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Stress in the onset and aggravation of learning disabilities

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Abstract

Despite substantial grounds for such research, the role of chronic exposure to stressors in the onset and aggravation of learning disabilities (LDs) is largely unexplored. In this review, we first consider the hormonal, (epi)genetic, and neurobiological mechanisms that might underlie the impact of adverse childhood experiences, a form of chronic stressors, on the onset of LDs. We then found that stress factors combined with feelings of inferiority, low self-esteem, and peer victimization could potentially further aggravate academic failures in children with LDs. Since effective evidence-based interventions for reducing chronic stress in children with LDs could improve their academic performance, consideration of the role of exposure to stressors in children with LDs has both theoretical and practical importance, especially when delivered in combination with academic interventions.

Keywords

learning disabilities; children; adverse childhood experiences; HPA axis; cortisol; gene-environment interaction

Learning disabilities (LDs), referred to in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as a family of specific learning disorders, are diagnosed when “there are specific deficits in an individual’s ability to perceive or process information efficiently and accurately. This neurodevelopmental disorder first manifests during the years of formal schooling and is characterized by persistent and impairing difficulties in learning foundational academic skills in reading, writing, and/or math” (American Psychiatric

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Association, 2016, p.3). LDs affect between 5.3% to 11.8% of schoolchildren (Katusic et al., 2001). However, despite numerous wide-ranging studies of the mechanisms of LDs (Fletcher & Grigorenko, 2017; Plomin & Kovas, 2005; Pugh et al., 2001), the understanding of their etiology is still far from comprehensive.

LDs are diverse in their presentation and etiology. Their presentation is multidimensional and they engage in numerous cognitive processes, including working memory, attention, and speed of processing, among others (Elliott & Grigorenko, 2014). Given this multidimensionality, variability of presentation, and a variety of theoretical perspectives on LDs, there are multiple criteria that are used to diagnose LDs (Fletcher et al., 2019). In addition, the etiology of LDs is complex. In general, it is assumed that these disorders are familial in nature, as the deficits, although they do not breed true, typically aggregate in families. Yet, there are sporadic cases of LDs related to the presence of both genetic (e.g., chromosomal aberrations) and environmental (e.g., exposure to adverse childhood experiences, ACEs) risk factors.

ACEs are a potential trigger for the onset of LDs as evidenced by greater likelihood of LDs associated with higher incidence of ACEs (Turney, 2020) and, to some extent, by the negative relationship between exposure to chronic stressors and academic performance observed in typically developing children¹ (Bethell et al., 2014; Blodgett & Lanigan, 2018; Burke et al., 2011; Delaney-Black et al., 2002). However, no direct evidence is available concerning the effect of exposure to chronic stressors on the onset of LDs. In this review, we argue that there are substantial grounds to conduct studies that can secure such data.

Regardless of the etiology of LDs, their perpetuation and even aggravation might be related to the ongoing stress of living with LDs, especially if they are not remediated. Similar to stress' contribution to the LDs onset, the contribution of stress to the aggravation of LDs is not well studied. Nonetheless, it is known that stress caused by academic struggles or failure is associated with negative outcomes, such as school anxiety (McClain, 1997) and low self-esteem (Alexander-Passe, 2008). Based on the relevant literature, we argue that systematic research into stress as an aggravator of LDs is both warranted and necessary.

To substantiate our argument, we structure this article as follows. First, we review insights on the hormonal, (epi)genetic, and neurobiological mechanisms that underlie the effects of exposure to chronic stressors associated with ACEs on academic performance and related cognitive processes. We explore to what extent these mechanisms may be involved in the etiology of heterogeneous disorders such as LDs. Second, we discuss the exposure to ACEs together or separately with stressors caused by poor academic performance in children with LDs of any etiology. Here, we assume that such exposures might lead to the aggravation of LDs. Importantly, whether resulting in the onset or aggravation of LDs, we argue that the underlying mechanisms are the same. Thus, the purpose of this review is to describe these mechanisms and consider their role in the effects of ACEs on the onset of LDs, and the effects of ACEs together or separately with academic-failure stress on the aggravation of LDs.

¹Here, we define “child” as a person 0–18 years of age in accordance with the Convention on the Rights of the Child UNICEF (1989).

PubMed was searched to identify relevant publications. We also examined relevant references in the identified articles. Selected studies considered the relationships between the exposure to chronic stressors, academic performance, and LDs, as well as the neurobiological, hormonal, and (epi)genetic mechanisms of these relationships. The search results were limited to full-text peer-reviewed articles written in English and representing original empirical studies. All differences discussed in this article are statistically significant at $p < 0.05$, unless otherwise stated. The effect sizes (ES) presented here are Cohen's d , a widely used indicator of effect size. When Cohen's d was stated in the original articles, it was extracted and presented here. In other cases, Cohen's d was calculated based on the data available in the original publications (e.g., mean values with standard deviations, correlation coefficients, odds ratios) using standard formulas (Borenstein et al., 2009; Cohen, 1988; Rosenthal & Rosnow, 2008). When Cohen's d was impossible to calculate, the unstandardized beta (B) or standardized beta (β) values were presented when available.

Chronic stress, academic performance, and LDs

Stress and learning and cognition

The stress response, or just stress, is an alteration in the biologic equilibrium of the organism in reaction to events is referred as stressors. Exposure to isolated short-term stressors leads to an acute stress response, which mobilizes the body's defense mechanisms and is therefore beneficial, or adaptive. Prolonged or repeatedly occurring (chronic) stressors, or the sense of danger that may precede or follow a stressogenic episode, in the absence of habituation or coping with that stressor, leads to a chronic stress response, or chronic stress, that is maladaptive and correspondingly detrimental to the organism (Shonkoff et al., 2012). Among others, ACEs are often considered to be chronic stressors.

An ACE refers to the exposure of children to potentially traumatic events that may have short- or long-term impacts on their mental and physical health (Felitti et al., 1998). Such events can include (1) child maltreatment (psychological, physical, or sexual abuse), (2) household dysfunction (lack of parental care, experiencing domestic violence, or living with household members who are incarcerated or substance-abusing, mentally or physically ill), (3) community violence (homicides, sexual assaults, robberies, and weapons attacks), and (4) wars and natural disasters (Felitti et al., 1998; van der Kolk, 2005). These experiences may or may not cause chronic stress and the attendant negative consequences, depending on the existing balance between risk and protective factors.

Among such factors are the intensity and/or duration of the child's exposure to a traumatic event and the presence of the buffering protection of significant others (Brown & Shillington, 2017), which, in turn, can create the prerequisites for children's emotional coping (Dennis, 2006), a factor that can promote children's resilience to chronic stressors. Such resilience has been illustrated by the fact that a child's emotional reactivity moderates the relationship between risk factors and child chronic physiological dysregulation. This can be indexed by hair cortisol levels: for children who showed more emotional reactivity, a higher level of risk factors (low socioeconomic status and low parental sensitivity) was related to higher child cortisol levels (Kao et al., 2019). However, there was no relationship

between risk factors and child cortisol levels for children who were less emotionally reactive (Kao et al., 2019).

The literature regarding the relationship between ACEs and academic performance in typically developing children is limited. In one of the available studies, Delaney-Black et al. (2002) found that first graders ($n = 299$) with higher ACEs exposure had lower reading performance (assessed by the Test of Early Reading Ability, $ES = 1.25$), and lower intellectual functioning (assessed by the Wechsler Primary and Preschool Scale of Intelligence–Revised, $ES = 1.09$). A related large-scale study of kindergarten to sixth-graders ($n = 2,101$) showed the association between higher number of ACEs and higher risk of behavioral/learning problems rated by school staff or documented in medical charts by pediatricians (academic failure, attendance concerns, and school behavior problems, $ES = 1.07$) (Blodgett & Lanigan, 2018). Another study ($n = 701$, mean age 8.13 years) demonstrated similar results with $ES = 1.92$ (Burke et al., 2011). A higher incidence of ACEs was associated with a higher risk of poor school attendance with $ES = 0.88$ (Blodgett & Lanigan, 2018) and failure to meet grade-level standards in mathematics, reading, or writing $ES = 0.68$ (Blodgett & Lanigan, 2018). Also, it has been shown that the number of problems in school increases with the number of ACEs. ACE scores ≥ 1 were associated with increased odds of reporting learning/behavior problems as documented in medical charts by pediatricians as compared to an ACE score of 0, $ES = 1.29$, while an ES at ACE scores ≥ 4 was 1.92 (Burke et al., 2011). An ACE score of 1 was associated with increased odds of reporting school behavior problems (externalizing, internalizing, or both), as compared to an ACE score of 0 with an $ES = 0.48$, while an ES in cases of ACE score ≥ 4 was 1.07 (Blodgett & Lanigan, 2018). Similarly, an ACE score of 1 was associated with increased odds of reported academic failure, defined as not meeting grade-level standards in reading, writing, or math, as compared to an ACE score of 0, $ES = 0.26$, while an ES in cases of ACE scores ≥ 4 was 0.68 (Blodgett & Lanigan, 2018). In a nationally representative sample of US children ages 0–17 ($n = 95,677$), aimed to assess the prevalence of adverse childhood experiences and associations between them and factors affecting children’s development and lifelong health using the 2011–12 National Survey of Children’s Health, children with two or more ACEs were reported to have a 2.67 times higher risk of repeating a grade than children without any such experiences (Bethell et al., 2014).

Regarding children with LDs, we identified one study that investigated the association between ACEs incidence and the likelihood of LDs (Turney, 2020). In a nationally representative sample of US children ages 0–17 ($n = 71,811$), aimed to estimate the association between number of ACEs and children’s health using the 2016–17 National Survey of Children’s Health, exposure to three or more ACEs, compared to exposure to no ACEs, was associated with a greater likelihood of LDs ($\beta = 0.96$). Reduction of risks was found from the age of 6 to the age of 17.

Importantly, although there are a number of studies similar to those described above, their explanatory power is limited because of their correlational nature. This is because causation research requires designs (e.g., randomization to having or not having ACEs) that are simply not appropriate for this research. Prospective cohort studies satisfy one essential criterion of a cause-effect relationship, temporal precedence of cause over effect, but they hardly meet

the other criterion, the absence of a “third variable”, i.e. an unobservable variable that might account for the observed intergroup difference in the absence of randomization. In light of this limitation, several strategies have been suggested (McLanahan et al., 2013). Taking into account available observational studies, authors reviewed strategies for deriving causal effects of traumatic events, such as a father’s absence, on various outcomes including reading and math ability. Most of these strategies include various mathematical modelling approaches (e.g., lagged dependent variable model, growth curve model, individual fixed effects model, sibling fixed effects model, propensity score matching), each with its own advantages and disadvantages, yet none provide a satisfactory substitution for the experimental approach.

To some extent, data obtained using animal experimental approaches can be informative in the context of this review, given that the molecular and cellular substrates of cognitive processes and the stress response are similar in animals and humans. For example, it was shown that chronically stressed rats exhibit profound changes in the morphology of the hippocampus accompanied by learning deficits (Sousa et al., 2000). Such data are of importance in this context since, for example, the hippocampal-dependent learning system plays a role in math learning and disruptions in the functioning of this system, regardless of their origin, could contribute to persistent low-achievement in math (Qin et al., 2014). The relevant animal literature is large, but it is outside the scope of this review. However, we will sample this literature again when causal relationships between exposure to chronic stressors and learning are considered below.

For now, based on this brief summary of the limited literature available, it appears that evidence for the causal connection between ACEs and academic performance in the general population is not sufficiently established, although there is circumstantial evidence (e.g., data from animal studies modeling the impact of ACEs on development and data from correlational studies capturing the associations between exposure to ACEs and academic performance).

If ACEs are associated with an onset of learning difficulties (defined as consistent difficulties related to the mastery of basic concepts, underlying the foundation of reading, mathematics, and other academic skills) or a decline in academic performance, the next question is whether there is a certain “threshold” of exposure to chronic stressors, the crossing of which could not only lead to a decline in academic performance, but also contribute to the onset of LDs. As mentioned above, no direct evidence is available concerning the effect of exposure to chronic stressors on the onset of LDs. However, at least three lines of evidence seem to indirectly support the significance of exposure to such stressors, which we will consider in greater detail later in this review. Briefly, they are: (1) the data on the contribution of stress system dysregulation to physical pathologies and cognitive decline, (2) the data on genetic vulnerability factors that make the carriers of certain genetic variants particularly susceptible to exposure to stressors, and (3) the data on the neurobiological bases that potentially underlie these effects of exposure to stressors.

Learning difficulties as sources of stress

The next question is if LDs can be aggravated by exposure to chronic stressors. In children with LDs, regardless of their etiology, feelings of inferiority and low self-esteem together or separately with ACEs might further compromise their academic performance. Several studies have reported that students with LDs are bullied more than other students, with ES = 0.65 (Nabuzoka & Smith, 1993) and 1.03 (Sabornie, 1994). Twenty-five to 30% of children with LDs have been reported to be socially rejected, compared with 8 to 16% of their typically-achieving peers (Greenham, 1999). In comparison with typically developing children in grades 3 to 5, children who demonstrate poor reading performance experience more sources of school stress, such as negative interactions with teachers (ES = 0.30) and peers (ES = 0.51), poor academic self-esteem (ES = 0.93), and a higher level of manifested school stress, both through emotional (fear, shyness, and loneliness, ES = 0.31) and physiological (nausea, tremors, and rapid heartbeat, ES = 0.26) manifestations (Alexander-Passe, 2008). Middle-school boys with LDs had less academic self-esteem (ES = 1.44) and experienced more anxiety (ES = 0.66 according to self-report, 1.06 as per parental report, and 1.29 according to teacher report) and depression (ES = 0.94, according to self-report, 1.02 as per parental report, and 1.02 according to teacher report) compared to the general education group (McClain, 1997). In addition to these studies, there are books that are partially or wholly devoted to describing the stressors that children with LDs experience (Eaude, 1999; Edwards, 1994; Miles, 2004). Again, all these studies are descriptive in nature and do not elucidate the underlying mechanisms of the observed associations.

Even though the effects of exposure to chronic stressors on the onset and aggravation of LDs have not yet been registered unequivocally, this issue permits and requires thorough investigation. In this review, we will consider biological mechanisms that could potentially underlie these effects. First, we briefly describe the organization of the stress system. Then, we will describe how chronic exposure to stressors is associated with alterations in brain structure and function, which might lead to both the onset and aggravation of LDs. Finally, we will review the genetic and epigenetic mechanisms that could, together with environmental factors, determine or alter stress vulnerability.

Hormonal mechanisms of exposure to stressors on cognition and LDs in children

General mechanisms of stress response

The stress response involves fast sympathetic nervous system activation followed by activation of the hypothalamic-pituitary-adrenal (HPA) axis – the neuroendocrine system crucial for the stress response (Gunnar & Quevedo, 2007). Despite the fact that genes and systems involved in stress resilience/vulnerability go beyond the HPA axis (Feder et al., 2009), the HPA axis is the main focus of our review, since its relationship with the cognitive processes, which are of particular interest to us in the context of LDs, is the most studied. The HPA system is hierarchically organized and very complex, with multiple feedback paths (Figure 1). Exposure to stressors activates the limbic system and the prefrontal cortex, triggering the release of corticotropin-releasing hormone (CRH) by the hypothalamus. CRH binds to CRH receptors in the anterior pituitary gland, leading to the release of

adrenocorticotrophic hormone (ACTH). ACTH binds to receptors in the adrenal cortex and this leads to the release of glucocorticoids (cortisol in humans and primates; corticosterone in rats and mice) from the adrenal cortex. To protect the body against further activation of the HPA axis, and therefore against excessive secretion of cortisol in response to stressors, negative feedback is activated. Glucocorticoids bind to their receptors in the hypothalamus, the anterior pituitary gland, and the hippocampus. This dampens the release of CRH by the hypothalamus and ACTH by the anterior pituitary gland, inhibiting HPA axis activity. Another negative feedback mechanism is the binding of co-chaperone FKBP5 (FK506-binding protein 51) to the glucocorticoid receptors (GRs). This binding lowers the affinity of cortisol to these receptors.

Cortisol, the major end product of the HPA axis, is the most researched among the hormones of the HPA axis. This attention stems from its widespread regulatory influences and well-proven role in the stress response, demonstrated in numerous studies and highlighted in meta-analyses that consider cortisol a reliable biomarker of response to stressors. Human studies have indicated that the average effect size of the cortisol response is medium to large (Michaud et al., 2008).

Adaptive responses of the HPA axis to stressors are manifested in the elevation of cortisol levels. This elevation allows the organism to deal with real and perceived threats through the mobilization of energy stores, heightened vigilance, and the activation of learning and memory processes (Sapolsky et al., 2000). However, not every stress response is adaptive. In children, situations in which intense and/or prolonged activations of stress response systems may take place, especially in the absence of support by a caring adult, can be associated with the occurrence of chronic stress response, one of the manifestations of which is HPA axis dysregulation. Such dysregulation may be expressed in both the hyper- (Azar et al., 2007) or hypo-activation (Ouellet-Morin et al., 2011) of this axis in response to exposure to stressors, and thus could be associated with negative outcomes for academic performance, which we will consider further. In addition, cortisol secretion has a diurnal rhythm: its level peaks in the morning to prepare the organism for the beginning of the day, then slowly decreases, plateauing in the middle of the day and reaching its lowest level in the evening. Deviations from this pattern of cortisol release can be also considered HPA axis dysregulation: both reduced morning baseline cortisol levels (Bernard et al., 2017) or increased morning and afternoon cortisol levels (Cicchetti & Rogosch, 2001) are observed during the day in children subjected to ACEs. As revealed in some cases of chronic exposure to stressors, reduced cortisol levels could reflect the phenomenon of hypocortisolism, a form of HPA axis dysfunction. Hypocortisolism is presumably associated with the overactivation of the negative feedback pathways to protect the organism from the persistent elevation of cortisol levels in response to chronic exposure to stressors. However, such mechanisms are not yet well understood.

One of the mechanisms highly involved in the regulation of the HPA axis activity is the epigenetic regulation of glucocorticoid receptor gene expression in the hippocampus (McGowan et al., 2009; Turecki & Meaney, 2016). At the molecular level, epigenetic processes are those that regulate gene expression without altering the DNA sequence (Ptashne, 2007). DNA methylation comprises one of the most studied epigenetic

mechanisms (Boyes & Bird, 1992; Hsieh, 1994) by means of which adversity gets under the skin (Hyman, 2009). One example is association between early-life adversity and an increase in the DNA methylation level of the GR gene in the hippocampus, and hence a decrease in its expression (McGowan et al., 2009; Turecki & Meaney, 2016). A decrease in the number of GRs in the hippocampus leads to an attenuation of the negative feedback of the HPA axis, which, in turn, results in an increase of cortisol level when an individual is exposed to stressors.

Cortisol as a marker of chronic exposure to stressors in academic performance and LDs

Multiple research designs have been used to investigate the connection between HPA axis dysregulation and developmental outcomes. Prospective cohort studies in older persons have shown that HPA axis dysregulation could predict an increased risk of negative outcomes. For example, elevated cortisol levels predict an increased risk of dying from cardiovascular disease across six years of follow-up, $ES = 0.89$ (Vogelzangs et al., 2010). Higher cortisol reactivity to a psychosocial stressor (assessed by the Trier Social Stress Test, TSST²) was associated with the heightened probability ($B = 0.01$, $p = 0.023$, $n = 129$) of developing cognitive impairment without dementia five years later (de Souza-Talarico et al., 2020). Elevated morning cortisol levels predicted an increased risk of deteriorated cognitive status ($ES = 0.26$) across one year of follow-up (Zhong et al., 2018). Therefore, HPA axis dysregulation may contribute to the pathology of physical and cognitive decline in older persons. In children, the only prospective cohort study we could find revealed that higher basal salivary cortisol levels at 7, 15, and 24 months of life were predictors of a lower level of academic performance at 60 months of life ($\beta = -0.07$, $p = 0.003$, $n = 1,292$), but only for children with concurrently moderate to high levels of salivary alpha-amylase, a marker of autonomic nervous system (ANS) activity (Berry et al., 2012). Since the ANS and HPA axis systems function in a coordinated manner to regulate stress physiology (Granger et al., 2007), it is not surprising that behavioral effects are influenced by both of them, such that both high cortisol and high alpha-amylase concentrations are associated with the most pronounced behavior problems.

Most of the studies on the role of cortisol in academic performance are cross-sectional (or cross-sectional with a delayed follow-up). It has been demonstrated (Jimerson et al., 2006) that a higher salivary cortisol response to school settings (school relative to home cortisol levels) was correlated with academic failure in 5 to 12 year old children ($ES = 0.49$ for language scores, $ES = 0.52$ for social studies scores, $ES = 0.47$ for science scores). Children aged 8 to 10 years who were given the TSST performed more poorly in the delayed memory retrieval test than children from the non-stressed group ($ES = 0.65$) (Quesada et al., 2012). Furthermore, in this study, the participants characterized by a higher cortisol response

²The Trier Social Stress Test (TSST) is a well-known, standardized laboratory psychosocial stress task that elicits a profound HPA axis activation Kirschbaum, C., Pirke, K. M., & Hellhammer, D. H. (1993). The Trier Social Stress Test - a Tool for Investigating Psychobiological Stress Responses in a Laboratory Setting. *Neuropsychobiology*, 28(1-2), 76-81. <https://doi.org/Doi10.1159/000119004>. It consists of three stages: preparation for giving a speech, giving a free speech for a mock job interview, and the math task (orally performed serial subtraction), the last two of which occur in front of an audience of evaluative experts and are videotaped. The experience of being exposed to potentially negative judgment by experts, and of anticipating an uncontrollable performance outcome is associated with the largest and the most reliable cortisol responses compared to other laboratory stressors Campbell, J., & Ehlert, U. (2012). Acute psychosocial stress: does the emotional stress response correspond with physiological responses? *Psychoneuroendocrinology*, 37(8), 1111-1134. <https://doi.org/10.1016/j.psyneuen.2011.12.010>

committed more errors ($ES = 0.80$) during the delayed retrieval than those who showed a lower cortisol response. No statistically significant association was found between cortisol levels during school standardized math testing and academic test performance, although an increase in cortisol level was observed almost exclusively (87.5%) in students with low test performance (Lindahl et al., 2005). Interestingly, this work demonstrated that the lack of an effective coping strategy (reported children's reactions to performance demands, "I get worried and will have problems solving other tasks too") was accompanied by an increase in cortisol levels during the test situation. Higher levels of salivary cortisol reactivity to the testing of various cognitive processes were associated with poorer working memory for numbers ($ES = 0.66$), weaker working memory for words ($ES = 0.88$), and lower performance on quantitative concepts tasks in grade 1 children ($ES = 0.55$) (MacKinnon McQuarrie et al., 2014).

Together, these studies show a rather straightforward relationship of high cortisol levels with low levels of academic performance and memory retrieval, with ES s ranging from small to large. These associations may either indicate a more pronounced stress reaction in low achieving students, a negative impact of strong cortisol response on academic performance, or both. Given that HPA axis dysregulation may contribute to the pathology of physical and cognitive decline in older persons, its contribution to the development of cognitive deficits in children, particularly LDs, is quite possible.

It is notable that studies on the association of ACEs and cortisol level with academic performance have been conducted separately, and there is a lack of research examining cortisol level as a mediator of the associations between ACEs and academic performance. Importantly, however, there is evidence that previously institutionalized children exhibited hypocortisolism at ages 1.5–4.5 years, and this predicted problems with attention and externalizing behaviors during kindergarten (Koss et al., 2016). These early deficits might form the foundation for subsequent weaknesses in academic performance.

Regarding children with LDs, we found three studies that investigated their HPA axis activity. In the first study, children with one type of LD, specific reading disability (SRD), and mean age of 12.61 years showed lower baseline cortisol levels and hypo-activation of the HPA axis in response to an acute psychosocial stressor (TSST). Specifically, more children who were non-reactive to the stressor were found in the group of children with SRD (64.7%; $n = 11$) than in the group of typically developing children (27.3%, $n = 6$), with no statistically significant differences in cortisol reactivity between these groups (Espin et al., 2019). In the second study (Huang et al., 2020), the basal level of cortisol in children with SRD (average age of 10.09 years), remained consistently low throughout the day without any signs of the diurnal rhythm normally seen in typically developing children ($Z = -7.65$, -6.97 , and -6.77 for morning, afternoon, and night cortisol, correspondingly; all $p < 0.001$, $n = 144$). Finally, a third study investigated the associations between HPA axis activity and academic performance. Children at the mean age of 6.5 years with math disabilities had significantly lower scores on a working memory task involving numbers and letters (letter-number sequence task) when they had higher cortisol reactivity to the testing procedures, $ES = 1.28$ (MacKinnon McQuarrie et al., 2014). Unfortunately, these studies lack data on the children's levels of chronic exposure to stressors. Taking into account the fact that children

with LDs are often bullied (Greenham, 1999; Nabuzoka & Smith, 1993; Sabornie, 1994), and the evidence that bullying as a form of psychological maltreatment heightens cortisol response to acute psychosocial stressors (Chen et al., 2018), studying the role of stress in their academic performance is of particular importance.

Thus, currently available data indicate that ACEs are associated with the dysregulation of the HPA axis, expressed in both its hyper- and hypoactivity. It has also been shown that elevated cortisol levels are associated with lower academic performance. Since cortisol plays a significant role in memory processes (de Kloet et al., 1999; Oitzl & de Kloet, 1992; Roozendaal et al., 2010), its reduction can also negatively affect them (Marin et al., 2011). An essential link between the components of the HPA axis and behavioral outcomes, including academic performance, is brain morphophysiology. In the next section, we will discuss the role of stress on the brain's morphophysiology and the potential role of these effects in the onset and aggravation of LDs.

Neurobiological mechanisms of effects of exposure to stressors on cognition and LDs in children

Memory is one of the most intensively studied processes in research on the role of exposure to stressors on cognitive processes. Cortisol levels are related to memory and learning, but not in a straightforward way. Moderate cortisol levels positively affect memory formation and modulation (de Kloet et al., 1999; Oitzl & de Kloet, 1992; Roozendaal et al., 2010), playing an adaptive role, since long-term memories allow one to remember and effectively cope with dangerous conditions upon repeated encounters with them. However, exposure to chronic stressors could potentially lead to a number of negative consequences for structural and functional brain organization, which may potentially underlie deleterious effects on cognitive processes, including low academic performance. Of note, in addition to glucocorticoids, a number of molecular mediators of the negative neurophysiological effects of chronic exposure to stressors have been revealed (Cameron et al., 1997; McEwen et al., 2016; Sandi, 2004; Smith et al., 1995).

Data on cellular alterations in brain structure under the influence of chronic stressors come from animal studies. In rats, chronic exposure to stressors leads to: the reduction of dendritic spine density (Radley et al., 2006) and dendritic length (Radley et al., 2004) in pyramidal neurons of the medial prefrontal cortex, the reduction in the dendritic length of hippocampal pyramidal neurons (Watanabe et al., 1992), the suppression of neurogenesis in the hippocampus (Pham et al., 2003), and an increase in neuronal death in the cerebral cortex (Bachis et al., 2008). Since these changes are accompanied by learning deficits (Sousa et al., 2000), it is likely that these same mechanisms, at least partially, cause the associations between children's exposure to stressors and low academic performance.

Numerous studies have shown a correlation between children's brain structural outcomes and exposure to ACEs. The severity of exposure to stressors during early childhood (through 5 years of age) was negatively associated with the left (ES = 0.59) and right (ES = 0.67) hippocampal volumes in 9–13-year-old children (Humphreys et al., 2019). Post-institutionalized children with median age at adoption of 12 months had smaller left

hippocampal volumes than non-adopted children at the age of 12–14 years with $ES = 0.46$ (Hodel et al., 2015). It has been demonstrated (Tyborowska et al., 2018) that children who experienced more negative ACEs before age 5 showed the largest grey matter volume decrease of the prefrontal cortex at the age of 12–14 years ($p < 0.05$, $n = 37$). The data on the relationship between the volume of the amygdala and the ACEs exposure are contradictory and revealed both an increase (Mehta et al., 2009; Tottenham et al., 2010) and a decrease (Hodel et al., 2015; Tyborowska et al., 2018) in its volume.

It can be seen from the above examples that the hippocampus, the prefrontal cortex, and the amygdala are the main targets of exposure to stressors among the brain structures, which has been partly explained by the presence of the high number of GRs (Sanchez et al., 2000). A decrease in the number of neurons and the volume of brain areas enriched with GRs, along with the changes in cell morphology described above, can potentially lead to a corresponding reduction in the number of GRs. This decrease can attenuate the negative feedback pathways (Figure 2), which, in turn, can increase stress hyperactivity. Furthermore, exposure to chronic stressors downregulates the expression of GRs (at both the mRNA and protein levels) in the hippocampus and the prefrontal cortex. This can also diminish the effectiveness of the negative feedback in the HPA axis (Chiba et al., 2012; Mizoguchi et al., 2003), reflecting HPA axis dysregulation associated with various negative outcomes in academic performance, as we described earlier.

In addition to enabling negative feedback in the regulation of HPA axis activity, these brain structures are involved in cognitive functioning: the hippocampus plays a critical role in memory consolidation and retrieval (Lisman et al., 2017), and the prefrontal cortex is involved in executive functions, memory, and verbal fluency (Siddiqui et al., 2008). These brain areas also play a role in mastering reading and math skills (Grigorenko et al., 2019) and, therefore, may be relevant in the pathogenesis of LDs, not least due to the fact that children with LDs are characterized by the disruption of memory processes and executive functioning (Alloway, 2018). Of note, the list of brain areas involved in reading- and math-related networks is much more extensive than, but not limited to, the hippocampus and the prefrontal cortex (Grigorenko et al., 2019; Pugh et al., 2001).

Taking into account the aforementioned associations of exposure to stressors and cognitive functions, and given the widespread distribution of GRs in the brain beyond the hippocampus and the prefrontal cortex (Siamatras & Stratakis, 2017), it could be said that this exposure may also affect the structure and the functioning of other brain areas, at both macro and micro levels. It should be also noted that the parameters commonly used in studies of the negative impact of exposure to stressors on the brain – specifically brain surface area, volume, and cortical thickness – are very general characteristics of the brain. Therefore, even in the absence of changes in these indicators, it is impossible to exclude alterations at the microstructural cellular and molecular levels of the brain, whose study is limited in humans. As has been concluded, structural and functional brain connectivity changes are also among the neurophysiological consequences of chronic exposure to stressors (Teicher et al., 2016).

The associations between this exposure and macrostructural deficits described in the human brain, as well as the causal relationships between chronic exposure to stressors and microstructural deficits in the animal brain, suggest that exposure to chronic stressors can potentially lead to changes in the neuronal substrates. These substrates enable the emergence of academic skills, such as reading, writing, and math, therefore changes in these substrates may compromise this functioning, causing the onset and aggravation of LDs. We assume that stress affects these two processes in a spiral cyclic manner: stress caused by ACEs exposure leads to or is a factor in the macro- and microstructural changes in the brain that can provoke the emergence of academic failures that qualify as LDs. The manifestation of LDs, regardless of their etiology, in turn, can provoke bullying, feelings of inferiority, and low self-esteem in a school context that continuously demands high levels of performance from struggling students. These additional stressors could cause further macro- and microstructural changes in the brain, resulting in further deterioration of academic performance, that is, the aggravation of LDs. As children grow older, this spiral can potentially lead to deeper and broader consequences, as illustrated by data on elevated rates of LDs among youth involved with the Juvenile Justice System (Grigorenko, 2006).

An essential modulator of the association between ACEs and the development of cognitive functions could be a genetic predisposition to stress vulnerability. In the next section, we will consider the origins of children's resilience or vulnerability to stress, as determined by genetic and epigenetic mechanisms that control HPA axis functioning, which could play a role in the onset and aggravation of LDs.

Genetic and epigenetic factors in the vulnerability and resilience to exposure to stressors

Stress vulnerability and resilience are usually understood as the inability or ability to cope with exposure to stressors, respectively. Coping efficiency could be assessed by the level of hormonal response to a stressor, by a circadian pattern of cortisol secretion, or by the incidence of pathological outcomes of stress. Stress vulnerability can manifest as neuroendocrine hypo- and hyperactivity of the HPA axis in response to a stressor, an abnormal change in the circadian pattern of cortisol secretion, or the induction of stress outcomes and stress-related psychopathologies, such as depression, anxiety, post-traumatic stress disorder (PTSD), or attention-deficit/hyperactivity disorder (ADHD). Correspondingly, the adaptive reactivity of the HPA axis to stressors, the normal circadian pattern of cortisol secretion, or the minimal incidence of stress outcomes can be regarded as stress resilience.

One of the key factors influencing children's stress coping strategies, and therefore their stress resilience, is their relationships with attachment figures. Secure attachment has been shown to be effective in the reduction or prevention of cortisol increases to exposure to stressors at the age 12–18 months old (Luijk et al., 2010; Nachmias et al., 1996; Spangler & Grossmann, 1993; Spangler & Schieche, 1998). Less information is available for older ages. In girls aged 7–12 years, contact with mothers after taking the TSST almost eliminated the cortisol response, which was expressed in more rapidly decreasing and lower levels of peak

cortisol, compared to situations with no maternal contact (Seltzer et al., 2010). Of note, preparing for a public speech together with the parent at ages 9–16 becomes a less potent buffer of HPA axis activation in response to stress as pubertal stage increases (Doom et al., 2015; Hostinar et al., 2015). Taken together, these data indicate the importance of the social regulation of stress resilience.

Regarding the genetic basis of stress vulnerability/resilience, we will provide some examples of the role of the polymorphisms in HPA axis genes in stress reactivity, which can constitute either protective or risk factors. The role of genetic factors in non-HPA systems involved in stress resilience/vulnerability, specifically SNP alleles and genotypes³, has been previously discussed (Feder et al., 2009). In addition, we will review the data on the impact of genome-environment interactions on stress vulnerability/resilience.

The variety of genetic variants in the HPA-axis genes underlies the interindividual variability in HPA axis activity and, eventually, stress vulnerability or resilience. Such variants are called “risk” or “protective” alleles, correspondingly. Generally, the HPA axis genes’ polymorphisms can moderate cortisol reactivity and recovery and the presence of certain genetic variants can lead to the prolongation of the HPA axis activation, which can result in chronically elevated cortisol levels after repeated exposure to stressors. This has been revealed in the relevant genetic association studies, and these results are summarized in Table S1. It is important to note that the literature on the role of genetic variability on stress vulnerability/resilience is primarily based on studies in adults with a minor proportion of research conducted with children.

Notwithstanding, there is evidence of gene-environment interactions⁴: ACEs can modulate the associations between genetic polymorphisms and stress vulnerability/resilience, potentially presenting a double risk/benefit to the allele carrier (for review, see Normann & Buttenschøn, 2020). An important outcome of stress vulnerability/resilience is academic performance in children, but we found only one relevant study (Halldorsdottir et al., 2019), Table S1. It reported that children with genetic risk who were prenatally exposed to stress via violence from the mother’s partner, are characterized by high, prolonged stress-induced cortisol reactivity in test situations designed to induce fear and frustration (mask presentation, barrier procedure, arm restraint procedure, and toy removal procedures) at the age of 15 (ES = 0.13) and 24 months (ES = 0.20). Furthermore, reading ability in primary school grades (1, 2, and 5) was lower in these children (ES = 0.39). Thus, both genetic and environmental factors determine stress resistance and vulnerability, and the HPA axis genes’ polymorphisms moderate the risk for negative outcomes after ACEs.

The mechanisms modulating the associations of ACEs with HPA axis activation can include epigenetic mechanisms, particularly DNA methylation (for review, see Krause et al., 2020).

³SNP (single nucleotide polymorphism) is a variation of a single base pair at a specific position in DNA sequence (due to substitution, deletion or insertion) found in a population. A particular single nucleotide variant (SNV) is called an allele, and a group of SNVs that are inherited together is called a haplotype. The combination of the gene alleles in a diploid individual genome is called a genotype.

⁴Gene-environment interaction is defined as “a different effect of an environmental exposure on disease risk in persons with different genotypes,” or, alternatively, “a different effect of a genotype on disease risk in persons with different environmental exposures.” Ottman, R. (1996). Gene-environment interaction: definitions and study design. *Preventive Medicine*, 25(6), 764–770. <https://doi.org/10.1006/pmed.1996.0117>

In addition to the sole involvement of epigenetic mechanisms, their interactions with genetic polymorphisms can also take place. For example, the carriers of the risk alleles of HPA axis genes with specific DNA demethylation levels in these genes are characterized by more exaggerated or prolonged cortisol reactivity to stressors (Table S1).

Data on the role of polymorphisms in HPA axis genes and epigenetic regulation of HPA axis activity in modulating reactivity to stressors in children with LDs are currently not available and remain to be explored. However, based on the data described above, it may be that polymorphisms of the HPA axis genes and the epigenetic statuses of these genes might play an essential role in the influence of exposure to stressors on the onset and aggravation of LDs. Currently, there are no data showing that all children who are exposed to ACEs will develop LDs in the future, and this seems unlikely. It is more probable that children who later develop LDs could have some kind of innate vulnerability to LDs and, when exposed to stressors, LDs may be expressed. Among the candidate mechanisms of this vulnerability, there are undoubtedly genetic mechanisms that are far from being limited to only the HPA axis genes (Fletcher & Grigorenko, 2017).

Conclusions

In this review, we hypothesized that many associations between chronic exposure to stressors and low academic performance could be at least in part caused by dysregulation of the HPA axis. We discussed a number of sources of indirect evidence of this causal pathway and also examined genetic factors that could have an effect on these processes. A theoretical framework of factors that potentially contribute to the onset and aggravation of LDs is summarized in the diagram (Figure 3).

Genetic and epigenetic factors, exposure to stressors and poor stress-coping strategies may moderate cortisol reactivity and recovery and determine stress vulnerability, expressed in dysregulation of the HPA axis. Dysregulation of the HPA axis influences brain structure and functioning, which, in parallel, are guided by a wide range of genes (Lenroot & Giedd, 2011). Altered brain structure, function, and connectivity induced by ACEs could influence a decline in academic performance that ultimately, at a certain threshold, may become classified as LDs. Children with LDs may then be subjected to even higher exposure to stressors as their learning difficulties are associated with more frequent experiences of failure, lower self-esteem, and increased peer victimization, thus possibly leading to further dysregulation of the HPA axis, and, ultimately, to aggravation of LDs.

Considering all above-mentioned prerequisites, future research directed towards testing our hypothesis on the influence of exposure to chronic stressors on the onset and further aggravation of LDs seems promising in terms of both its theoretical and practical importance. To study the role of exposure to chronic stressors in the onset of LDs, prospective cohort studies could be performed with children without LDs, who are naturally subjected to different levels of chronic stressors, while subsequently monitoring the incidence of LDs depending on children's chronic stress response. Our hypothesis is that children showing the most pronounced chronic stress response will have a higher incidence of LDs. To reveal the role of stress in the aggravation of LDs, a prospective cohort design

should also be utilized to measure the level of exposure to chronic stressors, level of chronic stress response, and the severity of LDs at the beginning of the study, with subsequent measurements of these three indicators longitudinally. We hypothesize that in children with LDs who are showing the most pronounced chronic stress response to chronic stressors, the severity of LDs will increase over time.

In both cases, cortisol levels, particularly within hair, appear to be a well-established and a reliable marker of chronic stress response. Thus, among the sources of cortisol to be analyzed (e.g., saliva, blood, urine, cerebrospinal fluid, and hair), hair cortisol concentration is the most cumulative measure, meaning it is not subjected to diurnal fluctuations seen in blood and saliva, and can be used as a retrospective measure of cortisol secretion for periods up to 6 months (Kirschbaum et al., 2009). Also, hair cortisol level has been positively associated with ACEs (Simmons et al., 2016).

The assumption that chronic stress response induced by chronic exposure to stressors may be involved in the onset and aggravation of LDs can lead to the following conclusion: effective science-based interventions for reducing chronic stress levels, thus improving the academic trajectories of children at risk for LDs, need to be created and implemented. Current educational interventions are mainly aimed at the cognitive aspects of LDs, namely instruction and teaching of the affected skills. These programs could become more effective if they included elements of intervention aimed at stress management and coping. 15-minute relaxation exercises, given once a week for a school year, raised reading performance and lowered anxiety among readers with disabilities (Frey, 1980). Mindfulness-based interventions show promise in relieving stress, anxiety, and depression and improving academic performance in children with LDs (Beauchemin et al., 2008; Peddrew & McNamara, 2019). Taken together, these approaches might have long-term benefits for at-risk children.

There are a number of limitations to the current review. First, we did not consider the role of children's gender and age. Gender and age differences in HPA axis activity take place in childhood, but the evidence is not unequivocal (Hollanders et al., 2017; van der Voorn et al., 2017). Given the existence of sensitive periods – times of increased brain plasticity when the brain may be particularly susceptible to negative influences – the timing of chronic exposure to stressors could influence its effects on children's cognitive development (Teicher et al., 2016). Second, we did not take into account the role of children's temperaments in vulnerability to stress, despite the availability of relevant data (Burenkova & Podturkin, 2020). Third, the impact of stress on various forms of LDs deserves separate consideration, since certain forms of LDs can potentially be more or less sensitive to the effects of stress, both in their onset and aggravation. Yet, although the remediation of these limitations requires empirical data and more theoretical work, we think that the main objective of this article has been accomplished: we have outlined possible mechanisms that could underlie the assumed effects of exposure to stressors on the onset and aggravation of LDs. Therefore, the link between ACEs and LDs should be studied in both children who have reported ACEs and may be at risk for the development of LDs, and in children with LDs, whose adverse experience might result in the aggravation of their LDs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

1. Stress plays a role in the onset and aggravation of learning disabilities (LDs).
2. The relevant possible mechanisms involve hormonal, (epi)genetic, and neurobiological pathways.
3. Stress-reducing interventions could improve academic performance in children with LDs.

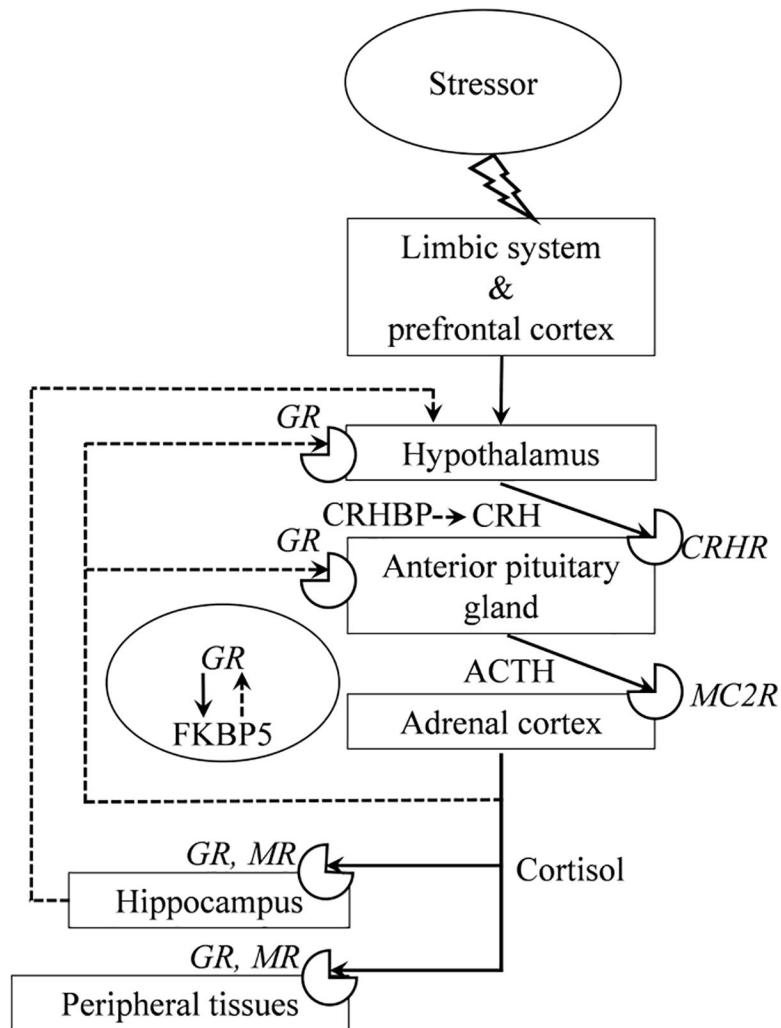


Figure 1. Scheme of the Hypothalamic-Pituitary-Adrenal (HPA) Axis

Note. Activating pathways are indicated by solid lines, inhibitory – with dashed ones; circular sector icons represent receptors. ACTH – adrenocorticotrophic hormone, CRH – corticotropin-releasing hormone, CRHBP – corticosterone-releasing hormone binding protein, CRHR – corticotropin-releasing factor receptor, FKBP5 – FK506-binding protein 51, GR – glucocorticoid receptor, MC2R – melanocortin-2 receptor, and MR – mineralocorticoid receptor.

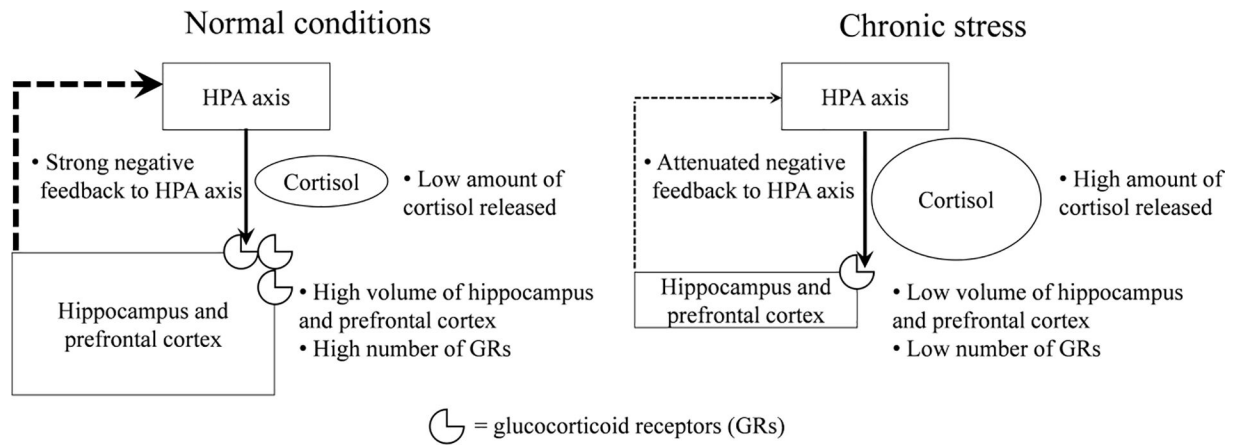


Figure 2.
The negative feedback mechanism in the HPA axis under normal conditions and under chronic stress

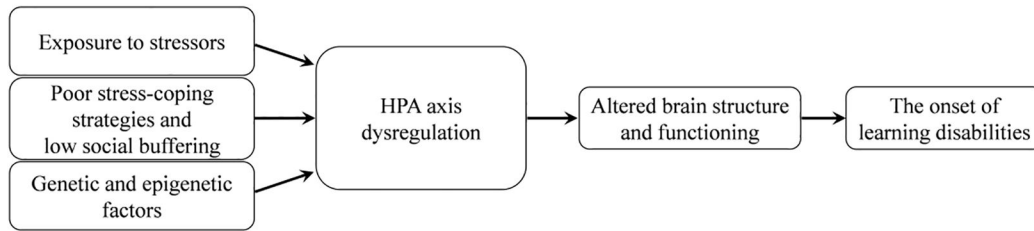
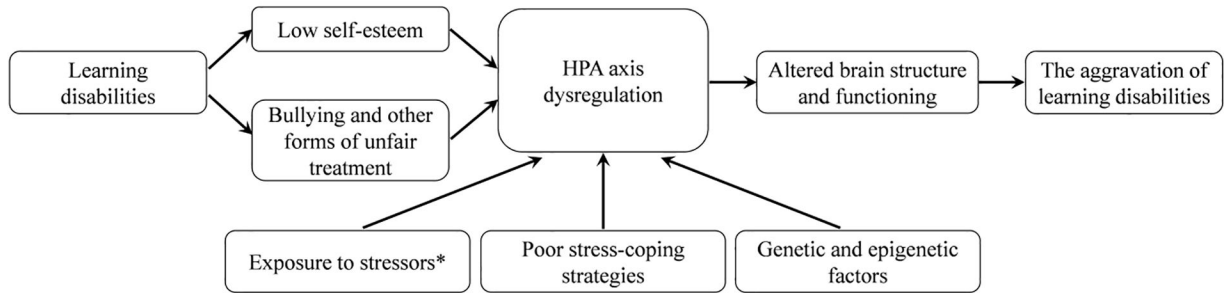
(A) The Onset of LDs**(B) The Aggravation of LDs**

Figure 3. A Theoretical Framework of Factors Potentially Contributing to the Onset (A) and Aggravation (B) of LDs

Note. *Exposure to stressors may or may not occur in parallel with bullying and low self-esteem.