental health. One AAP recommendation states, "The growing scientific knowledge base that links childhood toxic stress with disruptions of the developing nervous, cardiovascular, immune, and metabolic systems, and the evidence that these disruptions can lead to lifelong impairments in learning, behavior, and both physical and mental health, should be fully incorporated into the training of all current and future physicians".[157] Thus, "Identifying children at high risk for toxic stress is the first step in providing targeted support for their parents and other caregivers."[157]

Stress from early childhood adversity disrupts their first-time learning experiences; acclimatizes them toward a pathway of either positive (supportive, nurturing) or negative (fear inducing) reinforcement of affiliated experiences; shaping them toward internalizing or externalizing behaviors, and impeding self-regulation in general. Indeed, cognitive hypervigilance, autonomic dysfunction, and emotional instability have been identified as components of several idiopathic disorders associated with chronic/recurrent pain and disability, often involving somatic, visceral, and behavioral manifestations[158]. Four or more ACEs were also linked with the early onset of chronic non-communicable diseases ranging from metabolic to cardiovascular diseases, cancer to mental health disorders, smoking to drug abuse and other risk-taking behaviors, with graded relationships occurring at all age groups (18-44, 45-64, and 65-89 years)[159].

Children raised in affluent societies are currently exposed to three somewhat related, dangerous overarching trends. *First*, progressively increasing early life exposures to parental use of psychotropic drugs and substances,[80,160,161] including nicotine,[162,163] alcohol and,[164-166] prescribed pain medications.[167-170] *Second*, disordered or distracted parenting due to the behavioral effects of these drugs, parental separation or incarceration, or parent unavailability from

the compulsive/addictive use of smartphones and other electronic devices resulting in lowered parent sensitivity, lack of parental consistency, or social buffering by parents.[171-174] The addition of each negative experience results in a deeper layering of nervous system dysregulation spanning across major brain centers and affecting multiple behavioral and health domains. *Third*, children are less exposed to nature and social engagement, unstructured, exploratory, and non-technologically-dependent play activities. Thus, many children are falling short of developmentally appropriate self-regulation, coping skills, and meaningful engagement with peers. They are often prescribed pharmaceuticals for enforced behavioral compliance as opposed to mindfulness, reflection, or behavioral therapies to guide their self-development.

Ineffective self-regulation coupled with risk-taking behaviors increases the likelihood of detrimental outcomes. Self-regulation is dependent on a bio-behavioral system that is hierarchically organized and reciprocally integrated through bottom-up (limbic and brainstem structures) regulation of stress and emotional arousal, competing with the top-down (prefrontal cortex) regulation of attention and executive functions.[175-177] Parental risk-taking behaviors are more commonly linked with cognitive vulnerability, depression, and suicidal ideology in their children than was previously acknowledged,[178] potentially underlying the intergenerational transmission of these behaviors.[179-182]

3. Clinical Implications

We have explored the antecedents and consequences of CNS dysregulation mostly from a psychoneuroendocrine perspective, although their underlying processes are very likely dependent on genetic, epigenetic, neuroimmune, and multiple other regulatory pathways. When clinicians are confronted with an assortment of medically unexplained signs and symptoms across multiple domains in their patients, they may choose to obtain a history of adverse conditions in early childhood, consider confirmatory testing to evaluate the neuroendocrine and autonomic systems discussed above, and develop a multidisciplinary approach that combines the benefits of both pharmacological and non-pharmacological modalities, coupled with lifestyle changes and social supports.

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